A GOOD FIRST STEP?!

Presentation, treatment, and quality of life in preaxial polydactyly of the foot

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Table of contents

CHAPTER 1

Introduction

Polydactyly is a congenital malformation characterized by additional digits of the hand and/or foot. Based on the orientation of the extra digit, it can be classified as preaxial polydactyly (extra finger or toe present at the side of the thumb or hallux), postaxial polydactyly (extra finger or toe present at the side of the little finger or toe), or central polydactyly (extra finger or toe present in the middle of the hand or foot). In the foot, preaxial polydactyly is also called medial polydactyly, referring to the presence of the extra toe at the medial side of the foot, and postaxial polydactyly is also called lateral polydactyly, referring to the presence of the extra toe at the lateral side of the foot.

The presence of extra fingers and extra toes has already been described in the Old Testament.[1] The second book of Samuel Verses 21:20 refers to 'a huge man with six fingers on each hand and six toes on each foot—twenty-four in all', who is the son of the giant called Rapha. Coincidentally, the painter Raphael is one of the Renaissance painters who painted several paintings, picturing persons with polydactyly of the foot.[1] Examples of his paintings with polydactyly of the foot are: 'The Marriage of the Virgin' (left barefoot of St Joseph) and 'Mond Crucifixion' (left foot of the Virgin).

The development of bipedal movement in humans caused a clear difference in the function of the upper limb and the lower limb.[2] While the hands are important for the usage of tools, the feet are needed for standing and movement. Because human locomotion depends on bipedal movement, the feet have an important role in human daily life, which is confirmed by the fact that foot pain results in a significant decrease of quality of life in adults.[3] Foot function is even more important in the life of a child, as dysfunctional legs and feet may result in a stagnating development of the child due to impossibility to walk and expand its living environment.[4,5] Moreover, it is shown that locomotion is important in toddlers, as it introduces independency, which has a significant impact on psychological development.[6]

Despite the important function of the feet, literature about foot polydactyly is scarce, in contrast to the large amount of studies about the clinical presentation, surgical techniques, and treatment outcomes in hand polydactyly.[7-12] As a result, exact characteristics of the patient group with polydactyly of the foot are undefined and treatment choices are still based on expert opinion. Moreover, information about postoperative dynamic foot function and patient experiences is currently lacking. Especially in preaxial polydactyly of the foot this information is of great value, as the hallux has an essential contribution to walking and standing. For example, changes in hallux position result in changes in balance and plantar pressures.[13-15] Because of this important function, reconstruction of a functional hallux in preaxial polydactyly of the foot is challenging and more important than reconstruction of a little toe in postaxial polydactyly of the foot. In order to describe the specific patient

characteristics in patients with preaxial polydactyly and to appoint the challenges in the treatment of these patients, this thesis will focus on the presentation and treatment of preaxial polydactyly of the foot.

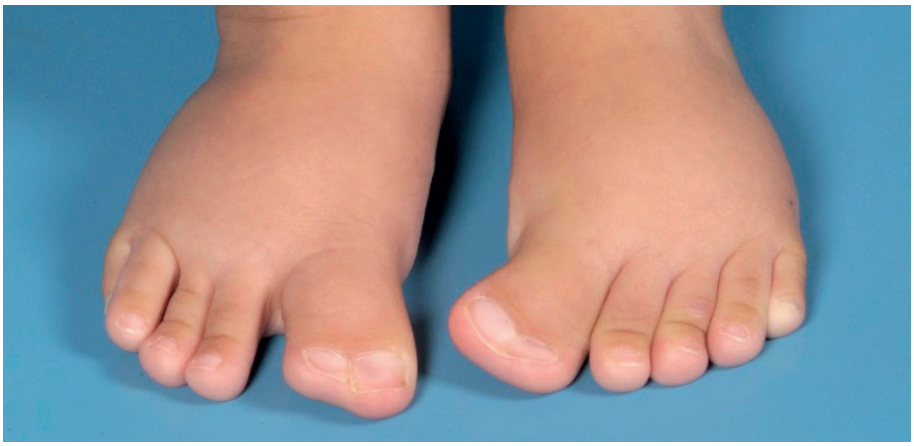

Figure 1. Preaxial polydactyly of the foot

INCIDENCE

With a prevalence between 0.5 and 2.3 per 10,000 births, polydactyly of the foot is less prevalent than polydactyly of the hand, which has a prevalence of approximately 8.4 per 10,000 births.[16,17] Within polydactyly of the foot, postaxial polydactyly is the most common type, with a prevalence of approximately 1.7 per 10,000 births, followed by preaxial polydactyly of the foot, with a prevalence of approximately 0.4 per 10,000 births.[17] Central polydactyly is very rare, and no reliable prevalence numbers are available for this type of polydactyly. In all types of polydactyly, prevalence differs between race and geographical location.[18] For example, a ten times higher risk for postaxial polydactyly of the foot was reported in persons with African descent compared to persons with Caucasian descent.[18,19] The numbers on unilateral or bilateral polydactyly are never reported, but bilateral polydactyly is more associated with syndromes instead of an isolated occurrence.

GENERAL EMBRYOLOGY OF LIMB AND DIGIT FORMATION

Limb development in the human embryo takes place between week 4 and week 8, starting with formation of limb buds from the lateral plate mesoderm.[20,21] The limb buds of the lower

extremities develop in the lumbar/sacral region of the embryo and development starts 1-2 days after the formation of the upper limb buds. Identification of the lower limb is regulated by the presence of T-box transcription factor 4 (*TBX4*) and paired-like homeodomain 1 (*Pitx1*), resulting in the formation of lower extremity structures, such as the femur, tibia, and fibula.[21,22]

Three developmental axes can be distinguished during limb development: the proximal-distal axis, the dorsal-ventral axis (dorsum of the foot-plantar side of the foot), and the anterior-posterior axis (tibial-fibular).[23] Development of every axis is controlled by specific signaling centers and molecules. The proximal-distal axis is established by interactions between the lateral plate mesoderm and the ectoderm, leading to the formation of the apical ectodermal ridge (AER)[21]. The AER controls the proximal to distal limb outgrowth by inducing the expression of Fibroblast growth factor 8 (*Fgf8)* and *Fgf10*, acting as a positive feedback loop. Absence of *Fgf10* results in failure of limb outgrowth. Regulation of the dorsal-ventral axis is done by Wingless-type7A (*Wnt7A*) and Engrailed-1 (*EN-1*).[24] *Wnt7a* in the dorsal side of the limb bud regulates the identification of the dorsal side of the foot. In the ventral side of the foot, *EN-1* is expressed, which inhibits the expression of *Wnt7a*, resulting in formation of the plantar side of the foot. The zone of polarization (ZPA) controls the development of the anterior-posterior axis of the limb bud.[23] The ZPA is present at the posterior limb mesoderm and secretes a morphogen called sonic hedgehog (*SHH*), which is responsible for the digit identification in the limb bud by regulation of zinc finger protein *Gli3*.[21-24] The ratio of the activator and repressor form of *Gli3* is thought to be an important regulator for digit identity.[23] Additionally, the time-dependent concentration of *SHH* is also related to digit identity.[23] In absence of *SHH*, *Gli3* is cleaved into a repressor form, inhibiting transcription of target genes. In the presence of *SHH*, *Gli3* becomes activated and upregulates the expression of target genes. At the anterior side (thumb and hallux), the concentration of *SHH* is lower or even absent and therefore the *Gli3* repressor form is present. At the posterior side (little finger and little toe), concentrations of *SHH* are higher and the activated form of *Gli3* is present. Dysregulation of the balance of *SHH* and *Gli3* can result in polydactyly at the anterior (preaxial) or posterior (postaxial) side of the limb. [25]

PHENOTYPES AND GENOTYPES IN PREAXIAL POLYDACTYLY OF THE FOOT

As illustrated, the general system of limb and digit formation is extensively regulated and subject to different types of inhibition and activation. In preaxial polydactyly of the foot, an increase of *SHH* expression at the anterior side will result in preaxial polydactyly.[25] It is plausible to assume that several mechanisms can cause an increase of *SHH*, instead of

one specific pathway. For example, it can be related to a mutation in *Gli3* leading to an afunctional repressor and therefore increased levels of *SHH* or it can be related to decreased levels of *Gli3* due to a mutation in the protein and therefore decreased transcription. It is thought that these different mechanisms are one of the reasons for the different phenotypic presentations of preaxial polydactyly of the foot (i.e. duplication level; presence of syndactyly*; hypoplastic rays).[25] Furthermore, more than 130 genes are related to syndromic and non-syndromic polydactyly phenotypes and this list is still expanding, as in more than 100 polydactyly phenotypes the related gene is still unknown.[26] Nevertheless, patients can present with different types of preaxial polydactyly in both feet, which indicates that the genotype of a patient does not have a one-on-one relationship with the phenotype.

In approximately 50-60% of the cases, preaxial polydactyly of the foot is an isolated malformation, not associated with other malformations or other recognized syndromes.[17] Subsequently when compared to other types of polydactyly, a large percentage of patients present with a syndrome.[17] The exact amount of syndromes that present with preaxial polydactyly is unknown, but phenotypic presentation can be very different due to different genes that are affected. Currently, specific phenotype-genotype correlations for preaxial polydactyly of the foot are not found. Characterization of the patient group that presents with preaxial polydactyly might help to elucidate the relationship between genotype and phenotype further. Moreover, description of the specific phenotypes of preaxial polydactyly of the foot might clarify a relation between the type of duplication and specific genetic pathways.

In *Gli3*-mediated polydactyly, several efforts have been made to clarify the genotype-phenotype relationship.[27-30] A well-known syndrome that is part of the group *Gli3*-mediated polydactyly is Greig syndrome, which is characterized by preaxial polydactyly of the foot, postaxial polydactyly of hand and feet, syndactyly* of hand and feet, and specific craniofacial malformations (broad forehead, hypertelorism, and macrocephaly).[31,32] A substantial number of patients with the characteristics of Greig syndrome have a mutation in the *Gli3* gene.[31] However, there are patients with Greig characteristics where no mutation has been found in this gene. Furthermore, patients have been described with a mutation in the *Gli3* gene, but lacking some phenotypic characteristics of Greig syndrome. For example, preaxial and postaxial polydactyly is present, while no craniofacial malformations could be observed. The exact mechanism behind the development of these different phenotypes is still unknown. However, the type (truncating* or non-truncating) and location (at the C-terminus or the N-terminus) of the mutations in *Gli3*-mediated postaxial polydactyly and preaxial polydactyly

* Truncating mutations: A change in the DNA that can truncate or shorten the protein.

* Syndactyly: two or more digits are fused together by skin, soft tissue and/or bones.

appear to be different.[30,33] This might result in different concentrations of *Gli-3* at different locations and different moments in the development of the embryo. Despite several efforts, clear phenotype-genotype correlation in *Gli3*-mediated polydactyly are not yet established and the exact relation between the type of mutation and the development of a certain type of polydactyly is not yet defined.

CLASSIFICATION SYSTEMS

Classification systems of congenital malformations can have different functions. They can focus on the morphology, describing the anatomic differences between malformations, classify the type of disease severity or disability, or score the outcome of a treatment in terms of recovery, function, or appearance. In congenital malformations of the limbs, classification systems are often used to describe the types of malformations and to improve communication between clinicians on treatment decisions and treatment outcomes.[34] Effective classification systems can therefore help to guide treatment and to predict outcome, while there are easy to use and can be adapted when new characteristics of the malformation present.[35]

Swanson introduced the Swanson classification for limb malformations, which consists of seven different groups to describe limb malformations (failure of formations of parts, failure of differentiation of parts, duplication, overgrowth, undergrowth, congenital constriction band syndrome, and generalized skeletal abnormalities).[36] Similar to other classification systems developed in this period, this classification system is based on the morphology of the malformation rather than the embryological/etiological cause of the malformation. Because of the increasing knowledge on the embryological development of the limb, this classification received some comments over the years, which resulted in a new classification system for hand malformations. The Oberg, Manske, Tonkin (OMT) classification distinguishes malformations, deformations, and dysplasias.[34,35,37] The group of malformations are further divided by failure of development in a specific axis (proximal/distal, ventral/dorsal, radial/ulnar). Unfortunately, the developers of this classification system only focus on upper limb malformation and lower limb malformations are not included. Indeed, malformations of the upper and lower limb demonstrate a lot of similarities, but if this new OMT-classification can also be used in lower limb malformations remains unclear.

The anatomic diversity of foot polydactyly has resulted in many morphological classification systems over the years to describe the malformations of the foot. Temtamy and McKusick were the first to identify four different preaxial polydactyly types, two different postaxial polydactyly types, and several complex polydactyly types, such as mirror-image polydactyly.[38] In this classification, hand and foot polydactyly are combined

in one classification system. Preaxial polydactyly type 1 (PPD type I) is characterized by polydactyly of the biphalangeal thumb or hallux, preaxial polydactyly type 2 (PPD type II) is characterized by a triphalangeal thumb or hallux, sometimes combined with polydactyly of thumb or hallux, preaxial polydactyly type 3 (PPD type III) is characterized by duplication of index finger or toe, and preaxial polydactyly type 4 (PPD type IV) is characterized by a combination of preaxial polydactyly of the foot and hand, together with postaxial polydactyly and syndactyly of foot and hand. Another method for classification of hand and foot polydactyly is the classification system of Blauth and Olason.[39] This system is more specific, aiming to describe duplication based on location, using a Roman number for the affected ray and a description for the duplication level (distal phalanx, middle phalanx, proximal phalanx, metacarpal or metatarsal, carpal or tarsal). However, it still combines hand and foot polydactyly in one classification system, which makes it less specific.

In the same period as the development of the general polydactyly classification systems, several classification systems were exclusively developed for foot polydactyly. Venn-Watson published a classification for foot polydactyly based on the anatomy of the metatarsal [40], which was expanded by Masada to a classification where also the proximal phalangeal duplications could be classified.[41] Subsequently, Watanabe was the first who split preaxial, postaxial, and central polydactyly in different groups.[42] Unfortunately, he used drawings to describe the specific characteristics of the feet, which made it difficult to use the classification in another population. Recently, Seok introduced the SAM-classification[43], which was the first that included presence of angulation and syndactyly, alongside the classification of osseous structures. Again, this classification system combines preaxial and postaxial polydactyly of the foot and denies the anatomic differences between these two types.

As outlined above, many classification systems for preaxial polydactyly of the foot exist. However, the present classification systems are not specifically developed for preaxial polydactyly of the foot, leading to an incomplete description of the malformation not taking into account the important characteristics of these feet, which are used in clinical decision making.

SYMPTOMS AND TREATMENT

In preaxial polydactyly of the foot, surgeons of congenital limb malformations are often consulted by the parents of children directly after birth because of the different appearance of the foot. At this first consultation, children are not able to walk yet and therefore functional performance of the foot is unclear. Besides the different appearance of the foot, the literature

indicates that children might develop pressure sores at a later age and shoe fitting can be problematic when the duplication is treated conservatively.[40,44] Therefore, surgical removal of the extra hallux is often recommended at a young age to prevent foot complaints during childhood related to shoe fitting and pressure sores.

The aim of surgical treatment in preaxial polydactyly of the foot is to obtain a functionally adequate foot, that fits in a normal shoe and appears like a normal foot.[19] Although proper shoe fitting is the most important goal of surgical treatment in preaxial polydactyly of the foot [44], maintaining or restoring the function of the hallux is also an important goal, because the hallux has an important role in balance[14] and distribution of the load on the foot[45] during walking. Besides these functional goals, it has been shown that changed foot appearance can lead to emotional problems[46], which underlines the need for special attention towards the aesthetic outcomes after surgical treatment.

As the duplication of the hallux can present as a simple duplication of only the distal phalanx or as a complete ray duplication, the surgical procedure should be adapted towards a type-specific procedure. Nevertheless, treatment goals remain identical in every type of preaxial polydactyly of the foot.

Surgical procedure

Most authors recommend to operate above the age of one year, because maturation of the different structures in the foot improves visibility of the structures during surgery.[19,47] Furthermore, below the age of one, an increased anesthesia risk exists, due to increased risk for cardiac arrest and problems with intubation in these young children.[48] In addition, the influence of anesthesia on neurodevelopment in these young children is also debated. Animal studies and some epidemiological studies have shown that anesthesia in young children might lead to abnormal attention, language problems, and behavior changes.[49,50] However, other clinical studies could not find this relationship,[51] and in a large prospective multicenter study that included healthy children with a single exposure to general anesthesia (the PANDA-study) no effect on cognitive outcomes could be found at a mean age of 10 years.[52] In preaxial polydactyly of the foot, the age for surgery is between 12-18 months, in order to reduce the anesthesia risks, while diminishing the functional effects of the operation when children are older and learn to walk. A recent study showed that timing of surgery in foot polydactyly did not influence final functional outcomes.[53]

Prior to surgery, proper imaging of the malformations is important to map the osseous anatomy of the foot. Based on the osseous anatomy and the outside appearance of the foot, the surgeon decides if the lateral or medial hallux should be removed. The procedure begins

with the removal of the osseous structures and nail of the redundant hallux. The additional skin will be preserved for the reconstruction of a new web or side wall at the end of the procedure. The neurovascular bundles of the removed hallux are treated diathermically in order to prevent bleeding and possible neuroma formation. During surgery, the surgeon aims to visualize all the aberrant tendons and ligaments, and will assess the possibility of these structures to be used in the reconstruction and realignment of the preserved hallux. Additionally, and if necessary, osteotomies will be performed to narrow foot width or change the orientation of the hallux. [40,41,44] The goal is to bring the preserved hallux in line with the other toes without compromising its function. After realignment of the hallux, the nail and nail wall are reconstructed, and the skin is closed. During skin closure, it is essential not to use plantar skin on the dorsal side of the foot. The plantar skin is thicker and contains callus and pulpa to protect the structures on the plantar side of the foot during walking. The dorsal skin of the foot is thinner and has a less protective function. In the literature, it is suggested that the placement of the scar should be on the dorsal side of the foot instead of the medial side, because of pain complaints on the medial side. However, clinical experience show that it is easier to fit the skin around the foot when using a medial scar.

Treatment outcomes

Outcome assessment in preaxial polydactyly of the foot is currently limited to static characteristics of the foot obtained by clinical examination and X-rays.[41,42,44,54] Partly, this is due to the young age of the patients at their first consultation, as these children come before the age of one year and thus cannot walk yet. Moreover, reliable measurements in these young patients can be difficult. Another reason for the scarce information on the treatment outcomes is the rarity of the malformation, which makes it hard to include a large and comparable patient group. Nevertheless, previous studies already described specific surgical methods and these studies also provide information about the complications that can occur after surgery.[39,44,55,56]

Excision of the medial toe is often recommended to provide good shoe fitting and to prevent recurrent medial deviation of the toe (hallux varus).[40] However, other studies argue that medial excision is not always the better choice and even unfavorable, especially when the lateral hallux is hypoplastic.[19,41] Unfortunately, no clear guidelines for excision side in preaxial polydactyly exist and only Masada evaluated treatment outcomes based on osseous anatomy.[41] Seven feet with a proximal phalangeal duplication were evaluated in that study, of which the medial hallux was resected in six feet and the lateral hallux in one foot. The foot where the lateral hallux was removed became symptomatic due to recurrent hallux varus.

In metatarsal duplication, Masada treated all four feet with resection of the lateral ray. To realign the preserved medial hallux, reinsertion of the adductor hallucis and an osteotomy was used. In one foot, medial deviation of the reconstructed hallux occurred. Because of the small numbers, no definite conclusions could be drawn about preferred excision side in preaxial polydactyly of the foot.

In all studies, hallux varus position was the most frequently reported complication after surgery in preaxial polydactyly.[19,41,44] Techniques to prevent hallux varus position vary from correction on osseous level using osteotomies, to rebalancing of soft tissue using reinsertion of tendons and reconstruction of the intermetatarsal ligament.[40,44,56] Some authors find reconstruction of the intermetatarsal ligament the most important technique and do not recommend the insertion of aberrant tendons[19,47], while others always use insertion of tendons to correct hallux varus position.[41,44,57]

Altogether, several descriptive studies on specific treatment methods are performed and several recommendations are given regarding the treatment of different types of preaxial polydactyly of the foot. Unfortunately, these studies all include only static measurements of the foot, while the feet are especially important for movement. The dynamic function of the foot after surgical treatment would be of interest to learn more about the effects that removal of the extra hallux has on foot function and the differences between surgically treated feet with preaxial polydactyly and healthy children. Furthermore, to our knowledge, patient's experiences have never been investigated and the impact of preaxial polydactyly on daily life is unclear. Foot function is often assessed by the clinician, while patient-reported outcomes regarding foot function, participation in daily life, and emotional experiences are of increasing importance in health care. Knowledge on dynamic foot function and patient experiences in preaxial polydactyly of the foot is expected to increase our understanding of this condition and improve future clinical decision making in treating preaxial foot polydactyly.

RESEARCH AIMS AND OUTLINE OF THIS THESIS

As introduced in the previous paragraphs, preaxial polydactyly is a congenital malformation of the foot with a diverse presentation. Not only the accompanied malformations in these children range from no malformations to severe malformations, also the phenotypic presentation of the feet show large variation, ranging from a minor duplication of the distal phalanx of the hallux to a complete first ray duplication. The diversity of the phenotypic presentation and the sometimes mild accompanied malformations in people with preaxial polydactyly of the foot can make it difficult for the clinician to recognize patients with a

syndromic background. Therefore, the first part of this thesis will focus on the phenotype and genotype of preaxial polydactyly of the foot. In **Chapter 2,** a literature review and the patient population of the Erasmus University Medical Center is used to provide an overview of the presentation of preaxial polydactyly of the foot. With this overview, practical guidelines are formulated for genetic diagnostics and referral to a clinical geneticist in people with preaxial polydactyly of the foot. To improve description of the anatomic malformations and to enhance communication between clinicians about these malformations, a specific classification system for preaxial polydactyly of the foot is developed in **Chapter 3,** based on the literature and assessment of our own patient population. Intra-rater and interrater reliability is tested and the prevalence of different types of preaxial polydactyly is evaluated. Furthermore, the diversity in presentation have led to several questions regarding the genotypic background of these patients and the relationship between this genotype and the specific phenotypes. What can be the mechanism behind the different levels of duplication and is the foot type related to the type of mutation or the affected gene? To further clarify this relationship, **Chapter 4** evaluates the relationship between the location of the genetic mutation and the phenotypic presentation of GLI3-mediated polydactyly syndromes.

The diverse presentation of preaxial polydactyly of the foot is also reflected in the challenges that surgeons of congenital limb malformations face in treating these feet. The surgical goal is to obtain a functional foot, that fits in a normal shoe and appears like a normal foot. But what is a functional and normal appearing foot? How does the surgically treated foot with preaxial polydactyly differ from the normal foot? To answer these questions, we studied the differences in foot function of patients surgically treated for preaxial foot polydactyly and healthy controls in **Chapter 5**. Subsequently, we studied the treatment outcomes after removal of the lateral or medial hallux in **Chapter 6**. General surgical techniques are described in the literature for the removal of the duplicated hallux, but the patient-specific characteristics of every foot leads to foot-specific treatment decisions that are based on the clinical experiences of the surgeon. Surgeons often ask themselves which hallux should be removed when the development of the lateral and medial hallux is comparable. Is it legitimized to excise the lateral hypoplastic ray when the normally developed ray is heavily deviated and correction of this deviation is proven to be difficult? These dilemma's in treatment of preaxial polydactyly of the foot might depend on the type of polydactyly and are discussed in **Chapter 6**. The last chapter of Part Two, **Chapter 7**, will present the treatment outcomes of a patient with mirror type polydactyly of the foot, a rare type of preaxial polydactyly.

In order to be able to investigate patients' perspectives in clinical care, patient-reported outcome measures are needed that can be used in the specific target population.

Unfortunately, most patient-reported outcome measures in foot and ankle problems are developed for adults and do not focus on children. Only one general foot and ankle questionnaire for children exists, the Oxford Ankle and Foot Questionnaire for children, but only in English, Danish, and Italian. Therefore, we translated and validated this quality of life questionnaire into the Dutch language in **Chapter 8**. In **Chapter 9**, we focus on the quality of life in children and adults with preaxial polydactyly, in order to assess the effects of this congenital malformation for daily-life functioning. The last part of this thesis, **Chapter 10**, will discuss the results of this thesis and will give several recommendations for future research.


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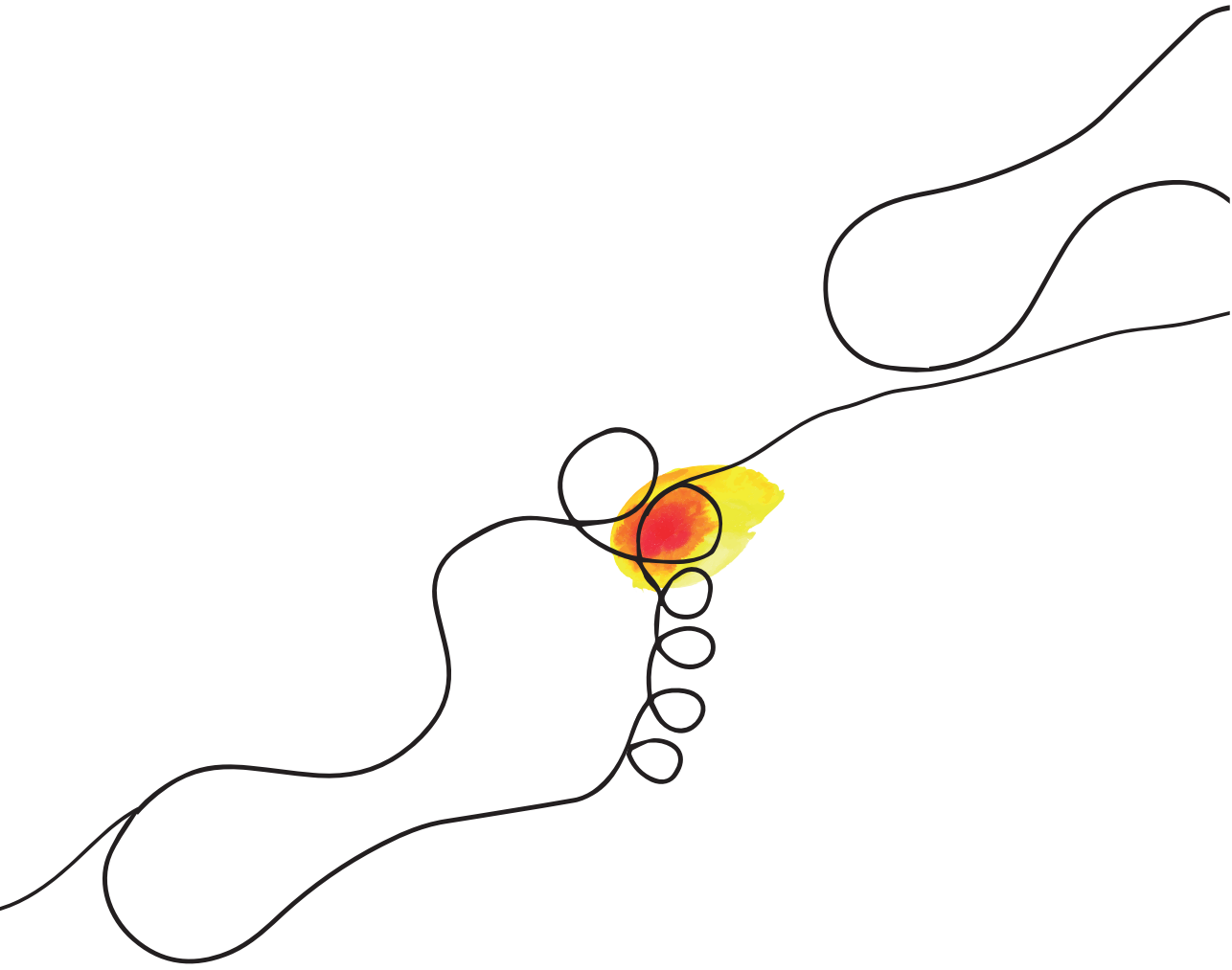

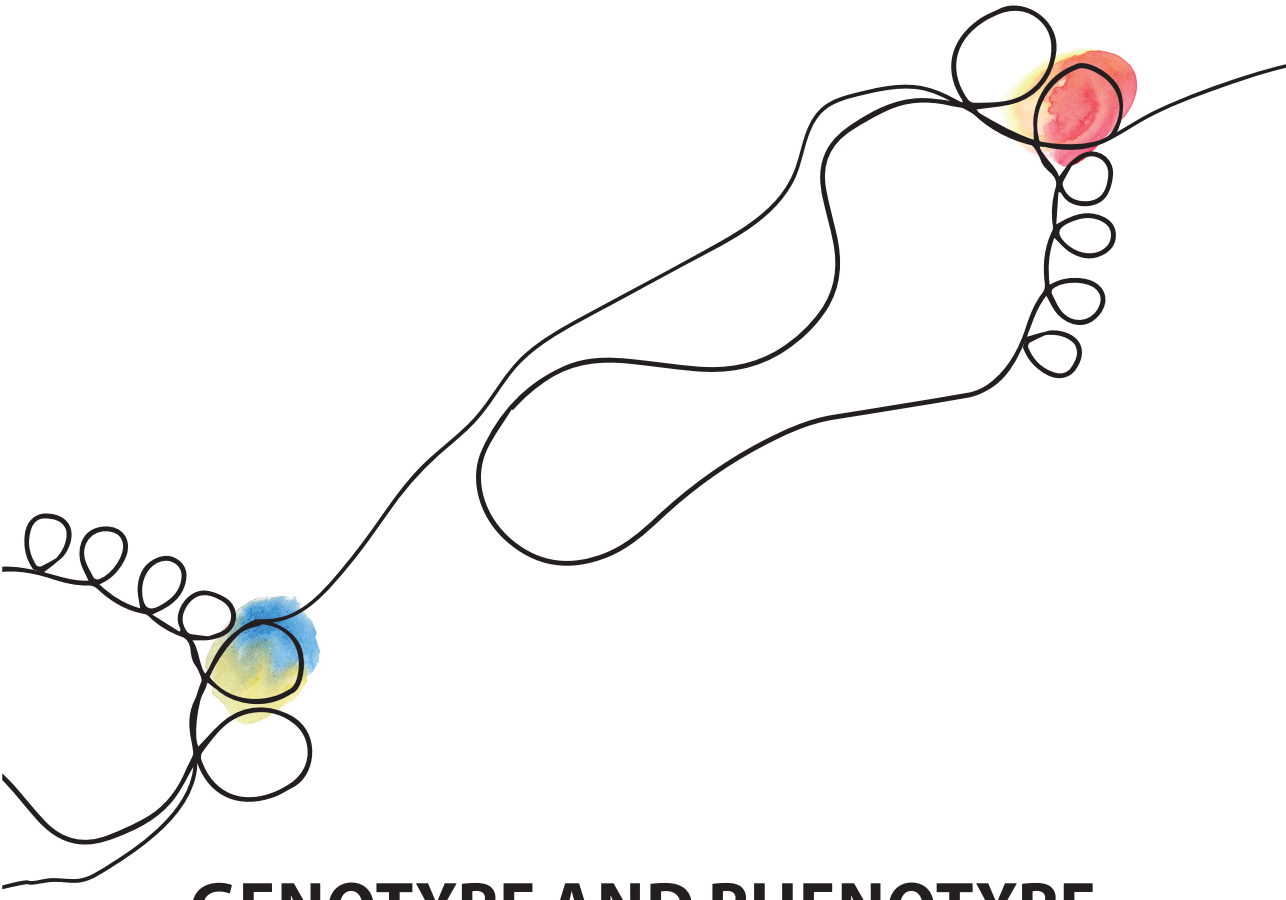

GENOTYPE AND PHENOTYPE

CHAPTER 2

Preaxial polydactyly of the foot:

Clinical and genetic implications for the orthopedic practice based on a literature review and 76 patients

E.B. Burger, M. Baas, S.E.R. Hovius, A.J.M. Hoogeboom, C.A. van Nieuwenhoven

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ABSTRACT

Preaxial polydactyly of the foot is a rare malformation and clinicians are often unfamiliar with the associated malformations and syndromes. In order to give guidelines for diagnostics and referral to a clinical geneticist, we provide an overview of the presentation using literature review and our own patient population.

Literature review was based on the Human Phenotype Ontology (HPO) project. From the HPO dataset, all phenotypes describing preaxial polydactyly were obtained and related diseases were selected. An overview was generated in a heatmap, in which the phenotypic contribution of 12 anatomical groups to each disease is displayed. Clinical cases were obtained from our hospital database and were reviewed in terms of phenotype, genotype, heredity, and diagnosed syndromes.

From the HPO dataset, 21 diseases were related to preaxial polydactyly of the foot. The anatomical groups with the highest phenotypic contribution were lower limb, upper limb, and craniofacial. From our clinical database, we included 76 patients with 9 different diseases, of which 27 had a *GLI3* mutation. Lower limb malformations (n=55), upper limb malformations (n=59), and craniofacial malformations (n=32) were most frequently observed. Malformations in other anatomical groups were observed in 27 patients.

Preaxial polydactyly of the foot often presents with other upper and lower limb malformations. In patients with isolated preaxial polydactyly of the foot, referral to a clinical geneticist is not mandatory. In patients with additional malformations, consultation of a clinical geneticist is recommended. When additional limb malformations are present, analysis of *GLI3* is most feasible.

INTRODUCTION

Polydactyly of the foot is a congenital malformation which can be classified as preaxial: extra hallux; postaxial (most common): extra fifth toe; and central (rarest): middle 3 toes involved. Despite the high prevalence of hand and foot polydactyly in newborns, preaxial polydactyly of the foot is rare. A recent report on congenital limb defects in the northern part of the Netherlands estimated a birth prevalence of 0.4 patients per 10,000 births in preaxial polydactyly of the foot compared to 2.1 patients per 10,000 births in preaxial polydactyly of the hand.[17]

Although rare, knowledge about the presentation of preaxial polydactyly of the foot is important, because almost half of the cases multiple congenital anomalies, such as syndactyly and atrial septum defects, have been reported.[17] Furthermore, preaxial polydactyly of the foot may be associated with syndromes including more severe malformations, such as craniosynostosis or corpus callosum agenesis.[58,59] Due to the low prevalence, most clinicians are unfamiliar with these additional malformations and associated syndromes, which may therefore not be recognized.

The surgical literature mainly addresses the surgical treatment of preaxial polydactyly [40,41,44], whereas the geneticists mainly focus on the genetic background of polydactyly, such as studies on *GLI3* and *HOXD13*. [60,61] The lack of a clear overview of phenotypes that present with preaxial polydactyly of the foot makes it difficult for the surgeon to identify associated malformations and to recognize related syndromes. Associated malformations may be minimal or their detection requires additional diagnostic methods, such as an echocardiogram for cardiovascular anomalies. Therefore, a clear overview of the phenotypic and genotypic characteristics would be helpful.

To clarify the phenotypic and genotypic characteristics of syndromes and diseases which can present with preaxial polydactyly of the foot, we combined review of genetic databases with clinical evaluation of a large surgical population with preaxial polydactyly of the foot. The combination of information from genetic databases and a case series will lead to a more complete overview of the malformation, together with a practical guideline for referral to the clinical geneticist.

METHODS

Review of the human phenotype ontology (HPO) database

We extracted all diseases which can present with preaxial polydactyly of the foot from the HPO dataset.[62] Data extraction was performed according to the CulaPhen protocol [63],

which was modified to select only phenotypes related to preaxial polydactyly of the foot. The protocol uses the HPO annotation files accessible at the HPO's Jenkins page. Accession date, search terms used for this extraction and the URL are available in Appendix 1. A wide spectrum of HPO terms were used (from "broad hallux" to "mirror image polydactyly") to ensure inclusion of all possible diseases. Both subclasses and parental classes were included to assure that all related diseases were included. All diseases that were obtained through this search were manually reviewed by MB and EB to confirm the presence of preaxial polydactyly in the phenotypic descriptions of that disease in literature. For each of the diseases that passed manual review, a list of standardized phenotypes according to HPO nomenclature was available. These HPO phenotypes were categorized based on the Rotterdam registration form for congenital upper anomalies and the CulaPhen protocol (12 groups: CULA, Circulatory, Respiratory, Digestive, Urogenital, Nervous System, Vertebral Column, Musculoskeletal, Head/Neck, Lower limb, Skin, Others).[63,64] For each disease, the number of phenotypes among the 12 different anatomical groups was counted and was expressed in a ratio reflecting the contribution of that anatomical group to the total disease presentation. The obtained ratios can be converted to a heatmap in which the contribution of that anatomical group to the total disease presentation is expressed by a color gradient (0=white, 1=red). If multiple subtypes of a disease were present, the individual diseases were grouped. In addition, when possible the diseases in the heatmap were grouped according to the classification of genetic skeletal disorders.

Review of clinical patients

Our hospital database was retrospectively searched for patients with preaxial polydactyly of the foot diagnosed between 1993 and 2016. All subjects were reviewed in terms of phenotype, sex, heredity, and present gene mutations and syndromes. Assessment of phenotypes in these patients was done based on review of documentation on clinical examination performed by the clinical geneticist and other specialized clinicians. Also, documentation of medical imaging and blood tests were used to identify internal congenital malformations. Because children repeatedly visit the hospital for follow-up of their foot problems until the age of 18, additional verification of malformations presenting at a later age was also performed using medical documentation. Congenital malformations were classified in 12 different anatomical groups, similar to the groups used in the classification of phenotypes in the genetic databases.

At first consultation at our department, a clinical geneticist decided if genetic testing was indicated. Genetic testing usually consisted of array analysis and targeted sequencing

of candidate genes (such as *GLI3*, *FGFR2*, etc.). Alternatively, if a first degree relative with the same congenital condition was already diagnosed with a genetic disease, this diagnosis was considered valid for the included patient as well. Patients without gene mutations documented in the patient documentation were classified as test not indicated, results not present in patient documentation, or no mutation found in genetic testing.

Ethics, funding, and potential conflicts of interest

The institutional medical ethics committee (MEC) reviewed the protocol and agreed that MEC approval was not needed for this study (MEC-2015-679), November 10, 2015. The project was funded by the Esser Foundation. No competing interests were declared.

RESULTS

Review of the HPO database

We selected 13 HPO phenotypes that could match preaxial polydactyly of the foot from the HPO database (Appendix 1). Using these phenotypes, we extracted 123 different diseases. By manual literature review, we excluded 83 diseases. The remaining 40 diseases included 9 diseases with multiple subtypes. Combining the different subtypes in 1 disease group led to a total of 21 unique diseases. The related genes to these diseases are presented in Appendix 2. Most of these diseases (18/21) can be grouped in 3 main categories: polydactyly/syndactyly/triphalangeal syndromes, syndromes with craniofacial malformations (including craniosynostosis), and syndromes with mental retardation as a key aspect [65]. Out of the 3 remaining diseases, 2 are ciliopathies and 1 is a dysplasia syndrome [65]. The anatomical groups that contributed the most to the 21 diseases were lower limb, upper limb, craniofacial, and nervous system. Disease specific contributions of the anatomical groups are presented in Figure 1. The phenotypic presentation of preaxial polydactyly of the foot and examples of the related phenotypes are presented in Figure 2.

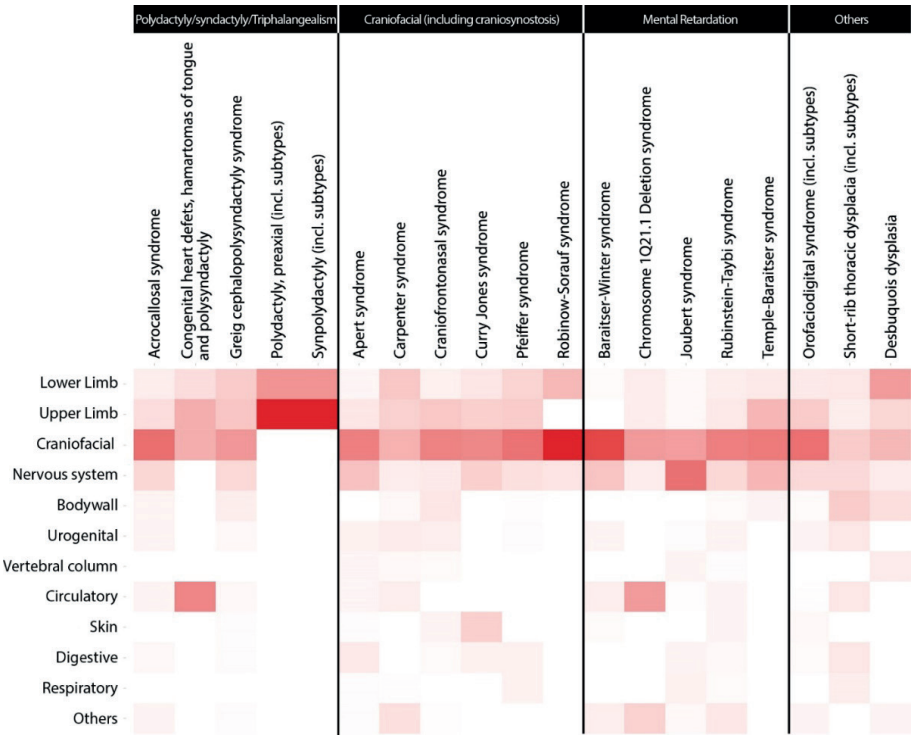

Figure 1. Heatmap showing the contibution of each anatomical group per disease related to preaxial polydactyly of the foot.

The contribution of each anatomical group per disease is expressed by a red color gradient. No contribution = white; maximal contribution = red. The group of preaxial polydactyly consists of preaxial polydactyly type 1, preaxial polydactyly type 2, and preaxial polydactyly type 4. These subtypes are considered as independent disease entities, but are combined in one colomn because contribution of each anatomical group is similar in every type.

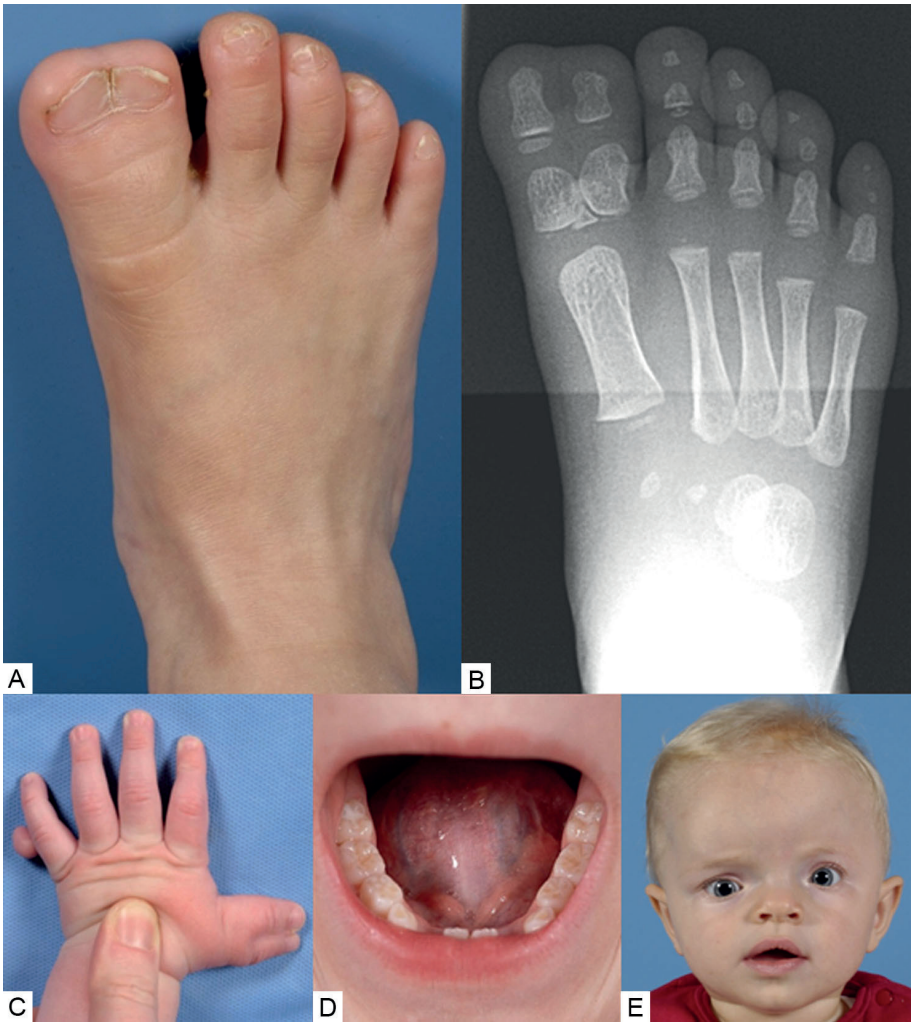

Figure 2. Example of preaxial polydactyly of the foot and related phenotypes.

A) Clinical photograph of preaxial polydactyly of the foot. B) X-ray of preaxial polydactyly of the foot. C) Typical hand malformation in Greig syndrome: Preaxial and postaxial polydactyly of the hand. D) Typical malformation in orofacial-digital syndrome: Tongue malformation. E) Typical craniofacial malformations in craniofacial dysplasia syndrome: Craniosynostosis, hypertelorism, and asymmetric face.

Database Rotterdam

Preaxial foot polydactyly was present in 76 patients (Table 1). 55 patients were bilaterally affected. Most cases (n=41) were hereditary. In 3 patients familial occurrence could not be confirmed due to adoption (n=2) or donor conception (n=1).

Table 1. Patient characteristics of the observed population with preaxial polydactyly of the foot.

Characteristics	N = 76
Sex	
Male	30
Female	46
Affected foot	
Right	15
Left	6
Bilateral	55
Hereditary	
Yes	41
No	32
Unknown	3

Nine out of 21 disease entities and syndromes reported in the HPO dataset were present in our population (Table 2). Besides syndrome diagnosis, 3 different subtypes of preaxial polydactyly (PPD) were used in clinic: type 1, 2 and 4.[38] 9 cases showed PPD type 1, characterized by only preaxial polydactyly of the feet and/or the hands. 3 cases showed PPD type 2, characterized by preaxial polydactyly of the feet and triphalangeal thumbs or halluces. 8 cases showed PPD type 4, characterized by 'crossed polydactyly' (preaxial polydactyly of the feet with postaxial polydactyly of the hands). Preaxial polydactyly of the foot was often accompanied with hand, foot, and craniofacial malformations. 27 patients were affected with malformations in other anatomic groups (Table 2).

Twenty-two patients never received a genetic test or test results were not documented. In 5 of the 6 patients with unilateral PPD type 1, genetic testing was never performed. In contrast, all patients with a triphalangeal thumb and preaxial polydactyly (PPD type 2) were tested for genetic mutations.

In the cohort that was tested for genetic mutations, genetic testing was performed in 39 patients and in 15 affected parents of the patients. In 43 cases this resulted in confirmation of a mutation (Table 3). A *GLI3* mutation was confirmed in the largest part of the population (n=27). In patients with only hand and foot malformations, 14 out of 16 confirmed mutations were in *GLI3*. In patients with anomalies in the different anatomical groups, 13 out of 27 confirmed mutations were in *GLI3*.

Table 2. Phenotypes of the specific syndromes and diseases in the observed population

Syndrome		Acro-callosal syndrome	GLI3-mediatedpoly-dactyly	Preaxial polydactyly type I	Preaxial polydactyly type II	Preaxial polydactyly type IV	Apert syndrome	Carpenter syndrome	Cranio-frontonasal dysplasia	Pfeiffer syndrome	Saethre-Chotzen syndrome	Oro-facial-digital syndrome	Multiple malforma-tions, no disease diagnosis	Total N
	Total N	**1**	**26**	**9**	**3**	**8**	**7**	**2**	**2**	**1**	**2**	**2**	**13**	**76**
1	**Lower limb***	1	25	1	2	7	7	2	1	1	0	1	7	**55**
2	**Upper limb**	1	24	1	3	8	7	2	0	1	2	1	9	**59**
3	**Craniofacial**	1	11	0	0	0	7	2	2	1	2	2	4	**32**
4	**Neurological**	1	1	0	0	0	0	0	0	0	0	0	1	**3**
5	**Body wall**	1	0	0	0	0	0	0	1	0	1	1	3	**7**
6	**Urogenital**	0	0	0	0	0	0	2	0	1	0	0	1	**4**
7	**Vertebral**	0	0	0	0	0	0	0	0	0	0	0	0	**0**
8	**Circulatory**	0	1	0	0	0	2	2	0	1	0	1	4	**11**
9	**Dermatological**	0	1	0	0	0	0	0	0	0	1	0	3	**5**
10	**Digestive**	0	0	0	0	0	0	1	0	0	1	0	0	**2**
11	**Respiratory**	0	1	0	0	0	0	1	0	1	0	0	0	**3**
12	**Other**	0	1	0	0	0	5	0	1	1	1	0	2	**11**

* Other lower limb malformations than preaxial polydactyly of the foot.

Table 3. Genetic testing and observed gene mutations

Genes	Total (N = 76)	Cases with exclusively upper/lower limb malformations (N=35)	Cases with other anomalies besides upper/lower limb malformations (N=41)
EFBN1	2	0	2
FGFR2	8	0	8
GLI3	27	14	13
LMBR1	1	1	0
RAB23	2	0	2
TBX5	1	1	0
TWIST1	2	0	2
Genetic test not performed	15	10	5
No mutation found	11	6	5
No test result documented	7	3	4

DISCUSSION

Evaluation of the genetic databases showed that 21 disease entities are associated with preaxial polydactyly of the foot. However, the spectrum of observed malformations and disease entities in our own population only included 9 disease entities. Our series mainly consisted of *GLI3*-mediated polydactyly, PPD type 1, and PPD type 4. This observation shows that patients with preaxial polydactyly of the foot commonly present without malformations in other anatomic groups. Therefore, the combination of genetic databases and patient populations in rare malformations or diseases is needed to create a thoroughly, but also realistic picture for clinical practice.

When focusing on the phenotypic presentation of preaxial polydactyly of the foot, 3 main groups in our patient population can be distinguished. The first group includes patients with an isolated preaxial polydactyly without any other anomalies. The second group includes patients with combined hand and foot malformations, but without severe anomalies in other parts of the body. The third group includes patients with preaxial polydactyly of the foot and several anomalies in other parts of the body.

The first group, patients with an isolated preaxial polydactyly of the foot, are not commonly tested for genetic mutations in our clinic: most patients with an unilateral preaxial polydactyly in our population were never tested for genetic mutations. Reason for limited testing in isolated preaxial polydactyly is the low detection rate of mutations in patients with isolated limb anomalies.[66] Furthermore, Orioli and Castilla showed that most cases of isolated preaxial polydactyly of the foot occur sporadically.[67] However, in a molecular review

by Johnston et al. 2 patients from a GLI3 family presented with bilateral isolated preaxial polydactyly of the foot.[68] Conclusively, genetic testing might be justified for bilateral and/or familial cases. Nevertheless, in most cases with isolated preaxial polydactyly of the foot testing for a mutation has little consequences for clinical practice.

The second distinctive group is formed by patients with additional limb malformations. Often occurring limb malformations in patients with preaxial polydactyly of the foot are preaxial and postaxial polydactyly of hands and feet, in combination with syndactyly, also named PPD type 4. These patients with multiple limb malformations are often successfully tested for *GLI3* mutations. When specific craniofacial features, such as frontal bossing, macrocephaly, hypertelorism, and a broad nasal bridge, are also present, this phenotype can be classified as Greig syndrome.[31] However, craniofacial malformations in patients with Greig syndrome can be minimal and easily missed, which makes the distinction between PPD type 4 and Greig syndrome difficult.[29] Therefore, in our population we have chosen to classify patients with a *GLI3* mutation as *GLI3*-mediated polydactyly in order to avoid bias due to the retrospective character of this study and underreporting of craniofacial anomalies in our patient documentation.

The third group of patients with preaxial polydactyly of the foot is clinically distinctive by several malformations in different organ systems besides preaxial polydactyly of the foot. Specific features of these patients, such as craniosynostosis or cardiac septal defect, lead to a differential diagnosis resulting in a focused search for gene mutations and eventually syndrome diagnosis. Despite the focused search for gene mutations, a mutation cannot be found in all patients. This is illustrated in our population by the 13 (of 76) patients with multiple congenital anomalies, but without a disease diagnosis. The combination of malformations found in these patients could be coincidental. However, it is also possible that these patients suffer from a disease that was not recognized in counseling, or they might have a different genetic mutation not addressed in targeted analyses. In the end, based on our population study we would advise that at least any patient with several malformations in different organ systems should be referred to a clinical geneticist for evaluation.

Although our study provides an overview of the phenotypic and genotypic spectrum of patients with preaxial polydactyly of the foot, it cannot be used for any measure of risk or prevalence in this population because there is no birth registration for limb malformations in the southern part of the Netherlands. In addition, our distribution of included phenotypes could be influenced by selection bias. However, both isolated preaxial polydactyly of the foot and more complex phenotypes are present in our patient population, which makes selection bias based on patients phenotypes less likely. Furthermore, the retrospective character might

have led to underreporting of specific features due to absence of a standardized research protocol for clinical examination prior to the introduction of the Rotterdam registration form for congenital anomalies.[64] Nevertheless, previous literature reported that one third of patients with preaxial polydactyly of the foot do have a recognized condition, which is comparable in our patient population. Lastly, the actual prevalence of genetic aberrations might be underestimated. Genetic testing in our population consisted of targeted tests of commonly affected genes. Next Generation Sequencing (NGS) would allow for all related genes to be tested at once, which might improve the diagnostic yield due to the detection of variants in the less commonly affected genes.

We distinguished the different phenotypes associated with preaxial polydactyly of the foot from both literature and our clinical experience. Our research is a starting point in the search for suspected syndromes presenting with preaxial polydactyly of the foot. Furthermore, we formulated a practical guideline for referral to a clinical geneticist. In patients with isolated preaxial polydactyly of the foot, referral to a clinical geneticist is not mandatory. Detection rate of gene mutations is low in these patients and implications for clinical practice in case of genetic mutations are limited. When additional limb malformations are present besides preaxial polydactyly of the foot, *GLI3* mutations are likely and consultation of a clinical geneticist should be considered to discuss genetic testing. In patients with multiple malformations in different parts of the body, referral to a clinical geneticist is advised to obtain a complete phenotypic description of the malformations, followed by specified genetic testing in order to confirm or exclude syndrome diagnosis.

ACKNOWLEDGMENTS

We thank the patients who have contributed to this study.

APPENDICES

Appendix 1. HPO data source and HPO codes for all phenotypes related to preaxial polydactyly of the foot

Search terms HPO database	HPO - code
Preaxial polydactyly	HP:0100258
Preaxial foot polydactyly	HP:0001841
Foot polydactyly	HP:0001829
Polysyndactyly of hallux	HP:0005873
Duplication of the phalanx of the hallux	HP:0010066
Duplication of the proximal phalanx of the hallux	HP:0010093
Partial duplication of the distal phalanx of the hallux	HP:0010097
Broad hallux	HP:0010055
Broad phalanx of the toes	HP:0010174
Broad hallux phalanx	HP:0010059
Broad distal hallux	HP:0008111
Broad distal phalanx of the hallux	HP:0010077
Mirror image polydactyly	HP:0010689

Data source: http://compbio.charite.de/jenkins/job/hpo.annotations.monthly/

Dataset: ALL_SOURCES_ALL_FREQUENCIES_diseases_to_genes_to_phenotypes.txt

Last accession date: 22/02/2017

Appendix 2. Genes related to the selected diseases

Disease	OMIM/Orphanet ID	Related Gene
Acrocallosal Syndrome	OMIM:200990	KIF7
Apert Syndrome	OMIM:101200	FGFR2
Baraitser-Winter Syndrome	OMIM:243310	ACTB
Carpenter Syndrome (incl subtypes)	OMIM:201000, ORPHANET:65759	MEGF8, RAB23
Chromosome 1Q21.1 Deletion Syndrome, 1.35-Mb	OMIM:612474	GJA5, GJA8
Congenital Heart Defects, Hamartomas Of Tongue, And Polysyndactyly; CHDHTP	OMIM:217085	WDPCP
Craniofrontonasal Syndrome	OMIM:304110	EFNB1
Curry Jones Syndrome	ORPHANET:1553	SMO
Desbuquois Dysplasia	OMIM:251450	CANT1
Greig Cephalopolysyndactyly Syndrome	OMIM:175700	GLI3
Joubert Syndrome (incl. subtypes)	ORPHANET:475, ORPHANET:220493, ORPHANET:2318	AHI1, ARL13B, B9D1,C5ORF42, CC2D2A, CEP104, CEP290, CEP41, CSPP1, HYLS1, INPP5E, KIAA0556, KIAA0586, MKS1, TCTN1, TCTN2, TMEM138, TMEM216, TMEM231, TMEM237, TMEM67, ZNF423
Orofaciodigital Syndrome (incl. subtypes)	OMIM:277170, ORPHANET:2750, OMIM:258860	C5ORF42, OFD1, TCTN3
Pfeiffer Syndrome (incl. subtypes)	OMIM:101600, ORPHANET:93258, ORPHANET:93259, ORPHANET 93260	FGFR1, FGFR2
Polydactyly, Preaxial (incl. subtypes)	OMIM:174500	LMBR1 (ZRS, Intron 5)
Robinow-Sorauf Syndrome	OMIM:180750	TWIST1
Rubinstein-Taybi Syndrome (incl. subtypes)	OMIM:180849, OMIM:613684	CREBBP, EP300
Short-Rib Thoracic Dysplasia (incl. subtypes)	OMIM:263520	NEK1
Synpolydactyly (incl. subtypes)	OMIM:186000	HOXD13
Temple-Baraitser Syndrome	OMIM:611816	KCNH1


2

CHAPTER 3

The Rotterdam foot classification:

A classification system for preaxial polydactyly of the foot

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ABSTRACT

Polydactyly at the medial side of the foot ("preaxial polydactyly" of the foot) is a rare and diverse congenital anomaly. In order to plan and evaluate surgical treatment, the classification of preaxial polydactyly is useful. The aim of our study was to develop a reliable and valid classification system for preaxial polydactyly of the foot that is more useful than previous systems for preoperative evaluation and surgical planning.

A review of the literature and the clinical experience of a single experienced surgeon were used to determine classification categories. We identified all patients with preaxial polydactyly who had preoperative radiographs and clinical photographs and were treated at our hospital between 1993 and 2014. All affected feet were assessed according to our proposed classification system, the Rotterdam foot classification. The intrarater and interrater reliability among 5 observers who evaluated 30 feet were assessed with use of the Cohen kappa (κ) statistic.

We developed a classification system that describes duplication type, syndactyly, the presence of a hypoplastic ray, and deviation of the hallux. Seventy-three feet were classified according to the system. Seven duplication types were distinguished. Complete metatarsal duplication was most frequently seen (in 29%). Twelve feet showed a broad hallux without external expression of duplication. Syndactyly between medial and lateral (duplicate) halluces was present in 30 feet; between the lateral hallux and second toe, in 13 feet; and between both duplicated halluces and the lateral hallux and second toe, in 18 feet. A hypoplastic ray was seen in 75% of the feet. Intrarater agreement for duplication, hypoplastic rays, syndactyly, and deviation were, respectively, $\kappa = 0.79$, 0.75, 0.59, and 0.78. Interrater agreement for duplication, hypoplastic rays, syndactyly, and deviation were, respectively, $\kappa = 0.72$, 0.54, 0.48, and 0.64.

The proposed classification system contains 4 anatomic features of the foot. Classification of all categories shows moderate to good reliability. Use of the Rotterdam classification in evaluating preaxial polydactyly improves type-specific description, which may, in the future, enhance the evaluation of surgical treatment.

INTRODUCTION

Polydactyly is a congenital malformation characterized by extra digits of hands or feet and can be divided in preaxial, postaxial, and central polydactyly.[61] A report on prevalence in the Netherlands showed 8.4 patients per 10,000 births with polydactyly, with only 0.4 patients per 10,000 births with preaxial polydactyly, also known as medial polydactyly (involvement of the medial side of the foot). Forty percent of these patients were diagnosed with a syndrome.[17]

Preaxial polydactyly of the foot is not extensively studied and cohorts are usually small. A reason for the deficit in literature may be the low prevalence and the relative minor functional problems.[17,40,44] However, the hallux is important for pressure distribution and directional control during walking.[13,14,45] Furthermore, Phelps and Grogan reported the necessity of treatment in most patients with polydactyly due to shoe fitting problems and unsatisfactory esthetic appearance.[19] Consequently, preservation of foot function and the reduction of shoe fitting problems with preaxial polydactyly are challenging and require individualized treatment based on anatomical and clinical appearance of the foot. The use of a clear, uniform classification system will result in simplified communication and improved comparison of different features.[35,69]

Ideally, classification systems can help to guide management of treatment and provide prognosis. However, developing a classification system is challenging. The system should be easy to use and allow for adaptation and extension of the system.[35] Furthermore, it must be valid and reliable.[70] Reliability is easy to measure with an analysis of interrater and intrarater agreement. Validity is a broader concept with content validity, construct validity, and criterion validity being the most important types. Content validity refers to the extent to which a classification represents all important factors of a condition. When items are selected carefully and within reason, the content validity is higher. Construct validity refers to the extent to which a test measures the construct it claims to be measuring. For example, when a classification system is unable to differentiate between different types, it has a low construct validity. Criterion validity refers to the degree the classification correlates with other measures or outcomes. For example, if the classification corresponds to treatment results, then it has a high degree of criterion validity.[70]

Unfortunately, current classifications for preaxial polydactyly do not fulfill the important factors for a good classification system (Table 1). The comparison of feet of different phenotypes is difficult with some classification systems because of the impossibility of classifying all types. For example, the classifications of Seok et al. and Venn-Watson do not describe polydactyly of the distal phalanx.[40,43] Likewise, by the classification system by Masada

et al., no distinction between polydactyly of the distal or proximal phalanx is made, which also results in difficulty in classifying feet.[41] Moreover, Watanabe et al. described preaxial polydactyly on the basis of their own patient population and distinguished between tarsal, metatarsal, proximal phalangeal, and distal phalangeal types.[42] This resulted in 15 different groups for preaxial polydactyly that were specific for that population and without a clear analogy among the different types. The drawings used to describe specific characteristics of the feet, such as hypoplastic rays and deviation, lack universal properties and are not easy to use. Furthermore, preaxial and postaxial foot polydactyly are sometimes grouped together in classification systems; both Blauth and Olason and Seok et al. combined postaxial and preaxial polydactyly in one classification system.[39,43] We think that this decreases the content validity of the classification of preaxial polydactyly because Venn-Watson described a difference in the anatomical properties of preaxial polydactyly compared to postaxial polydactyly.[40] In addition, it is known that the hallux has a more important function than the fifth toe, which may also result in a decrease in criterion validity.[14,45]

We believe that the present classification systems do not provide a comprehensive description of preaxial polydactyly. Therefore, the aim of this study was to develop a more valid, reliable, and easy-to-use, classification system. In order to improve the content validity of this new classification, we performed a literature review and held a consensus meeting to determine all of the important contributing factors to be considered in the classification of preaxial polydactyly. Next, we tested the usability of the developed descriptive classification system by assessing our own population, and an agreement analysis was performed among five different observers to test the reliability of the classification system.

Table 1. Present classification systems for polydactyly of the foot and their limitations

Classification	Why adaptation?
Watanabe et al.	
Tarsal type (with 1 subtype) Metatarsal type (with 3 subtypes) Proximal phalangeal type (with 5 subtypes) Distal phalangeal type (with 6 subtypes)	1. Uniform classification of different subtypes is impossible. 2. Subtypes are specific for that patient population.
Seok et al.	
S0: no syndactylism S1: incomplete syndactylism S2: complete syndactylism A0: angulation <15 A1: angulation between 15 and 30 A2: angulation >30 M0: no metatarsal extension M1: wide metatarsal head M2: metatarsal shaft not shared (complete or incomplete)	1. Combination of postaxial and preaxial polydactyly in 1 classification system. 2. No description of polydactyly of the phalanges.
Venn-Watson	
Complete duplication of the metatarsal Wide metatarsal head Short block metatarsal Y metatarsal T metatarsal	1. No description of polydactyly of the distal phalanges. 2. Classification possible only for duplication level.
Masada et al.	
Type 1: ray duplication Type 2: completely duplicated phalangeas Type 3: incompletely duplicated metatarsal Type 4: incompletely duplicated phalanges	1. No description of differences between polydactyly of the distal and the proximal phalanx. 2. Classification possible only for duplication level.
Blauth and Olason	
Tarsal type Metatarsal type Proximal phalangeal type Middle phalangeal type Distal phalangeal type With addition of the digit localization indicated by a Roman number (I-V)	1. Combination of postaxial and preaxial polydactyly in 1 classification system. 2. Classification possible only for duplication level.

MATERIALS AND METHODS

Development of the classification system

An Embase literature search (see appendix) for classification systems for polydactyly of the foot was done in October 2014 in order to develop a representative list of contributing factors in preaxial polydactyly. The article titles and abstracts were reviewed to identify studies about classification systems. All classifiable aspects of preaxial polydactyly were extracted and reviewed by an experienced plastic surgeon (CAvN) and the principal investigator (EBB). Relevant categories were chosen based on occurrence of the category in literature and the influence on function and esthetic outcome according to the literature.

Classification of our population

We searched the hospital database of the congenital hand team of our department for patients with preaxial polydactyly of the foot seen between 1993 and 2014. Patients with Apert syndrome were excluded from this initial search because foot anatomy is evidently different in these patients. Patients without preoperative radiographs and clinical photographs were also excluded. Foot anomalies were classified according to the new classification system by the principal investigator (EBB). The occurrence of each type was analyzed.

Agreement assessment

An analysis was performed in order to test intrarater and interrater agreement. The principal investigator (EBB) randomly chose 30 feet from our database. Five raters, who included 2 plastic surgeons (SERH and CAvN), 1 orthopaedic surgeon (BJB), 1 medical student, and the principal investigator, classified the presented clinical and radiographic images according to the developed classification system. The principal investigator was excluded in the intrarater agreement analysis because we expected a biased outcome due to multiple case views by the principal investigator during the study. We chose to involve the 2 specialties because patients consult both plastic and orthopaedic surgeons. Radiographs and clinical photographs were presented via LimeSurvey, a protected computer program used for questionnaires and assessments. Two classification rounds were performed within approximately 4 to 6 weeks. Raters performed the classification independently and were blinded to the clinical information of the patients.

The intrarater and interrater agreement was assessed with use of the Cohen's Kappa (κ) statistic. Guidelines of Landis and Koch were used for interpreting κ-values.[71] The κ value of

intrarater agreement was calculated using the classification for each pair of observations of the 4 observers in the first and second rounds and then averaged to provide a single k value. The average percentage of agreement among the observers was also calculated. Interrater agreement was calculated by comparing the first-round classifications among the different raters. Again, an average of κ and the percentage of agreement were calculated. Because no gold standard for the classification was present, the agreement among the observers was analyzed using the classification that was most chosen by the 5 observers as the gold standard. Statistical analyses of κ values were performed using SPSS software (version 22.0; IBM). The percentages of agreement were calculated using Excel software (2010; Microsoft).

The study was approved by the Institutional Ethical Review Board of the Erasmus Medical Centre, Rotterdam (mec-2014-263) and is in accordance with the Declaration of Helsinki.

RESULTS

Development of the classification system

The search of the literature resulted in 650 articles. After our review of the titles and abstracts, 46 articles remained. We compiled a list of contributing factors that were mentioned and the number of articles describing each (Table 2). Ray involvement was the second most mentioned factor in literature, however this classification system is exclusively for polydactyly of the first ray, which was the reason to exclude this factor. Consensus was reached about the other 4 most mentioned categories: duplication level, syndactyly, hypoplastic ray, and deviation.

Duplication level was included because the surgeon should be informed about duplicated osseous structures. Syndactyly was included because planning of incision and the need for tissue grafting will be influenced by the presence of syndactyly. Furthermore, expected deviation after surgery depends on the presence of syndactyly between the preserved hallux and second toe. Hypoplastic ray was added to the classification because the choice of excision side may be influenced by the presence of a hypoplastic ray. Deviation of the hallux was included because it influences the surgical techniques used to achieve correct orientation of the hallux. As the classification system is only for preaxial polydactyly, involvement of rays other than the first ray was not included.

Table 2. Number of extracted terms from literature review

Extracted terms	N of articles describing these terms
Duplication level	*22*
Ray involvement	12
Valgus deformity/deviation	*12*
Syndactyly	*6*
Hypoplastic ray/rudimentary ray	*4*
Triphalangism	3
Polysyndactyly	3
Triplication	3
Floating hallux	2
Mirror foot	2
Delta phalanx	2
Shape of the metatarsal	1
Rotation	1
Vascular and nerve deformities	1
Upper and lower limb deformities	1

Selected terms for the Rotterdam foot classification are indicated in Italic.

The proposed classification is illustrated in Figure 1. The appearance of a floating hallux or polydactyly without osseous structures is classified as category 0. The duplication type is scored by roman numerals, corresponding to the Rotterdam classification for radial polydactyly and initially derived from the Wassel classification, starting with category I for distal phalangeal duplication to category VIII for duplication of the tarsal bones.[72] Even numbers represent complete duplication of the osseous structure, and odd numbers represent incomplete duplication.

Syndactyly is abbreviated by the letter 'S' and is classified by S0, S1, S2 or S1S2. S0 represented the presence of a broad hallux, without appearance of syndactyly. S1 indicates the presence of syndactyly between medial and lateral (duplicate) halluces. S2 indicates the presence of syndactyly between the lateral hallux and the second toe. S1S2 indicates syndactyly between duplicate halluces and between the lateral hallux and the second toe. No distinction was made between complete or incomplete syndactyly. In cases in which no syndactyly was present, no "S" classification was made.

A hypoplastic ray is abbreviated by the letter 'H' followed with 'M' or 'L', representing a medial or lateral hypoplastic structure. In the classification of a hypoplastic ray, all hypoplastic osseous structures are taken into account. In addition, a preaxial ray with both lateral and medial hypoplastic structures can be scored as HLHM. In cases in which no hypoplastic structure was present, no "H" classification was made.

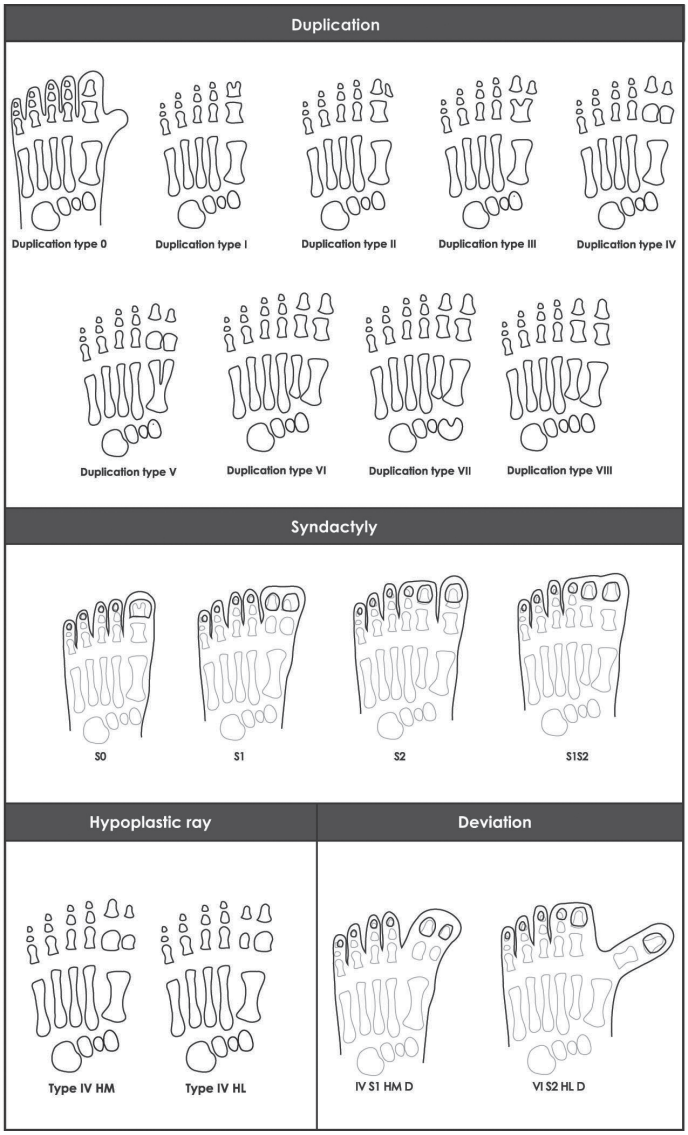

Figure 1. The Rotterdam foot classification

Suggested classification for medial polydactyly with overview of associated deformities and abbreviations.

Level of duplication is assigned by Roman numbers starting with 0 for a duplication without osseous structures and ending with VIII with duplication at the tarsal bones. Partial duplication is assigned with odd numbers and complete duplication with even numbers. Abbreviations can be used for the different associated deformities: S for syndactyly the number corresponding to the location of webbing; H for hypoplastic ray with the assignment of the affected side (L for lateral and M for medial); D for presence of deviation.

Deviation of the hallux, abbreviated as the letter "D," is noted when the alignment of the hallux, which we determined on the basis of clinical photographs, is not in alignment with the rest of the foot.

Classification of our population

A total of 64 patients with preaxial polydactyly of the foot were identified from hospital database. Twenty-one patients were excluded; 11 patients did not have preoperative radiographs because of conversion to electronic patient systems, 3 did not have clinical photographs, and 7 did not undergo surgery in our hospital. The available radiographs or clinical photographs of these 21 patients were reviewed, and no foot types different from those of our included population were suspected in this group. Therefore, selection bias is not likely. Of the included 43 cases, 16 were male and 27 were female (Table 3). Radiographs and clinical photographs were made between the age of 6 and 18 months in the majority of the cases. Preaxial polydactyly of the foot was seen in 73 feet; 39 right feet and 34 left feet. In most (70%) of the cases, bilateral involvement was noted.

Table 3. Patient characteristics

N = 43 patients (73 affected feet)	N of patients (%)
Sex	
Male	16 (37%)
Female	27 (63%)
Foot side	
Only left	4 (9%)
Only right	9 (21%)
Bilateral	30 (70%)
Lateral foot polydactyly	12 (28%)
Syndrome diagnosis	25 (58%)

All of the feet could be classified according to the classification system (Table 4). Seven types of duplication were noted. Duplication type VI was most frequently seen (in 29% of the feet). Partial duplication was mostly seen in the distal phalanx (Duplication type I; 15%). Twelve feet (16%) showed a broad hallux (S0) without the expression of two nails. A hypoplastic ray was seen in 75% of the feet (medial n=21; lateral n=34). Deviation of the hallux medially was seen in the majority of the cases (73%).

With respect to duplication in combination with syndactyly, we found that a larger proportion of feet with duplication type II (61%) and type IV (79%) had syndactyly between 2 halluces (S1) and a larger proportion with duplication type VI (57%) had syndactyly between a lateral hallux and the second toe (S2) (Figure 2). Furthermore, duplication type VI

never involved a medial hypoplastic ray, whereas phalangeal duplications (type II and type IV) involved a medial hypoplastic ray in the majority of feet.

The combined classification showed a wide variety of different presentations of preaxial polydactyly. Fourteen foot types were only scored once. Larger groups of one specific type were present in type IV and type VI duplications. Eight feet were classified as IV S1 HM D, and eleven feet were scored as VI S2 HL D.

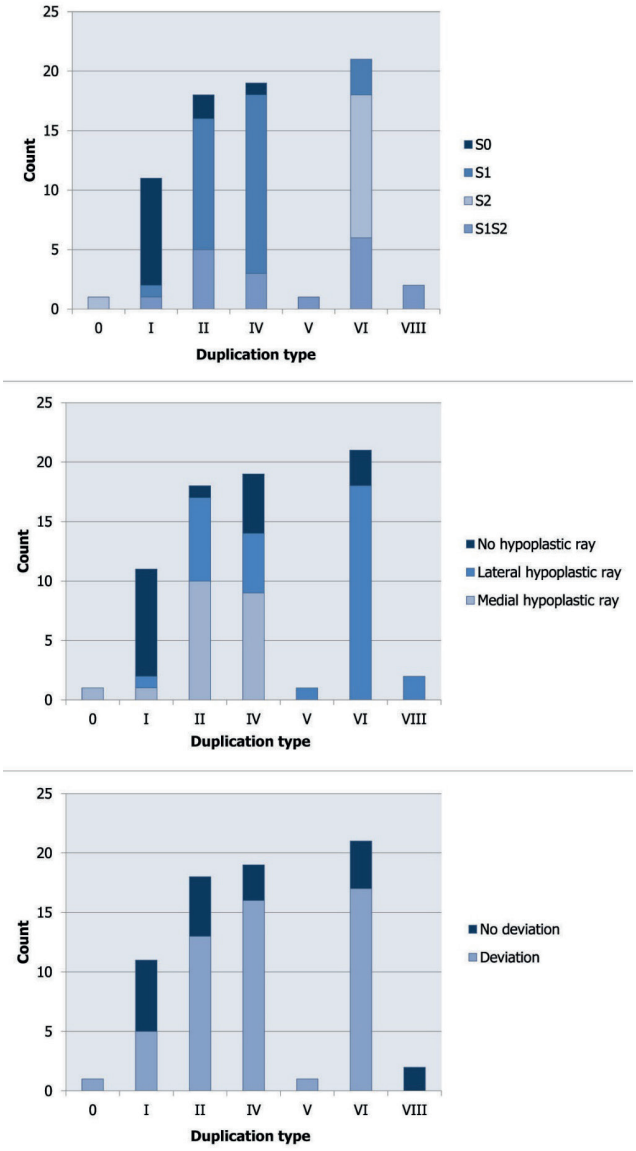

Figure 2. Distribution of syndactyly, hypoplastic ray, and deviation in different duplication levels

Table 4. Distribution of occurrence of duplication, syndactyly, hypoplastic ray and deviation in medial polydactyly

N = 73 feet		N of feet (%)
Duplication		
	0	1 (1%)
	I	11 (15%)
	II	18 (25%)
	III	0 (0%)
	IV	19 (26.0%)
	V	1 (1%)
	VI	21 (29%)
	VII	0 (0%)
	VIII	2 (3%)
Syndactyly		
	No	0 (0%)
	S0	12 (16%)
	S1	30 (41%)
	S2	13 (18%)
	S1S2	18 (25%)
Hypoplastic ray		
	No	18 (25%)
	HL	34 (47%)
	HM	21 (29%)
Deviation		
	No	20 (27%)
	D	53 (73%)

Agreement assessment

Intrarater agreement and interrater agreement of the Rotterdam foot classification is shown in Table 5. Classification of all categories shows moderate to good reliability. Intrarater agreement had the lowest κ for syndactyly (κ= 0.59), with an agreement of 69%. The other three categories showed a mean κ that was >0.7. The mean κ-value for interrater reliablity in all four categories was lower than that for intrarater agreement.

Table 5. Intrarater and interrater agreement

	Categories	Overall Kappa (range)	Agreement	Clinician Kappa (range)	Non-clinician Kappa
Intrarater					
	Duplication	0.79 (0.56-0.87)	82%	0.71 (0.56-0.83)	0.87
	Hypoplastic ray	0.75 (0.59-0.93)	85%	0.81 (0.66-0.93)	0.59
	Syndactyly	0.59 (0.46-0.78)	69%	0.52 (0.46-0.64)	0.78
	Deviation	0.78 (0.49-1.00)	92%	0.71 (0.49-0.84)	1.00
Interrater					
	Duplication	0.72 (0.61-0.83)	88%	0.70 (0.61-0.83)	0.82
	Hypoplastic ray	0.54 (0.23-0.76)	82%	0.74 (0.70-0.76)	0.46
	Syndactyly	0.48 (0.37-0.78)	79%	0.45 (0.37-0.60)	0.78
	Deviation	0.64 (0.53-1.00)	93%	0.62 (0.53-0.76)	0.53

DISCUSSION

Preaxial polydactyly of the foot is a rare congenital anomaly.[17] The diversity of the anomaly requires individualized treatment to diminish shoe-fitting problems and improve aesthetic appearance.[40,44] In order to plan and evaluate surgical treatment, the classification of preaxial polydactyly is useful.[44] However, current classifications are not able to classify all feet and are less feasible to use in clinical practice. Therefore, the aim of current study was to develop a reliable and valid classification system for preaxial polydactyly of the foot.

A search of the literature resulted in 15 different potential categories. We included the four most mentioned terms, with the exception of ray involvement, because it is plausible to presume that these terms are important in the description of preaxial polydactyly. The classification of our own population resulted in a variety of groups, indicating the diversity of anomalies in preaxial polydactyly. However, more specific description of the appearance of the feet also revealed frequent combinations. For example, syndactyly between lateral and medial halluces was mostly seen with the duplication of the proximal or distal phalanx, while syndactyly between the lateral hallux and the second toe was more frequently seen in metatarsal duplication. In addition, in all cases with a lateral hypoplastic ray, metatarsal duplication was present. Comparable results were also seen in the population of Watanabe et al..[42] Moreover, medial hypoplastic rays were mostly identified with duplication of the proximal and distal phalanx, as was previously reported by Masada et al..[41] Group sizes for distal phalangeal (I and II), proximal phalangeal (III and IV), and metatarsal (V and VI) duplications were comparable in our population, while for other populations in the literature[42,44], more proximal phalangeal and metatarsal duplications compared with distal

phalangeal duplications have been reported. In contrast to patient populations of Seok et al., Belthur et al., and Masada et al., our population showed more frequently an incomplete distal phalangeal duplication.[41,43,44] Both of these differences in findings might be the result of the absence of clear external appearance of polydactyly and the inability to classify distal phalangeal duplication with their classification systems. In our study, no feet with type III and type VII duplications were present. However, in thumb polydactyly these duplication types do exists, and also in the study of Watanabe two feet with type III duplication are described.[42] This prompted us to include these types in the classification. All feet in our population could be classified with the proposed system. However, it is known that phenotypic variations are present in different parts of the world; other types of preaxial polydactyly may be present. By conducting a review of the literature, we have tried to include all described types in our classification. However, triplications and triphalangism are also described in polydactyly.[39,72] We did not include these categories because of the rarity of these anomalies. Therefore, we suggest describing rare types in more detail by adding specific terms to the classification system. Moreover, if frequently occurring categories are found to be missing, the classification system allows adaptation.

Classification by all observers was performed with use of digital clinical photographs and digital radiographs, the latter also being used in clinical practice. Therefore, duplication level and hypoplastic rays were assessed in a similar manner during the classification sessions compared to clinical practice.

However, part of the osseous structures of the foot are not visible on radiographs between 6 and 18 months.[73] Consequently, the original duplication level can be different than the observed. Despite this lack of precision, assessment of duplication level in this study is comparable with assessment of duplication in clinical practice. Syndactyly was assessed using digital clinical photographs, while assessment in clinical practice is done by physical examination. As syndactyly is not always clearly visible on photographs, this may have led to increased uncertainty for observers compared to observation of syndactyly in clinical practice. This could have resulted in the lower κ value found for this category.

It is not yet clear whether or not the categories of the Rotterdam system can effectively be used for planning of treatment and the prediction of postoperative functional outcome. However, Belthur et al. compared the modified Venn-Watson classification and the more extensive Watanabe classification for surgical planning.[44] They concluded that the comprehensive Watanabe classification is more useful because of the complete description of the foot, including the presence of a hypoplastic ray, deviation, and tarsal duplication. Unfortunately, the Watanabe classification system only describes types on the basis of

their population and does not contain a consistent and uniform description of preaxial polydactyly.[42] Furthermore, it requires drawings for complete description. The Rotterdam foot classification is based on types described in the literature and evaluated in our own population. Furthermore, the four categories make specific description easier and more analogous between observers.

In this study, we developed a new classification system for preaxial polydactyly of the foot based on a review of the literature and clinical experience. The results of the application of the classification system to our own population and the agreement analysis showed that the Rotterdam foot classification is a usable system to describe preaxial polydactyly. Therefore, we recommend this system for the description of preaxial polydactyly of the foot. In the future, we hope to demonstrate how this classification system can contribute to surgical planning and evaluation.

ACKNOWLEDGMENTS

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APPENDIX

EMBASE literature search

('polydactyly'/exp OR (polydactyl*

OR synpolydactyl* OR ((duplicat* OR malform* OR deformit* OR anomal* OR abnormal*) NEAR/3 (foot OR toe* OR hallux OR leg OR 'lower limb' OR 'lower extremity' OR 'big toe' OR 'great toe'))):ti,ab) AND ('hallux'/exp OR (foot OR toe* OR hallux OR leg OR 'lower limb' OR 'lower extremity' OR 'big toe' OR 'great toe'):ti,ab) AND ('classification'/exp OR (categor* OR classif*):ti,ab)


3

CHAPTER 4

Variant type and position predict two distinct limb phenotypes in patients with GLI3-mediated polydactyly syndromes

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ABSTRACT

Pathogenic DNA variants in the *GLI3* gene are known to cause multiple syndromes: e.g. Greig syndrome, Preaxial Polydactyly-type 4 (PPD4) and Pallister-Hall syndrome. Out of these, Pallister-Hall is a different entity, but the distinction between Greig syndrome and PPD4 is less evident. Using latent class analysis (LCA), our study aimed to investigate the correlation between reported limb anomalies and the reported *GLI3* variants in these *GLI3*-mediated polydactyly syndromes. We identified two sub-classes of limb anomalies that relate to the underlying variant.

Both local and published cases were included for analysis. The presence of individual limb phenotypes was dichotomized and an exploratory LCA was performed. Distribution of phenotypes and genotypes over the classes were explored and subsequently the key predictors of latent class membership were correlated to the different clustered genotypes.

297 cases were identified with 127 different variants in the *GLI3* gene. A two-class model was fitted revealing two subgroups of patients with anterior versus posterior anomalies. Posterior anomalies were observed in cases with truncating variants in the activator domain (postaxial polydactyly; hand OR: 12,7; foot OR: 33,9). Multivariate analysis supports these results (Beta: 1,467, p=0,013 and Beta: 2,548, p<0.001, respectively). Corpus callosum agenesis was significantly correlated to these variants (OR: 8.8, p<0.001).

There are two distinct phenotypes within the *GLI3*-mediated polydactyly population: anteriorly and posteriorly orientated. Variants that likely produce haploinsufficiency are associated with anterior phenotypes. Posterior phenotypes are associated with truncating variants in the activator domain. Patients with these truncating variants have a greater risk for corpus callosum anomalies.

INTRODUCTION

GLI-Kruppel family member 3 (*GLI3*) encodes for a zinc finger transcription factor which plays a key role in the sonic hedgehog (SHH) signaling pathway essential in both limb and craniofacial development.[74,75] In hand development, SHH is expressed in the zone of polarizing activity (ZPA) on the posterior side of the handplate. The ZPA expresses SHH, creating a gradient of SHH from the posterior to the anterior side of the handplate. In the presence of SHH, full length *GLI3*-protein is produced (GLI3A), whereas absence of SHH causes cleavage of *GLI3* into its repressor form (GLI3R).[76,77] Abnormal expression of this SHH /GLI3R gradient can cause both pre- and postaxial polydactyly.[2]

Concordantly, pathogenic DNA variants in the *GLI3* gene are known to cause multiple syndromes with craniofacial and limb involvement, such as: Acro-collosal syndrome[59] (OMIM:200990), Greig cephalopolysyndactyly syndrome[78] (OMIM:175700), and Pallister-Hall syndrome[79] (OMIM:146510). Also, in non-syndromic polydactyly, such as preaxial polydactyly-type 4 (PPD4, OMIM:174700)[33], pathogenic variants in *GLI3* have been described. Out of these diseases, Pallister-Hall syndrome is the most distinct entity, defined by the presence of central polydactyly and hypothalamic hamartoma.[80] The other *GLI3* syndromes are defined by the presence of preaxial and/or postaxial polydactyly of the hand and feet with or without syndactyly (Greig syndrome, PPD4). Also, various mild craniofacial features such as hypertelorism and macrocephaly can occur. Pallister-Hall syndrome is caused by truncating variants in the middle third of the *GLI3* gene.[30,68,81] The truncation of *GLI3* causes an overexpression of GLI3R, which is believed to be the key difference between Pallister-Hall and the *GLI3*-mediated polydactyly syndromes.[68,80] Although multiple attempts have been made, the clinical and genetic distinction between the *GLI3*-mediated polydactyly syndromes is less evident. This has for example led to the introduction of sub-Greig and the formulation of an Oro-facial-digital overlap syndrome.[81] Other authors, suggested that we should not regard these diseases as separate entities, but as a spectrum of *GLI3*-mediated polydactyly syndromes.[27]

Although phenotype/genotype correlation of the different syndromes has been cumbersome, clinical and animal studies do provide evidence that distinct regions within the gene, could be related to the individual anomalies contributing to these syndromes. First, case studies show isolated preaxial polydactyly is caused by both truncating and non-truncating variants throughout the *GLI3* gene, whereas in isolated postaxial polydactyly cases truncating variants at the C-terminal side of the gene are observed.[30,82] These results suggest two different groups of variants for pre- and post-axial polydactyly. Secondly, recent animal studies suggest that posterior malformations in *GLI3*-mediated polydactyly

syndromes are likely related to a dosage effect to GLI3R rather than due to the influence of an altered GLI3A expression.[83]

Past attempts for phenotype/genotype correlation in *GLI3*-mediated polydactyly syndromes have directly related the diagnosed syndrome to the observed genotype.[30,68,81,84] Focusing on individual hand phenotypes, such as preaxial and postaxial polydactyly and syndactyly might be more reliable because it prevents misclassification due to inconsistent use of syndrome definition. Subsequently, latent class analysis (LCA) provides the possibility to relate a group of observed variables to a set of latent, or unmeasured, parameters and thereby identifying different subgroups in the obtained dataset.[85] As a result, LCA allows us to group different phenotypes within the *GLI3*-mediated polydactyly syndromes and relate the most important predictors of the grouped phenotypes to the observed *GLI3* variants.

The aim of our study was to further investigate the correlation of the individual phenotypes to the genotypes observed in *GLI3*-mediated polydactyly syndromes, using LCA. Cases were obtained by both literature review and the inclusion of local clinical cases. Subsequently, we identified two sub classes of limb anomalies that relate to the underlying *GLI3* variant. We provide evidence for two different phenotypic and genotypic groups with predominantly preaxial and postaxial hand and feet anomalies, and we specify those cases with a higher risk for corpus callosum anomalies.

METHODS

Literature review

The Human Gene Mutation Database (HGMD Professional 2019) was reviewed to identify known pathogenic variants in *GLI3* and corresponding phenotypes.[86] All references were obtained and cases were included when they were diagnosed with either Greig or sub-Greig syndrome or PPD type 4.[30,68,81] Pallister-Hall syndrome and acrocollasal syndrome were excluded because both are regarded distinct syndromes and rather defined by the presence of the non-hand anomalies, than the presence of preaxial and postaxial polydactyly.[27,87] Isolated preaxial or postaxial polydactyly were excluded for 2 reasons: the phenotype/genotype correlations is better understood and both anomalies can occur sporadically which could introduce falsely assumed pathogenic *GLI3* variants in the analysis. Additionally, cases were excluded when case-specific phenotypic or genotypic information was not reported or if these two could not be related to each other. Families with a combined phenotypic description, not reducible to individual family members, were included as one case in the analysis.

Clinical cases

The Sophia Children's hospital database was reviewed for cases with a *GLI3* variant. Within this population, the same inclusion criteria for the phenotype were valid. Relatives of the index patients were also contacted for participation in this study, when they showed comparable hand, foot, or craniofacial malformations or when a *GLI3* variant was identified. Phenotypes of the hand, foot, and craniofacial anomalies of the patients treated in the Sophia Children's hospital were collected using patient documentation. Family members were identified and if possible, clinically verified. Alternatively, family members were contacted to verify their phenotypes. If no verification was possible, cases were excluded. The research protocol was approved by the local ethics board of the Erasmus MC University Medical Center (MEC 2015-679).

Phenotypes

The phenotypes of both literature cases and local cases were extracted in a similar fashion. The most frequently reported limb and craniofacial phenotypes were dichotomized. The dichotomized hand and foot phenotypes were preaxial polydactyly, postaxial polydactyly, and syndactyly. Broad halluces or thumbs were commonly reported by authors and were dichotomized as a presentation of preaxial polydactyly. The extracted dichotomized craniofacial phenotypes were hypertelorism, macrocephaly, and corpus callosum agenesis. All other phenotypes were registered, but not dichotomized.

Pathogenic GLI3 Variants

All *GLI3* variants were extracted and checked using Alamut Visual 2.14. If indicated, variants were renamed according to standard Human Genome Variation Society nomenclature.[88] Variants were grouped in either missense, frameshift, nonsense or splice site variants. In the group of frameshift variants, a subgroup with possible splice site effect were identified for sub-group analysis when indicated. Similarly, nonsense variants prone for nonsense mediated decay (NMD) and nonsense variants with experimentally confirmed NMD were identified.[89] Deletions of multiple exons, copy number variations and translocations were excluded for analysis. A full list of included mutations is available in the Appendix.

The location of the variant was compared to 5 known structural domains of the *GLI3* gene: 1) repressor domain, 2) zinc finger domain, 3) cleavage site, 4) activator domain, which we defined as a concatenation of the separately identified transactivation zones, the CPB binding domain and the mediator binding domain (MBD) and 5) the MID1 interaction region domain.[74,78,90-92] The boundaries of each of the domains were based on available literature

(Figure 1, exact locations available in the supplementary materials). The boundaries used by different authors did vary, therefore a consensus was made.

Latent class analysis (LCA)

To cluster phenotypes and relate those to the genotypes of the patients, an explorative analysis was done using LCA in R (R version 3.6.1 for Mac; Polytomous variable LCA, poLCA version 1.4.1). We used our LCA to detect the number of phenotypic subgroups in the dataset and subsequently predict a class membership for each case in the dataset based on the posterior probabilities.

In order to make a reliable prediction, only phenotypes that were sufficiently reported and/or ruled out were feasible for LCA, limiting the analysis to preaxial polydactyly, postaxial polydactyly, and syndactyly of the hands and feet. Only full cases were included. To determine the optimal number of classes, we fitted a series of models ranging from a one-class to a six-class model. The optimal number of classes was based on the conditional Akaike Information Criterion (cAIC), the non adjusted and the sample-size adjusted Bayesian Information Criterion (BIC and aBIC) and the obtained entropy.[93] The explorative LCA produces both posterior probabilities per case for both classes and predicted class membership. Using the predicted class membership, the phenotypic features per class were determined in a univariate analysis (Chi-Square, SPSS version 25). Using the posterior probabilities on latent class (LC) membership, a scatter plot was created using the location of the variant on the x-axis and the probability of class membership on the y-axis for each of the types of variants (Tibco Spotfire, version 7.14) . Using these scatter plots, variants that give similar phenotypes were clustered.

Genotype/phenotype correlation

Because a latent class has no clinical value, the correlation between genotypes and phenotypes was investigated using the predictor phenotypes and the clustered phenotypes. First, those phenotypes that contribute most to LC-membership were identified. Second those phenotypes were directly related to the different types of variants (missense, nonsense, frameshift, splice site) and their clustered locations. Quantification of the relation was performed using a univariate analysis using a Chi-Square test. Because of our selection criteria, meaning patients at least have two phenotypes, a multivariate using a logistic regression analysis was used to detect the most significant predictors in the overall phenotype (SPSS version 25). Finally, we explored the relation of the clustered genotypes to the presence of corpus callosum agenesis, a rare malformation in *GLI3*-mediated polydactyly syndromes which cannot be readily diagnosed without additional imaging.

Table 1. Baseline phenotypes and genotypes of selected population

Phenotypes		**Affected/reported cases (n)**
Hand	Preaxial polydactyly	124/294
	Postaxial polydactyly	170/292
	Syndactyly	124/297
Foot	Preaxial polydactyly	238/297
	Postaxial polydactyly	70/295
	Syndactyly	193/297
Cranium	Macrocephaly	85/228
	Hypertelorism	92/237
	Corpus callosum	16/145
Genotypes		**Cases (n)**
Included in analysis	Frameshift	107
	Nonsense	68
	Missense	60
	Splice	24
Excluded in analysis	CNV	29
	Translocation	3
	No specific information on mutation	6

RESULTS

We included 251 patients from the literature and 46 local patients[30,66,68,81,84,89,94-110], in total 297 patients from 155 different families with 127 different *GLI3* variants. Thirty-two of which were large deletions, copy number variations or translocations. In 6 local cases, the exact variant could not be retrieved by status research. The distribution of the most frequently observed phenotypes and variants are presented in Table 1. Other recurring phenotypes included developmental delay (n=22), broad nasal root (n=23), frontal bossing or prominent forehead (n=16), and craniosynostosis (n=13), Camptodactyly (n=8) and a broad first interdigital webspace of the foot (n=6).

The LCA model was fitted using the 6 defined hand/foot phenotypes. Model fit indices for the LCA are displayed in Table 2. Based on the BIC, a 2-class model has the best fit for our data. The 4-class model does show a gain in entropy, however with a higher BIC and loss of degrees of freedom. Therefore, based on the majority of performance statistics and the interpretability of the model, a 2-class model was chosen. Table 3 displays the distribution of phenotypes and genotypes over the 2 classes.

Table 1 depicts the baseline phenotypes and genotypes in the obtained population. Note incomplete data especially in the cranium phenotypes. In total 259 valid genotypes were present. In total, 289 cases had complete data for all hand and foot phenotypes (preaxial polydactyly, postaxial polydactyly and syndactyly) and thus were available for LCA. Combined, for phenotype/genotype correlation 258 cases were available with complete genotypes and complete hand and foot phenotypes.

Table 2 depicts the model fit indices for all models that have been fitted to our data.

Table 3 depicts the distribution of phenotypes and genotypes over the two assigned latent classes. Hand and foot phenotypes were used as input for the LCA, thus are all complete cases. Malformation of the cranium and genotypes do have missing cases. Note that for the LCA, full case description was required, resulting in 8 cases due to incomplete phenotypes. Out of these 8, one also had a genotype that thus needed to be excluded. Missing of genotypic data was higher in LC2, mostly due to CNV's (Table 1).

Table 2. Model fit indices for the one-class through six-class model evaluated in our LCA

Number of classes	Log Likelihood	Residual degrees of freedom	BIC	aBIC	cAIC	likelihood ratio	Entropy
1	-1072,0687	57	2178,316	2159,109	2184,316	299,59038	-
2	-966,4844	50	2006,632	1965,407	2019,632	88,42178	0,765
3	-949,9799	43	2013,288	1949,865	2033,288	55,41278	0,740
4	-942,9999	36	2038,993	1953,372	2065,993	41,45279	0,952
5	-937,2077	29	2067,074	1959,255	2101,074	29,86850	0,569
6	-933,5159	22	2099,355	1969,338	2140,355	22,48488	0,716

BIC: Bayesuian information criterion; cAIC: conditional Akaike information criterion; LCA: latent class analysis

In 54/60 cases, a missense variant produced a posterior phenotype. Likewise, splice site variants show the same phenotype in 23/24 cases (Table 3). For both frameshift and nonsense variants, this relation is not significant (52 anterior vs. 54 posterior and 26 anterior vs. 42 posterior, respectively). Therefore, only for nonsense and frameshift variants the location of the variant was plotted against the probability for LC2 membership in Figure 1. A full scatterplot of all variants is available in supplementary Figure 1.

Tabel 3. Distribution of phenotypes and genotypes in the two latent classes (LC).

		Latent Class 1 / posterior phenotype	Latent Class 2 / anterior phenotype
Number of cases in LC		88	201
Mean Probability of class membership		0.91 (0.88-0.94)	0.96 (0.95-0.97)
Phenotypes		**% of cases in class**	
Hand	Preaxial polydactyly	15,91%	52,74%*
	Postaxial polydactyly	96,59%	40,80%*
	Syndactyly	12,50%	53,73%*
Foot	Preaxial polydactyly	45,45%	95,52%*
	Postaxial polydactyly	69,32%	1,49%*
	Syndactyly	23,86%	83,08%*
Cranium	Macrocephalie	48,33%	33,33%
	Hypertelorisme	41,07%	38,42%
	Corpus callosum	18,18%	8,16%
Genotypes		**N cases**	
	Total	85/88	173/201
Included mutations	Frameshift	52	54
	Nonsense	26	42
	Missense	6	54*
	Splice	1	23*

** = p<0.01*

Figure 1 reveals a pattern for these nonsense and frameshift variants that reveals that variant at the C-terminal of the gene predict anterior phenotypes. When relating the domains of the *GLI3* protein to the observed phenotype, we observe that the majority of patients with a nonsense or frameshift variant in the repressor domain, the zinc finger domain or the cleavage site had a high probability of a LC2/anterior phenotype. This group contains all variants that are either experimentally determined to be subject to NMD (triangle marker in Figure 1) or predicted to be subject to NMD (diamond marker in Figure 1). Frameshift and nonsense variants in the activator domain result in high probability for a LC1/posterior phenotype. These variants will be further referred to as truncating variants in the activator domain.

The univariate relation of the individual phenotypes to these two groups of variants are estimated and presented in Table 4. In our multivariate analysis, postaxial polydactyly of the foot and hand are the strongest predictors (Beta: 2,548; p<0,001 and Beta: 1,47, p=0,013, respectively) for patients to have a truncating variant in the activator domain. Moreover, the effect sizes of preaxial polydactyly of the hand and feet (Beta: -0,797; p=0,123 and Beta: -1,772, p=0.001) reveals that especially postaxial polydactyly of the foot is the dominant predictor for the genetic substrate of the observed anomalies.

Table 4 shows exploration of the individual phenotypes on the genotype, both univariate and multivariate. The multivariate analysis corrects for the presence for multiple phenotypes in the underlying population.

Although the craniofacial anomalies could not be included in the LCA, the relation between the observed anomalies and the identified genetic substrates can be studied. The prevalence of hypertelorism was equally distributed over the two groups of variants (47/135 vs. 21/47 respectively, p<0.229). However for corpus callosum agenesis and macrocephaly, there was a higher prevalence in patients with a truncating variant in the activator domain (3/75 vs 11/41, p<0.001; OR 8,8, p<0.001). and 42/123 vs 24/48, p<0,05). Noteworthy is the fact that 11/14 cases with corpus callosum agenesis in the dataset had a truncating variant in the activator domain.

Table 4. Univariate and multivariate analysis of the phenotype/genotype correlation

			Univariate analysis	**Multivariate analysis**	
			OR frameshift/nonsense mutation '5 side of the zinc finger domain	**Beta**	**p-value**
Phenotype	**Hand**	Preaxial polydactyly	0,27 (CI:0,14-0,54)	-0,797	0,123
		Postaxial polydactyly	12,7 (CI:5,2-31,0)	1,469	0,013
		Syndactyly	0,3 (CI:0,16-0,57)	0,505	0,338
	Foot	Preaxial polydactyly	0,1 (CI:0,032-0,14)	-1,772	0,001
		Postaxial polydactyly	33,9 (CI:15,1-76,0)	2,548	<0.001
		Syndactyly	0,1 (CI:0,054-0,19)	-1,773	<0.001
Regression constant				-0,564	0,729

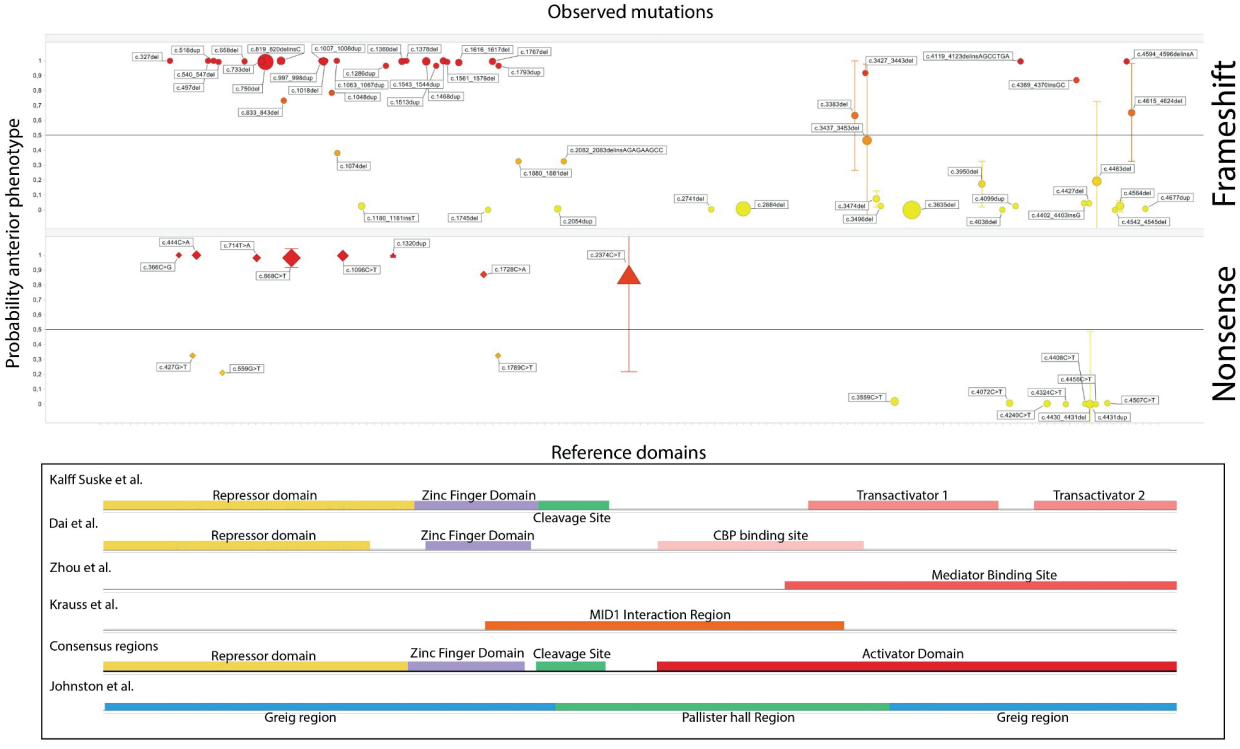


Figure 1. In this figure the posterior probability of an anterior phenotype is plotted against the location of the variant, stratified for the type of mutation that was observed. For better overview, only variants with a location effect were displayed. The full figure, including all variant types, can be found in the supplementary figure 1. Each mutation is depicted as a dot, the size of the dot represents the number of observations for that variant. If multiple observations were made, the mean posterior odds and interquartile range are plotted. For the nonsense variants, variants that were predicted to produce nonsense mediated decay, are depicted using a triangle. Again, the size indicates the number of observations

DISCUSSION

In this report, we present new insights in the correlation between the phenotype and the genotype in patients with *GLI3*-mediated polydactyly syndromes. We illustrate that there are two latent classes of patients, best predicted by postaxial polydactyly of the hand and foot for LC1, and the preaxial polydactyly of the hand and foot and syndactyly of the foot for LC2. Patients with postaxial phenotypes have a higher risk to have a truncating variant in the activator domain of the *GLI3* gene which is also related to a higher risk of corpus callosum agenesis. These results suggest a functional difference between truncating variants on the N-terminal and the C-terminal side of the *GLI3* cleavage site.

Previous attempts of phenotype to genotype correlation have not yet provided the clinical confirmation of these assumed mechanisms in the pathophysiology of GLI3-mediated polydactyly syndromes. Johnston et al. have successfully determined the Pallister-Hall region in which truncating variants produce a Pallister-Hall phenotype rather than Greig syndrome.[68] However, in their latest population study, subtypes of both syndromes were included to explain the full spectrum of observed malformations. In 2015, Demurger et al. reported the higher incidence of corpus callosum agenesis in the GCPS population with truncating mutations in the activator domain.[30] Al-Qattan in his review summarizes the concept of a spectrum of anomalies dependent on haplo-insufficiency (through different mechanisms) and repressor overexpression.[27] However, bases this theory mainly on reviewed experimental data. Our report is the first to provide an extensive clinical review of cases that substantiates the phenotypic difference between the two groups that could fit the suggested mechanisms. We agree with Al-Qattan et al. that a variation of anomalies can be observed given any pathogenic variant in the *GLI3* gene, but overall 2 dominant phenotypes are present: a population with predominantly preaxial anomalies and one with postaxial anomalies. The presence of pre- or postaxial polydactyly and syndactyly is not mutually exclusive for one of these 2 subclasses; meaning that preaxial polydactyly can co-occur with postaxial polydactyly. However, truncating mutations in the activator domain produce a postaxial phenotype as can be derived the risk in Table 4. The higher risk of corpus callosum agenesis in this population makes that differentiating between a preaxial phenotype and a postaxial phenotype, instead of between the different *GLI3*-mediated polydactyly syndromes, might be more relevant regarding diagnostics for corpus callosum agenesis.

We chose to use LCA as an exploratory tool only in our population for 2 reasons. First of all, LCA can be useful to identify subgroups, but there is no "true" model or number of subgroups you can detect. The best fitting model can only be estimated based on the

available measures and approximates the true subgroups that might be present. Second, LC-membership assignment is a statistical procedure based on the posterior probability, with concordant errors of the estimation, rather than a clinical value that can be measured or evaluated. Therefore, we decided to use our LCA only in an exploratory tool, and perform our statistics using the actual phenotypes that predict latent class membership and the associated genotypes. Overall, this method worked well to differentiate the two subgroups present in our dataset. However, outliers were observed. A qualitative analysis of these outliers is available in the appendix

The genetic substrate for the two phenotypic clusters can be discussed based on multiple experiments. Overall, we hypothesize two genetic clusters: one that is due to haploinsufficiency and one that is due to abnormal truncation of the activator. The hypothesized cluster of variants that produce haploinsufficiency is mainly based on the experimental data that confirms NMD in two variants and the NMD prediction of other nonsense variants in Alamut. For the frameshift variants, it is also likely that the cleavage of the zinc finger domain results in functional haploinsufficiency either because of a lack of signaling domains or similarly due to NMD. Missense variants could cause haploinsufficiency through the suggested mechanism by Krauss et al. who have illustrated that missense variants in the MID1 domain hamper the functional interaction with the MID1-α4-PP2A complex, leading to a subcellular location of *GLI3*.[92] The observed missense variants in our study exceed the region to which Krauss et al. have limited the MID-1 interaction domain. An alternative theory is suggested by Zhou et al. who have shown that missense variants in the mediator binding domain can cause deficiency in the signaling of GLI3A, functionally implicating a relative overexpression of GLI3R.[90] However, GLI3R overexpression would likely produce a posterior phenotype, as determined by Hill et al. in their fixed homo and hemizygous GLI3R models.[83] Therefore, our hypothesis is that all included missense variants have a similar pathogenesis which is more likely in concordance with the mechanism introduced by Krauss et al. To our knowledge, no splice site variants have been functionally described in literature. However, it is noted that the 15th and last exon encompasses the entire activator domain, thus any splice site mutation is by definition located on the 5' side of the activator. Based on the phenotype, we would suggest that these variants fail to produce a functional protein. We hypothesize that the truncating variants of the activator domain lead to overexpression of GLI3R in SHH rich areas. In normal development, the presence of SHH prevents the processing of full length *GLI3*[77] into GLI3R, thus producing the full length activator. In patients with a truncating variant of the activator domain of *GLI3*, thus these variants likely have the largest effect in SHH rich areas, such as the ZPA located at the

posterior side of the hand/footplate. Moreover, the lack of posterior anomalies in the *GLI3* $^{\Delta 699/-}$ mouse model (hemizygous fixed repressor model) compared to the *GLI3* $^{\Delta 699/\Delta 699}$ mouse model (homozygous fixed repressor model), suggesting a dosage effect of GLI3R to be responsible for posterior hand anomalies.[83] These findings are supported by Lewandowski et al., who show that the majority of the target genes in *GLI* signaling are regulated by GLI3R rather than GLI3A.[111] Together, these findings suggest a role for the location and type of variant in *GLI3*-mediated syndromes.

Interestingly, the difference between Pallister-Hall syndrome and *GLI3*-mediated polydactyly syndromes has also been attributed to the GLI3R overexpression. However, the difference in phenotype observed in the cases with a truncating variant in the activator domain and Pallister-Hall syndrome suggest different functional consequences. When studying Figure 1, it is noted that the included truncating variants on the 3' side of the cleavage site seldomly affect the CBP binding region, which could provide an explanation for the observed differences. This binding region is included in the Pallister-Hall region as defined by Johnston et al. and is necessary for the downstream signaling with *GLI1*.[68,81,91,112] Interestingly, recent reports show that pathogenic variants in *GLI1* can produce phenotypes concordant with Ellis von Krefeld syndrome, which includes overlapping features with Pallister-Hall syndrome.[113] The four truncating variants observed in this study that do affect the CBP but did not results in a Pallister-Hall phenotype are conflicting with this theory. Kraus et al. postulate an alternative hypothesis, they state that the MID1-α4-PP2A complex, which is essential for GLI3A signaling, could also be the reason for overlapping features of Opitz syndrome, caused by variants in MID1, and Pallister-Hall syndrome. Further analysis is required to fully appreciate the functional differences between truncating mutations that cause Pallister-Hall syndrome and those that result in *GLI3*-mediated polydactyly syndromes.

For the clinical evaluation of patients with *GLI3*-mediated polydactyly syndromes, intracranial anomalies are likely the most important to predict based on the variant. Unfortunately, the presence of corpus callosum agenesis was not routinely investigated or reported thus this feature could not be used as an indicator phenotype for latent class membership. Interestingly when using only hand and foot phenotypes, we did notice a higher prevalence of corpus callosum agenesis in patients with posterior phenotypes. The suggested relation between truncating mutations in the activator domain causing these posterior phenotypes and corpus callosum agenesis was statistically confirmed (OR 8,8, $p<0.001$). Functionally this relation could be caused by the GLI3-MED12 interaction at the MDB: pathogenic DNA variants in MED12 can cause Opitz-Kaveggia syndrome, a syndrome which presentation includes corpus callosum agenesis, broad halluces and thumbs.[114]

In conclusion, there are two distinct phenotypes within the *GLI3*-mediated polydactyly population: patients with more posteriorly and more anteriorly oriented hand anomalies. Furthermore, this difference is related to the observed variant in *GLI3*. We hypothesize that variants that cause haploinsufficiency produce anterior anomalies of the hand, whereas variants with abnormal truncation of the activator domain have more posterior anomalies. Furthermore, patients that have a variant that produces abnormal truncation of the activator domain, have a greater risk for corpus callosum agenesis. Thus, we advocate to differentiate preaxial or postaxial oriented *GLI3* phenotypes to explain the pathophysiology as well as to get a risk assessment for corpus callosum agenesis.

APPENDICES

Appendix 1. Structural domains GLI3 gene

Author	Domain	Amino acids
Kalf-Susske et al.[78]	Repressor	1-462
	Zinc Finger Domain	462-645
	Proteolytic Cleavage site	645-748
	TA1	1376-1580
	TA2	1044-1322
Dai et al.[91]	Repressor	1-396
	Zinc Finger domain	480-636
	CBP binding site	826-1132
Johnston et al.[68,81,112]	Pallister Hall region	667-1160
Kraus et al. [92]	Repressor	1-397
	Zinc Finger domain	480-632
	Cleavage site	650-750
	Activator domain	827-1132
	MID1-interaction region	568-1100
Zhou et al.[90]	Mediator binding domain	1006-1596

Appendix 2. Included variants in the analysis

Variant	Protein	Type	Observations	Median probability LC2
c.327del	p.Phe109Leufs*50	frameshift	1	0,999
c.497del	p.Pro166Leufs*50	frameshift	1	0,999
c.518dup	p.Ile174Hisfs*2	frameshift	1	0,999
c.540_547del	p.Asn181Cysfs*15	frameshift	1	0,994
c.658del	p.Arg220Valfs*3	frameshift	1	0,996
c.733del	p.Thr245Leufs*65	frameshift	2	0,997
c.750del	p.Tyr251Metfs*59	frameshift	11	0,967
c.819_820delinsC	p.Met274Trpfs*36	frameshift	3	0,999
c.833_843del	p.Arg278Thrfs*22	frameshift	1	0,733
c.997_998dup	p.Tyr334Profs*14	frameshift	1	1,000
c.1007_1008dup	p.Leu337Thrfs*11	frameshift	3	0,996
c.1018del	p.Ser340Valfs*7	frameshift	1	0,999
c.1048dup	p.Tyr350Leufs*62	frameshift	1	0,786
c.1063_1067dup	p.Leu357Serfs*10	frameshift	1	1,000
c.1074del	p.His358Glnfs*7	frameshift	1	0,383
c.1180_1181insT	p.Pro394Leufs*18	frameshift	2	0,025
c.1286dup	p.Met430Aspfs*12	frameshift	1	0,967
c.1360del	p.Gln454Serfs*48	frameshift	2	0,997
c.1378del	p.Val461Serfs*41	frameshift	1	1,000
c.1468dup	p.Glu490Glyfs*14	frameshift	3	0,996
c.1513dup	p.His505Profs*47	frameshift	1	0,967
c.1543_1544dup	p.Arg516Alafs*20	frameshift	2	0,999
c.1561_1576del	p.Ser521Profs*9	frameshift	1	0,994
c.1616_1617del	p.Arg539Thrfs*12	frameshift	1	0,996
c.1617_1633del	p.Arg539Serfs*7	frameshift	1	0,981
c.1745del	p.Gly582Valfs*47	frameshift	1	0,000
c.1767del	p.Asn589Lysfs*40	frameshift	2	0,997
c.1793dup	p.Asn598Lysfs*7	frameshift	1	0,967
c.1880_1881del	p.His627Argfs*48	frameshift	1	0,326
c.2054dup	p.Arg686Alafs*52	frameshift	2	0,006
c.2082_2083delinsAGAGAAGCC	p.Val695Glufs*45	frameshift	1	0,326
c.2741del	p.Gly914Alafs*38	frameshift	1	0,003
c.2884del	p.Asp962Metfs*41	frameshift	9	0,019
c.3383del	p.Asp1128Alafs*78	frameshift	2	0,632
c.3427_3443del	p.Phe1143Alafs*98	frameshift	1	0,919
c.3437_3453del	p.Leu1146Argfs*95	frameshift	4	0,466
c.3474del	p.Ile1160Phefs*46	frameshift	2	0,073
c.3496del	p.Ser1166Alafs*40	frameshift	1	0,024
c.3635del	p.Gly1212Alafs*18	frameshift	14*	0,005
c.3950del	p.Pro1317Glnfs*102	frameshift	2	0,173
c.4038del	p.Gln1347Argfs*72	frameshift	1	0,001

Variant	Protein	Type	Observations	Median probability LC2
c.4099dup	p.Ala1367Glyfs*45	frameshift	1	0,024
c.4119_4123delinsAGCCTGA	p.Pro1374Alafs*2	frameshift	1	0,996
c.4369_4370insGC	p.Ala1457Glyfs*32	frameshift	1	0,870
c.4402_4403insG	p.Leu1468Argfs*11	frameshift	1	0,043
c.4427del	p.Asn1476Thrfs*12	frameshift	1	0,043
c.4463del	p.Thr1488Lysfs*23	frameshift	4	0,355
c.4542_4545del	p.His1515Profs*3	frameshift	1	0,001
c.4564del	p.Ala1522Profs*2	frameshift	3	0,025
c.4594_4596delinsA	p.Ser1532Thrfs*2	frameshift	1	0,996
c.4615_4624del	p.Thr1539Glyfs*11	frameshift	2	0,654
c.4677dup	p.Gly1560Argfs*38	frameshift	1	0,006
c.1446C>G	p.Cys482Trp	missense	2	0,800
c.1498C>T	p.His500Tyr	missense	3	0,999
c.1559G>A	p.Cys520Tyr	missense	1	0,979
c.1627G>A	p.Glu543Lys	missense	3	0,211
c.1633C>A	p.Pro545Thr	missense	3	0,999
c.1658G>A	p.Cys553Tyr	missense	1	0,870
c.1733G>C	p.Cys578Ser	missense	1	0,996
c.1748G>T	p.Cys583Phe	missense	1	0,870
c.1786C>T	p.His596Tyr	missense	3	0,919
c.1787A>C	p.His596Pro	missense	2	0,999
c.1826G>A	p.Cys609Tyr	missense	11	0,019
c.1873C>T	p.Arg625Trp	missense	7	0,967
c.1874G>A	p.Arg625Gln	missense	4	0,994
c.2686G>A	p.Asp896Asn	missense	1	0,999
c.2690C>G	p.Pro897Arg	missense	6	0,996
c.2708C>T	p.Ser903Leu	missense	4	0,994
c.2721C>G	p.Ser907Arg	missense	2	0,997
c.3018C>A	p.Ser1006Arg	missense	4	0,984
c.3534G>C	p.Lys1178Asn	missense	1	0,980
c.366C>G	p.Tyr122*	nonsense	1	0,999
c.427G>T	p.Glu143*	nonsense	1	0,326
c.444C>A	p.Tyr148*	nonsense	4	0,990
c.559G>T	p.Glu187*	nonsense	1	0,211
c.714T>A	p.Tyr238*	nonsense	3	0,980
c.868C>T	p.Arg290*	nonsense	13	0,981
c.1096C>T	p.Arg366*	nonsense	6	0,997
c.1320dup	p.Glu441*	nonsense	1	0,999
c.1728C>A	p.Tyr576*	nonsense	2	0,870
c.1789C>T	p.Gln597*	nonsense	1	0,326
c.2374C>T	p.Arg792*	nonsense	18	0,895
c.3559C>T	p.Gln1187*	nonsense	3	0,019
c.4072C>T	p.Gln1358*	nonsense	2	0,005

Variant	Protein	Type	Observations	Median probability LC2
c.4240C>T	p.Gln1414*	nonsense	2	0,003
c.4324C>T	p.Gln1442*	nonsense	1	0,001
c.4408C>T	p.Gln1470*	nonsense	1	0,003
c.4430_4431del	p.Ser1477*	nonsense	3	0,000
c.4431dup	p.Glu1478*	nonsense	2	0,000
c.4432G>T	p.Glu1478*	nonsense	1	0,981
c.4456C>T	p.Gln1486*	nonsense	1	0,000
c.4507C>T	p.Gln1503*	nonsense	1	0,006
c.474-2A>G	p.?	splice	5	1,000
c.679+1G>T	p.?	splice	1	0,682
c.679+2_679+15del	p.?	splice	3	0,999
c.827-3C>G	p.?	splice	2	0,434
c.1497+1G>C	p.?	splice	1	0,870
c.1497+1G>A	p.?	splice	2	0,800
c.1497+1G>T	p.?	splice	2	0,987
c.1497+2T>G	p.?	splice	3	0,967
c.1498-1G>C	p.?	splice	3	0,996
c.1647+2_1647+3del	p.?	splice	2	1,000

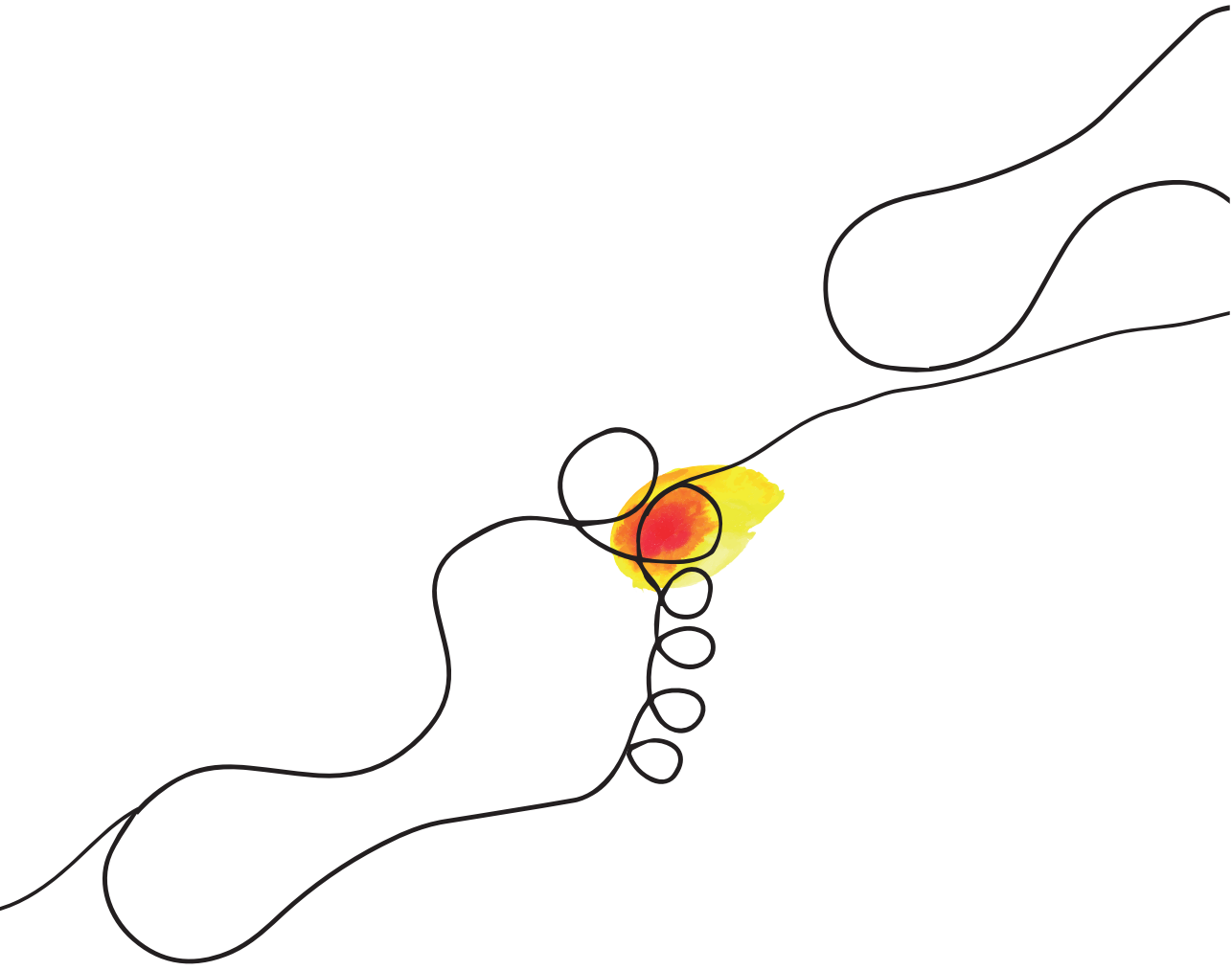
**One case misses complete phenotypic description*

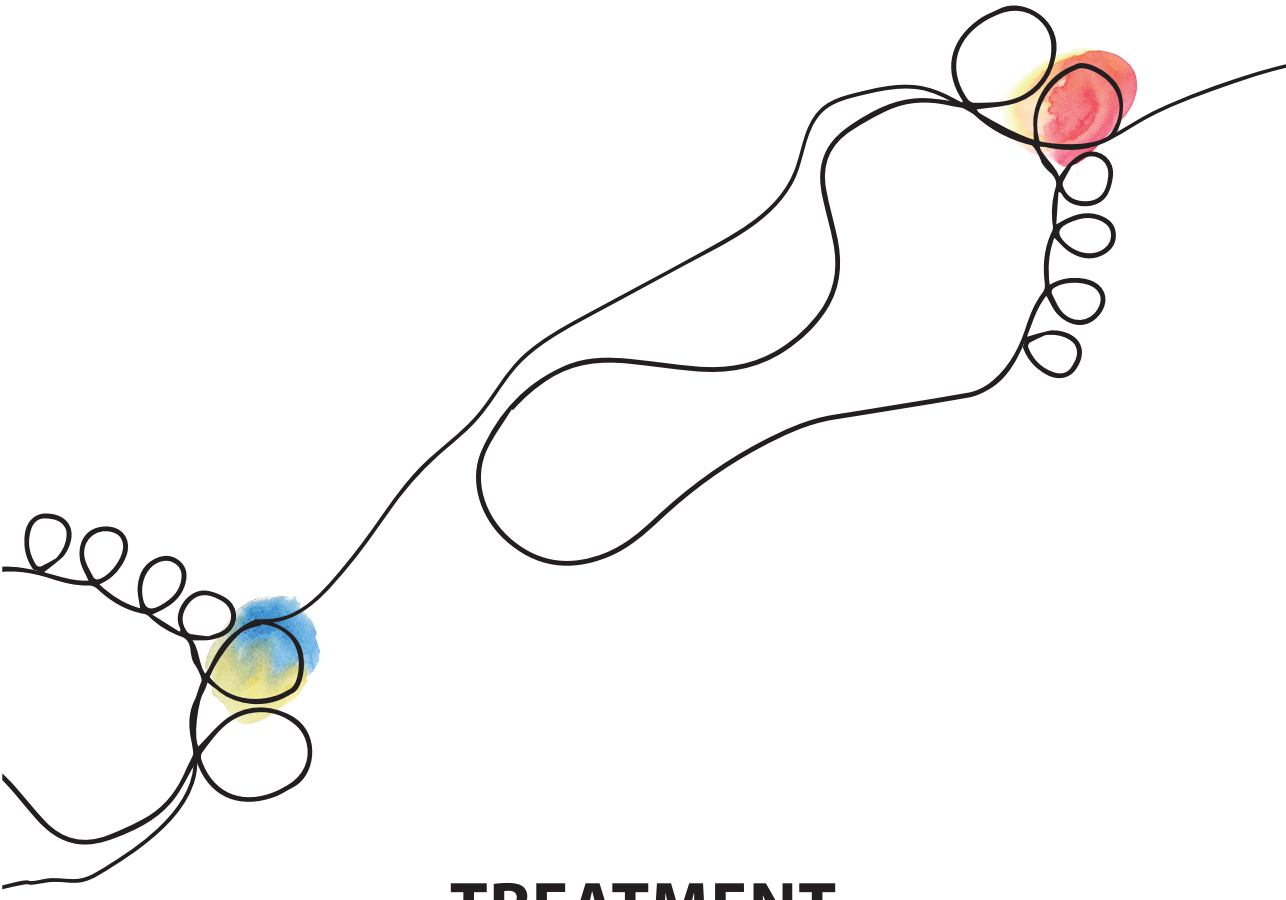
Appendix 3. Qualitative analysis of outliers in the phenotype/genotype correlation

Overall the distinction of genotypes based on phenotypes is well defined, however outliers in our analysis were present. Four outliers were identified in the group of truncating variants in the N-terminal side of the gene: c.427 G>T(p.Glu143*), c.559 G>T(p.Glu187*), c.1789C>T(p.Gln597*) and c.2374C>T(p.Arg792*) (Figure 1). Strikingly, the c.2374C>T(p.Arg792*) variant has been experimentally confirmed to produce NMD but produced a variable phenotype. In the case review of patients with this variant, the consensus phenotype of this variant is postaxial polydactyly of the hand, preaxial polydactyly of the foot and syndactyly, thus concordant with the rest of the haploinsufficiency variants. Looking at the effect measures in our regression analysis (Beta's +1,47, -1,77 and -1,77 respectively), this is rightfully classified a preaxial phenotype. The majority of frameshift variants on the 5' side of the cleavage site produced a preaxial phenotype, 3 outliers were observed: c.1074del(p.His358Glnfs*7), c.1180_1181insT(p.Pro394Leufs*18), c.1745del(p.Gly582Valfs*47). The c.1074del(p.His358Glnfs*7) variant was included as a single phenotypic description by the original authors although the variant was present in a larger pedigree. Thus the penetrance of e.g. postaxial polydactyly is unknown but could strongly affect the prediction. The c.1745del(p.Gly582Valfs*47) variant produced a true postaxial phenotype, this variant is located in the zinc finger domain. We hypothesize that the unaffected part of this domain could maintain some function in the produced protein. Frameshift variants on the 3' side of the zinc finger domain, more variability on the phenotype was observed: c.3383del(p.Asp1128Alafs*78), c.3427_3443del(p.Phe1143Alafs*98) ,c.3437_3453del(p.Leu1146Argfs*95), c.4119_4123delinsAGCCTGA(p.Pro1374Alafs*2), c.4369_4370insGC(p.Ala1457Glyfs*32), c.4594_4596delinsA(p.Ser1532Thrfs*2) and c.4615_4624del(p.Thr1539Glyfs*11) all showed a variable or preaxial dominant phenotype. The deletion of multiple nucleotides for most of these variants is noted, however no exact mechanism is apparent for the difference in phenotypic presentation. Alternative splicing could explain the preaxial phenotype, however was not predicted in Alamut. There was 1 missense variant with increased prevalence of postaxial polydactyly, on individual review these were the c.1627G>A(p.Glu543Lys) variants observed in our clinic. This local variant was classified as a variant of unknown significance according to the ACMG guidelines and was observed in all 3 tested cases. Two more family members are symptomatic, but were not tested for this variant. We chose to exclude these 2 unconfirmed cases due to the uncertain pathogenicity of the variant. Nevertheless it is noteworthy that the excluded cases had a preaxial phenotype. Moreover, the single case with a full anterior phenotype did have abducted, but normally sized, halluces. Further confirmation of this variant is required to confirm its pathogenicity and phenotype.

Appendix 4. Excluded variants

There are a number of variants not included in our analysis that have not been discussed in the manuscript, namely the variants that produced isolated hand or feet phenotypes. Supplementary figure 1 reveals that the included missense variants center around the MID1 interaction region. However, when reviewing the HGMD database, more missense variants are present on the N and C terminal side of the gene. These variants cause isolated preaxial polydactyly and postaxial polydactyly[30,78,106,110,115], but also atrial septal defects, urinary tract anomalies, esophageal atresia and medulloblastoma have been described[116-118]. Missense variants in the N-terminal side of the gene likely produce a non-functional repressor with a functional activator. Since GLI3A seems to have no separate role in the etiology of polydactyly (especially on the posterior side), the hand phenotype is indeed expected to be comparable to haploinsufficiency. On the other hand, C-terminal missense variants likely hamper the downstage signaling of the activator as suggested by Zhou et al., which as discussed in the manuscript leads to relative repressor overexpression.





TREATMENT

CHAPTER 5

Foot function in patients with surgically treated preaxial polydactyly of the foot compared to age- and sex-matched healthy controls

E.B. Burger, S.A. Lalé, S.E.R. Hovius, C.A. van Nieuwenhoven, S.A. Bus

Foot and Ankle International, April 2019

ABSTRACT

Treatment of preaxial foot polydactyly, a duplication of the first ray, consists of excision of an extra ray, aiming to improve shoe fitting and aesthetic appearance, while maintaining foot function. Currently, the effect of excision on foot function and foot-related patient experiences is unclear.

A cross-sectional comparison between 37 children treated for preaxial foot polydactyly and 37 age- and sex-matched healthy controls was performed. Dynamic foot function was assessed using plantar pressure measurements and static foot characteristics by physical examination. Patient-reported outcomes for foot function and footwear were evaluated, using the Oxford Ankle Foot Questionnaire for Children (score:0-100).

Compared with controls, patients had significantly lower median peak pressures at the hallux (148 kPa (IQR:98-245) vs. 272 kPa (IQR:205-381), $p<0.001$) and significantly higher peak pressures at the second metatarsal (217 kPa (IQR:147-338) vs. 166 kPa (IQR:141-235), $p=0.002$) and third to fifth metatarsals (214 kPa (IQR:147-290) vs. 161 kPa (IQR:135-235), $p<0.001$). Additionally, patients had a more medially deviated hallux, both while seated (15° (IQR:11-20) vs. 12° (IQR:10-15), $p=0.001$) and standing (20° (IQR:15-26) vs. 18° (IQR:15-20), $p=0.001$). No significant correlation between peak pressure distribution and hallux deviation was found. Patients reported minimal problems with foot function (87.5 (IQR:64.6-100)), but distinct problems with footwear use (50.0 (IQR:25.0-100)).

Patients with surgically treated preaxial foot polydactyly have a substantially altered plantar pressure distribution with more lateral foot progression than healthy controls. Although an increased hallux deviation was not related to altered foot function, it seems to be the reason for the patient-perceived problems with footwear.

INTRODUCTION

Polydactyly of the foot is characterized by the presence of supernumerary toes. Based on the location of the duplication, polydactyly is classified as preaxial (first ray), central (middle rays), or postaxial (fifth ray). The presentation of preaxial polydactyly of the foot is very diverse and duplication can be found at several levels (e.g. distal phalanx, proximal phalanx, metatarsal, and tarsal).[119] Depending on the type of malformation, treatment of preaxial polydactyly varies from conservative to complex surgical methods (Figure 1).[41,44] In most cases, surgical excision of the duplicated hallux is indicated before the infant starts to walk, aiming to improve shoe fitting and aesthetic appearance.[44] However, excision of the extra hallux changes the foot anatomy and this is likely to influence foot function, where as much as 50% of patients may experience foot problems after surgery due to recurrent medial deviation of the hallux[40], and as much as 40% of patients with preaxial polydactyly experience pain and deformity of the foot after surgery, compared to only 2% of patients with postaxial polydactyly.[57]

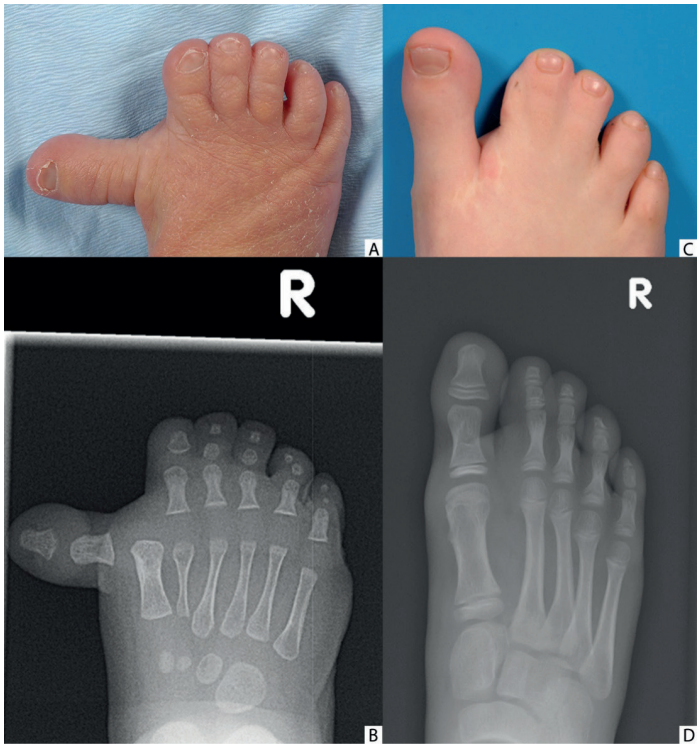


Figure 1. (A) Preoperative clinical photograph. (B) Preoperative radiograph x-ray. (C) Postoperative clinical photograph. (D) Postoperative x-ray.

Studies on preaxial polydactyly of the foot mostly use physical examination and X-rays to evaluate foot function after surgery, which does not provide information about important outcomes of dynamic foot function and patient satisfaction.[41,44,57] In general, weight distribution on the foot influences the osseous relationships in the foot, which may change foot dimensions and foot progression during gait.[120] Therefore, static measures may give incorrect assumptions about dynamic foot function. Furthermore, forefoot deformities can change dynamic foot function by an increased plantar forefoot pressure, which may lead to pain symptoms and clinical diagnoses, such as metatarsalgia.[121,122] Clinical experience shows that surgical treatment of preaxial polydactyly can also result in forefoot deformity[19,44], and, therefore, the plantar pressure distribution may be abnormal, possibly leading to forefoot pain. Additionally, patient satisfaction about foot function and foot appearance is often not reported in studies on preaxial polydactyly of the foot. Lack of information on these patient-reported outcomes limits our understanding of problems in daily life after treatment. Therefore, assessing dynamic foot function and patient satisfaction is expected to improve the evaluation of surgical treatment and improve future clinical decision making in treating preaxial foot polydactyly.

The aims of this cross-sectional patient-control study were to assess dynamic foot function and static foot characteristics in a cohort of children with surgically treated preaxial polydactyly and to compare these outcomes with a group of sex- and age-matched healthy controls. Furthermore, we assessed patient-reported outcomes after surgical treatment on aspects of foot function, footwear, and aesthetic appearance.

PATIENTS AND METHODS

Design and participants

This study was designed as a cross-sectional single center study. Prior to the recruitment of participants, the Ethical Committee of the Erasmus Medical Center in Rotterdam waived the need for ethical approval due to the incorporation of measurements in patient care.

The database of the Sophia Children's Hospital, Rotterdam, was searched for children between 4 and 18 years old with a documented history of surgically treated preaxial polydactyly. The duplication type was determined using pre-operative X-rays, based on the Rotterdam foot classification.[119] Included patients were matched to healthy controls based on sex and age. Healthy controls were recruited at the outpatient clinic for pediatric hand problems and were included if sex was similar to the patient, the age difference was <12 months, and their medical history did not contain orthopedic, neurological, and/or

musculoskeletal complaints that would affect their gait. Informed consent was obtained from parents of patients and controls, and from children themselves if they were above the age of 12.

Measurements were carried out at the outpatient clinic of the Sophia Children's Hospital or at the subject's home between June 2015 and March 2016. Measurements at home were only performed if patients did not have the time to come to the hospital and when sufficient space was available to conduct plantar pressure measurements. The study protocol was completed in one visit.

Procedures and outcome measures

Dynamic foot function

To assess dynamic foot function, plantar pressure measurements were obtained during walking using an EMED-X pressure platform (Novel GmbH, Munich, Germany). The platform consists of an array of pressure-sensing sensors at a spatial resolution of four sensors per cm^2 which are all sampled at 70Hz. The platform was set flush in a surrounding 6 by 1 meter modular walkway of hard foam material and subjects were instructed to walk barefoot over the platform at a comfortable self-selected speed. Both the affected and the non-affected foot were measured. A 2-step approach to the platform was used.[123,124] The youngest children were occasionally guided by lightly holding their hands when walking over the platform. We excluded trials with abnormal walking patterns, such as trials where children were running or jumping and trials where only part of the foot stepped on the pressure platform. A minimum of three successful trials per foot were obtained.

The pressure data of the affected foot were analyzed using Novel multimask software.[125] Foot masks were used to divide the foot into 10 anatomical regions: the medial and lateral hind foot, the medial and lateral midfoot, the first metatarsal (MT), the second MT, the third to fifth MT, the hallux, the second toe, and the third to fifth toes. For each region, the mean peak pressure over the steps taken was calculated. Furthermore, the lateral-medial area index of the maximum pressure picture was calculated per foot, which is the area on the lateral side of the center of pressure (COP) line minus the area on the medial side of the COP line, divided by the total foot area. The COP is defined as the point of application of the vertical ground reaction force vector. A positive value of the lateral-medial area index indicates a more medially loaded foot.

Foot characteristics

A trained clinical researcher physically examined the foot of patients and controls to obtain information about the static foot characteristics. Passive range of motion of the metatarsophalangeal (MTP) and interphalangeal (IP) joint of the first ray were measured with a goniometer in whole degrees.[126] Measurements were done in seated position, with the feet off the ground, and the knee and ankle in neutral position. Additionally, medial deviation of the hallux was measured with the subject in both seated and standing position by placing the proximal arm of the goniometer on the estimated dorsal midline of the first metatarsal and the distal arm over the estimated dorsal midline of the hallux. The circumference of the forefoot and the circumference of the hallux were measured with a measuring tape in whole millimeters, respectively at the level of the MTP-joint and IP-joint. The foot posture index was used to determine foot type. A score <0 reflects a supinated position of the foot, 0-5 a neutral foot, and >5 a pronated position.[127]

Patient-reported outcome measures

Subject-reported outcomes were only obtained in the patient group, because the control group was selected based on the fact that they did not experience any foot problems. We expected that children above the age of 7 were able to complete the questionnaires in a reliable manner.[128,129] For patients up to the age of 7, we asked parents to complete the proxy-version of the questionnaires. Proxy-versions are specifically developed for people close to the subject to measure patient-reported outcomes in an indirect way.

To assess foot-specific quality of life, the Dutch version of the Oxford Ankle Foot Questionnaire for Children (OxAFQ-c) was used.[130,131] The OxAFQ-c contains 15 different questions divided into four domains: physical, school & play, emotional, and footwear. All questions are scored on a 5-point Likert scale, from 0 (always) to 4 (never). Domain scores are calculated using the patient domain score divided by the maximum domain score, times 100. Consequently, scores range from 0-100, in which higher scores represent better outcomes.

To assess general quality of life, the Dutch version of the Pediatric Quality of Life Inventory (PedsQL) was used.[132] The PedsQL is a general health-related quality of life (HR-QoL) questionnaire for children consisting of 23 questions regarding physical functioning, emotional functioning, social functioning, and school functioning. All questions are scored on a 5-point Likert scale from 0 (never) to 4 (always). The domain and total scores are recalculated in a linear 0-100 scale, in which higher scores represent better HR-QoL.

To assess foot aesthetics, visual analogue scales (VAS) were used, ranging from 0

('completely dissatisfied') to 10 ('completely satisfied'). Foot aesthetics were evaluated for general foot appearance, foot width, toe size, nail appearance, and scar appearance.

Statistical analysis

For each patient, data on the affected foot was included in the statistical analysis. Outcomes of dynamic foot function and static foot characteristics were compared with the corresponding foot of the matched healthy controls. The distribution of the data was evaluated with the use of histograms, Q-Q plots, and the Shapiro-Wilk test. [133,134] For normally distributed data, we used a two-tailed paired t-test, for not normally distributed data the Wilcoxon matched pair tests. Additionally, correlation coefficients in the patient group between the lateral-medial area index, the hallux/lateral MTP peak pressure ratio, and foot characteristics were calculated. Foot characteristics were selected when they showed a significant difference between patients and controls. For normally distributed data, we used the Pearson correlation coefficient, for not normally distributed data the Spearman correlation coefficient. Statistical significance was defined as $p<0.05$. Outcomes of the patient questionnaires were analyzed using descriptive analysis. In order to explore the influence of duplication level on surgical outcome, sub-group analysis was performed based on duplication level. All statistical analyses were conducted using IBM SPSS Statistics software version 21.

RESULTS

Patient characteristics

Thirty-seven patients between the ages of 4 and 18 years, with a total of 64 surgically treated feet were included and matched to healthy control subjects, based on age and sex. The matching resulted in a median between-pair age difference of five months (IQR: 3-7, patients older), with a maximum age difference of nine months. Total group characteristics are summarized in Table 1.

Table 1. Patient characteristics

	Patient	Control	p-value
Number of participants (male/female)	37 (13 / 24)	37 (13 / 24)	
Number of treated feet (left/right)	64 (29 / 35)	0	
Incomplete distal phalangeal duplication	6		
Complete distal phalangeal duplication	10		
Complete proximal phalangeal duplication	14		
Complete metatarsal duplication	26		
Unknown duplication level	8		
Age (years)	8.2 (5.2-10.8)	8.0 (5.8-11.6)	0.001
Body weight (kg)	29.2 (20.9-38.1)	27.0 (22.7-47.8)	0.154
Time of post-operative assessment (months)	61 (37-113)	-	

Data are expressed as N or as median (interquartile ranges (IQR)).

Dynamic foot function

Median or mean values for peak pressures and the lateral-medial area index in patients and controls are shown in Table 2. Compared to controls, patients had significantly lower peak pressures at the hallux ($p<0.001$), and significantly higher peak pressure at the second MT ($p=0.002$) and third to fifth MT ($p<0.001$), and close to significantly higher peak pressures at the first MT ($p=0.050$). None of the other regions showed significant group differences.

The lateral-medial area index was smaller in the patient group than in the control group, almost reaching statistical significance ($p=0.052$). Excluding one statistical outlier in the patient group and two in the control group resulted in normally distributed data and a significant difference ($p=0.011$) between patients and controls (mean: 0.129 (SD: 0.110) and 0.171 (SD: 0.070), respectively). Sub-group analysis did not show an effect of duplication level on peak pressure differences between patients and controls, by showing that relative differences and significances found for the whole group were similar to those found in the four sub-groups.

Table 2. Dynamic foot function.

Median outcome values and interquartile ranges (IQR) for peak pressure per region of the foot and the lateral medial area index in the patient group and control group.

	Patient ***(N of feet=64)*** *median (IQR)*	**Control** ***(N of feet=64)*** *median (IQR)*	**p-value**
Peak pressures (kPa)			
Total	392 (289-540)	391 (313-440)	0.280
Medial heel	275 (219-355)	270 (205-342)	0.476
Lateral heel	257 (84) #	252 (84) #	0.731#
Medial midfoot	52 (41-65)	53 (38-79)	0.370
Lateral midfoot	63 (29) #	69 (26) #	0.153#
1st metatarsal bone	212 (135-341)	167 (126-258)	0.050
2nd metatarsal bone	217 (147-338)	166 (141-235)	0.002*
3th-5th metatarsal bone	214 (147-290)	161 (135-235)	<0.001*
Hallux	148 (98-245)	272 (205-381)	<0.001*
2nd toe	99 (73-146)	100 (80-149)	0.820
Toes 3-5	89 (50-136)	77 (60-99)	0.184
Lateral medial area index	0.128 (0.054-0.202)	0.174 (0.120-0.218)	0.052

(IQR) interquartile range.
(#) Normally distributed data: Mean outcome values and standard deviations 0(SD) are reported and the paired T-test is used for statistical testing.
(*) p-value < 0.05, statistical significant.

Foot characteristics

Patients had a significantly smaller plantarflexion of the first IP-joint compared to controls (p<0.001) (Table 3). No other significant differences in range of motion of the MTP-joint and IP-joint were observed. Patients had a significantly more medially deviated hallux than controls, both while seated (p=0.001) and while standing (p=0.001). No significant differences were present between the groups in forefoot circumference. The foot posture index between patients and controls differed significantly (p=0.028). Both patient and control feet were classified as neutral feet, with slightly more pronated feet in the patient group (Table 3). Sub-group analysis did not show an effect of duplication level on foot characteristics.

Correlations

Spearman correlation coefficients between hallux deviation in sitting and standing position and the lateral-medial area index were respectively r=0.221 (p=0.082) and r=0.219 (p=0.092).

Correlations between hallux deviation in sitting and standing position and hallux/lateral MTP peak pressure ratio were respectively r=-0.181 (p=0.157) and r=0.016 (p=0.906). Plantar IP-joint flexion and the lateral-medial area index showed a correlation coefficient of r=-0.020 (p=0.879). Correlation coefficient between plantar IP-joint flexion and hallux/lateral MTP peak pressure ratio was r=0.164 (p=0.215).

Table 3. Static characteristics of the foot

Median outcome values and interquartile ranges (IQR) for the different static characteristics of the foot in the patient and control groups.

	Patient		**Control**		**p-value**
	N of feet	**Outcome *median (IQR)***	**N of feet**	**Outcome *median (IQR)***	
Plantar flexion 1st MTP-joint (degrees)	59	35 (30-45)	60	40 (35-45)	0.259
Dorsal flexion 1st MTP-joint (degrees)	59	47 (15) #	60	50 (13) #	0.084#
Plantar flexion 1st IP-joint (degrees)	59	15 (10-20)	60	20 (15-30)	<0.001*
Dorsal flexion1st IP-joint (degrees)	59	15 (10-20)	60	15 (15-20)	0.083
Medial deviation hallux, seated (degrees)	63	15 (11-20)	62	12 (10-15)	0.001*
Medial deviation hallux, standing (degrees)	60	20 (15-26)	61	18 (15-20)	0.001*
Circumference of the hallux (cm)	52$	7.0 (1.0) #	62	6.9 (0.9) #	0.119#
Circumference forefoot, sitting (cm)	64	18.4 (2.6) #	62	18.5 (2.8) #	0.550#
Circumference forefoot, standing (cm)	64	19.4 (2.5) #	62	19.7 (3.0) #	0.175#
Foot posture index	61	3 (1-7)	61	2 (1-4)	0.028*

IP, interphalangeal; IQR, interquartile range; MTP, metatarsophalangeal.
(#) Normally distributed data: Mean and standard deviation are reported and the paired T-test is used for statistical testing.
(*) p-value < 0.05, statistical significant.
($) Impossibility to measure the circumference of the hallux due to syndactyly between the hallux and the second toe.

Patient-reported outcome measures

Both the physical domain and the emotional domain of the OxAFQ-c were rated by the patients with a median of 87.5 (IQR 64.6-100 and 62.5-100, respectively) (Table 4). The footwear domain had the lowest score of all OxAFQ-c domains: median: 50.0 (IQR:25.0-100).

The PedsQL showed median scores between 85.0 and 93.8, which are comparable to or higher than Dutch norm scores (Table 4).[132] The median VAS on the five aesthetics components were all between 7.3 and 7.5 (Table 4). A large variation was observed across patients (IQR≈4 points). Sub-group analysis did not show an effect of duplication level on patient-reported outcome measures.

DISCUSSION

The aim of this study was to compare dynamic foot function and static foot characteristics between children surgically treated for preaxial foot polydactyly and sex- and age-matched healthy controls. Additionally, patient experiences after surgery were assessed, using patient-reported outcomes on foot function, footwear, and foot appearance.

Plantar pressure measurements showed a 54% lower peak pressure underneath the hallux and a 31%-33% higher peak pressure underneath the metatarsals during barefoot walking in patients compared to controls. This shows a reduced use of the hallux during foot progression in stance, also evidenced by a more laterally running center of pressure (COP) line, and therefore loading, during barefoot walking. These outcomes illustrate an ineffective pressure transfer towards the hallux during terminal stance and push-off. Whether these outcomes are associated with a different hallux position in the patient group remains unclear. In previous studies on hallux valgus, both elevated and diminished peak pressures at the hallux have been reported.[135-139] We found no significant associations between the degree of hallux deviation and the lateral-medial area index or the hallux/lateral-MTP peak pressure ratio. Based on clinical experience, other factors may be contributory to the abnormal pressure distribution found. For example, in standing, some patients show halluces that are elevated from the floor, and that may therefore not effectively contribute to foot progression and push-off. Alternatively, a shorter first metatarsal sometimes found due to congenital deformations may lead to a more proximal MTP-joint and therefore an altered pressure distribution. From a behavioral perspective, patients may have become accustomed to avoid loading the hallux, due to the congenital abnormality present or maybe because of experienced issues with footwear. No definite conclusions on this matter can be drawn from the performed study. Future studies assessing hallux posture and motion more comprehensively as well as behavioral strategies are needed to better explain the abnormal dynamic plantar pressure distribution in these patients.

The abnormalities found in measured foot function and foot characteristics were not mimicked by a perceived abnormal foot function or a low HR-QoL. Physical and emotional function on the OxAFQ-c both showed a median 87.5 out of 100 score, which is similar to or higher than scores found in other pediatric foot disorders, such as juvenile idiopathic arthritis [140], club feet [141], and flat feet.[142] The participation domain of the OxAFQ-c (School & Play) even showed the maximum score of 100, indicating no problems in participation during physical education or on the playground. In addition,

Table 4. Patient-reported outcomes measures

Median outcome values and interquartile ranges (IQR) for the Oxford foot and ankle questionnaire for children (OxAFQ-c) (score range: 0-100), the PedsQL questionnaire (score range: 0-100), and the VAS for foot aesthetics (score range: 0-10).

	N of completed questionnaires	Outcome *median (IQR)*	Normative values PedsQL 8-12 year *mean (SD)*[15]
Oxford ankle foot questionnaire for children (OxAFQ-c)			
Physical domain	36	87.5 (64.6-100)	
School & Play domain	37	100 (90.6-100)	
Emotional domain	35	87.5 (62.5-100)	
Footwear domain*	37	50.0 (25.0-100)	
PedsQL questionnaire			
Physical functioning	37	93.8 (75.0-100)	82.1 (8.9)
Emotional functioning	35	85.0 (70.0-100)	84.9 (9.3)
Social functioning	37	95.0 (80.0-100)	80.6 (10.3)
School functioning	36	87.5 (71.3-100)	86.1 (12.3)
Total score PedsQL	34	89.1 (80.7-95.5)	78.7 (12.0)
VAS on foot aesthetics			
Foot appearance	64	7.3 (4.8-8.6)	
Foot width	64	7.4 (4.6-8.7)	
Toe size	63	7.5 (4.8-9.8)	
Nail appearance	61	7.5 (6.0-9.7)	
Scar appearance	63	7.4 (4.8-9.3)	

IQR: interquartile range.

** The footwear domain consists of one question asking if children have to stop wearing any shoes that they wanted to wear because of their foot or ankle.*

general HR-QoL, measured with the PedsQL, was comparable with a healthy Dutch reference group.[132] Therefore, we can assume that surgical treatment of preaxial foot polydactyly does not result in an abnormal perceived foot function or a reduced HR-QoL at this moment in life of the patient. However, the median age of the patient group was low (8.2 years), and the results do not guarantee a complaint free function later in life, where abnormal pressure distribution has been related to the development of forefoot pain by others.[143] Longer follow-up of patients during adult life is needed to further study this relationship.

Despite the primary goal of surgery to improve shoe fitting, footwear perception scored low in the patient group (median: 50 (IQR:25-100)), indicating moderate problems with shoe fitting in these children. Since we did not observe a difference in forefoot width between patients and controls, the significantly increased medial deviation of the hallux in patients may be a reason for the perceived problems with footwear. Other studies on

preaxial polydactyly also report that recurrent medial hallux deviation is a frequent problem, despite special surgical attempts to prevent deviation.[19,41,44] Consequently, the alignment of the preserved hallux should receive specific attention during surgery to prevent recurrent medial deviation and potential footwear problems.

The strengths of this study are the relatively large group of patients with preaxial polydactyly that could be recruited in one center and the matched patient-control design, which made it possible to include children of different ages and sex. Nevertheless, because of the rarity of preaxial polydactyly, we included patients with different assessment times after surgery, which might have affected the data on (perceived) foot function and aesthetics. Moreover, variation in duplication level and initial hallux deviation may have influenced decision-making during surgery, and therefore influenced study outcomes. Examples are the choice to remove either the lateral or medial hallux based on anatomic variations or the choice for a certain reconstruction technique. By performing an explorative sub-group analyses based on duplication level, we showed based on small sample sizes that duplication level and the malformation involved did not appear to have clear effects on differences in foot function and perceived outcomes found between patients and controls.

In conclusion, we showed that children surgically treated for preaxial foot polydactyly have a significantly altered plantar pressure distribution while walking barefoot, with substantially lower peak pressures under the hallux and higher peak pressures under the metatarsals compared to age- and sex-matched healthy controls. This implies a reduced use of the hallux and more laterally oriented foot progression, while explanations for this cannot be found in the data. These altered foot dynamics do not seem to be associated with any perceived loss of foot function or HR-QoL at the young age that the patients were assessed at, which does not exclude potential problems at older age. A relatively low score on footwear perception, despite the aim in surgery to improve shoe fitting, may indicate that alignment of the preserved hallux should receive more attention during surgery, as it might be a reason for the footwear problems perceived.

CHAPTER 6

Lateral versus medial hallux excision in preaxial polydactyly of the foot?

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Foot and Ankle International, December 2020

ABSTRACT

In preaxial polydactyly of the foot, the choice for excision of the lateral or medial hallux is not straightforward, in particular with proximal phalangeal (Type IV) and metatarsal (Type VI) duplication, because of anatomical characteristics. We evaluated whether medial or lateral hallux excision gives better outcomes in these duplication types, to help clinical decision making.

Children with Type IV or Type VI duplication (n=14, age: 4.4-17.2 years), who were operatively treated by excision of the lateral or medial hallux, were assessed for foot function using plantar pressure measurements and clinical examination. Foot aesthetics were scored by the child, an expert, and 10 laypersons, and additional patient-reported outcome questionnaires were obtained. Outcomes were compared between lateral and medial excision, per duplication type.

In Type IV duplication (n=11), lateral excision showed a better distribution of peak pressure between the hallux and first metatarsal with significantly lower median first metatarsal peak pressure (p=0.008). Lateral excision showed more medial hallux deviation (p=0.017). Foot aesthetics were not different between excision sides. In Type VI duplication (n=12), lateral excision showed a 59% higher hallux peak pressure, larger medial hallux deviation (p=0.004), and more reoperations. Foot aesthetics were scored significantly better after lateral excision by experts and laypersons.

Foot function by virtue of plantar pressure was better after lateral hallux excision in type IV and after medial hallux excision in type VI duplication. Surgeons and laypersons perceived the foot as more normal after lateral excision in type VI, while children reported no differences. These outcomes can be used in clinical-decision making.

INTRODUCTION

The diverse presentation of preaxial polydactyly of the foot (foot PPD) is often described in literature[19,41,44,57], yet the effect of these anatomic variations and the influence of the choice of excision side on treatment results is unknown. Treatment of foot PPD consists of excision of the lateral or medial hallux, aiming to provide good foot function and appearance.[19,44,57] Therefore, the operative goals are reduction of foot width and limiting medial hallux deviation in an attempt to better fitting of shoes and weight bearing (i.e. pressure distribution), to avoid the need for special footwear.

Anatomic variations in the level of duplication, maturation of osseous structures, and differentiation of soft tissue (e.g. syndactyly) are important factors that influence operative decision-making.[19,41,44] In the majority of cases, independent of duplication level, the lateral or medial hallux is poorly developed and excision is easily determined by removing the least developed hallux.[41,44] Especially for distal phalangeal duplication this is often the case. However, sometimes, the lateral and medial hallux are developed to a similar extent or removal of the hypoplastic hallux requires an extensive positional correction of the preserved hallux.[56] In these cases, the choice is more difficult.

Where the choice of excision side is difficult, duplication level is an important determinant in decision-making.[41,44,56] Proximal phalangeal duplication may only affect hallux function, while metatarsal duplication may also affect foot arch stability and foot biomechanics more extensively. Some authors advocate to always excise the medial hallux, in order to reduce foot width and overcome medial hallux deviation.[19,40,41,44] However, Masada advised lateral excision in metatarsal duplications in which the lateral ray is hypoplastic, to better preserve foot function and aesthetics.[41]

Because of the lack of more quantitative outcomes in foot PPD based on anatomic variations, treatment algorithms do not exist and treatment choices are expert-opinion based. The aim of this study was to investigate the effect of excision side on biomechanical, functional, and aesthetic outcomes in foot PPD, to help define a preferred excision side.

METHODS

Patient population

The Medical Ethical Committee of the Erasmus Medical Center waived the need for ethical approval for this study (MEC-2015-679). All patients with foot PPD, treated in the Sophia Children's hospital between 1987 and 2014 were identified from the hospital database and considered for study inclusion. Patients with no radiological and clinical photographs available or without operative reports were excluded. All remaining feet were classified

based on the preoperative photographs, using the Rotterdam foot classification (Figure 1).[119] Type IV (proximal phalangeal duplication) and Type VI (metatarsal duplication) feet with complete data sets were included for further evaluation.

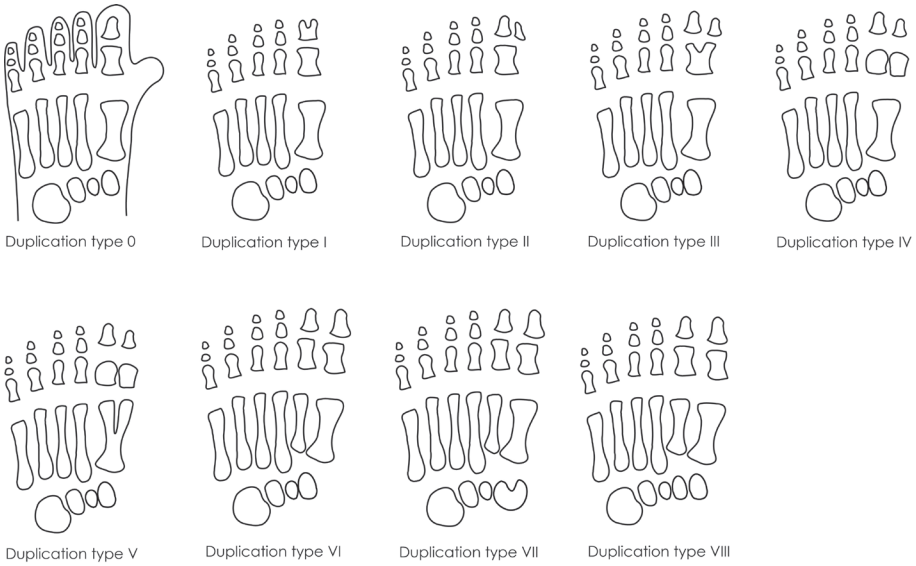

Figure 1. Duplication types in the Rotterdam foot classification.

Operative technique

Treatment of foot PPD aims to reconstruct the foot and hallux to a normal-looking, functional structure, with the hallux in line with the remaining toes. Examples of the surgical procedures are shown in Figures 2 and 3. In foot PPD, the surgeon chooses a technique to reconstruct the hallux based on the patient-specific conditions. As no standard procedure exists, a general overview is given with the essential steps for the procedure.

The procedure starts with excision of the supplementary osseous structures and nail, while keeping the neurovascular bundles of the preserved hallux intact. The nerves, arteries, and veins of the removed hallux are shortened, and the nerve ends are buried in the intrinsic muscles. Osteotomies can be used to correct angles and width of the preserved osseous structures, and align joints.[40,41,44] In an attempt to correct malalignments, transpositions of tendons of the amputated hallux are performed, with or without rebalancing of the articular capsule. Especially in resection of the lateral first ray, superfluous tendons are used to prevent medial deviation and attached on the lateral side to create a lateral force. When the preserved hallux is in line with the other toes, the nail will be reconstructed, and the skin is

closed. Adjusting skin surplus is important for the final appearance of the foot, as this will not correct during growth. Because the plantar skin of the foot has a different structure and color, it is essential not to use plantar skin on the dorsal side of the foot.

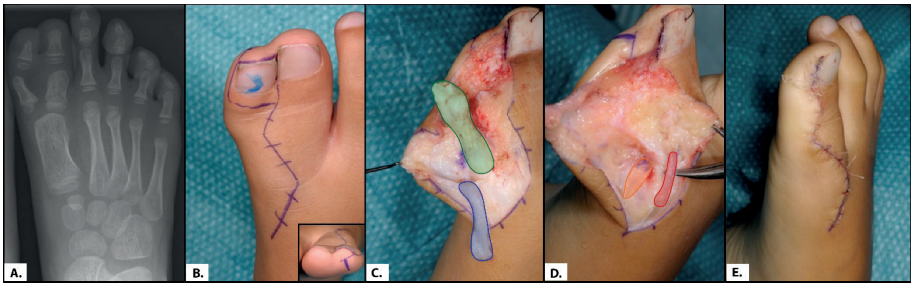

Figure 2. Operation technique for medial excision in type IV duplication.

A) Preoperative radiograph of type IV duplication (Type IV S1). B) Preoperative markings for excision of the medial hallux taking into account reconstruction of the medial nail wall C) The medial nail and nail matrix are removed. The medial distal and proximal phalanges (green) and the medial extensor hallucis longus (blue) are identified. D) The medial hallux (distal and proximal phalanges) is removed by de-articulation in the metatarsophalangeal joint, if needed the metatarsal is narrowed using osteotomies. The extensor hallucis longus of the lateral hallux is identified (orange) and the extensor hallucis longus of the medial hallux (red) can be attached on the lateral side of the proximal phalanx of the preserved hallux, depending on the preference of the surgeon. E) The medial nail wall is reconstructed, skin surplus is removed, and the skin is closed.

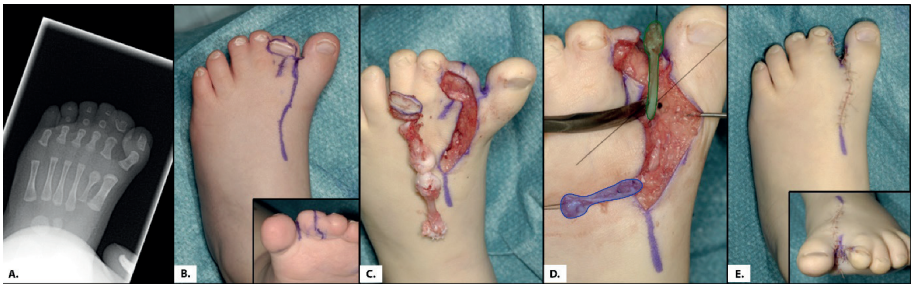

Figure 3. Operation technique for lateral excision in type VI duplication.

A) Preoperative radiograph of type VI duplication. B) Preoperative markings for excision of the lateral hallux taking into account reconstruction of the first web. C) The lateral ray including metatarsal, proximal phalanx, distal phalanx, and nail is excised. D) The flexor (green) and extensor (blue) of the lateral hallux are identified and these are reattached to the proximal phalanx of the medial hallux, on respectively the lateral and dorsal side. Furthermore, the first metatarsophalangeal (MTP) joint capsule is plicated towards the second MTP joint in order to reduce the width of the newly created first web. E) Skin surplus is removed, a first web is re-created, and the skin is closed.

Outcome assessment

Foot function

To evaluate static and dynamic foot function, plantar pressure measurements and clinical examination of the feet were postoperatively performed at the outpatient clinic between June 2015 and March 2016. The timing of postoperative evaluation differed between patients because the study had a cross-sectional design.

An EMED-X pressure platform (Novel GmbH, Munich, Germany) was used to obtain barefoot plantar pressure measurements during comfortable walking. In most cases, a 2-step approach to the platform was used.[123,124] When children were not able to correctly carry out the 2-step approach, a different number of steps was used. All trials in which the entire foot hit the pressure platform and the walking was undisturbed were used for analysis, with a minimum of three trials. Mean peak pressure was assessed for 10 different regions of the foot using the Novel multimask software: the medial and lateral hind foot, the medial and lateral midfoot, the first metatarsal, the second metatarsal, the third to fifth metatarsal, the hallux, the second toe, and the third to fifth toes.[125] The hallux and first metatarsal region are important weight-bearing regions and are of interest in patients with foot PPD. Therefore, the ratio in peak pressure between these regions was calculated as a mark of pressure distribution.

Clinical examination of the foot was performed by two trained researchers, who measured sagittal plane passive range of motion of the metatarsophalangeal (MTP) and interphalangeal (IP) joints of the first ray[126], hallux length measured from the MTP-joint, and forefoot circumference at the level of the MTP-joint. In order to correct for different foot sizes, the hallux length and the forefoot circumference were divided by foot length. To define the medial hallux deviation in relation to the other toes, the distance between the mid-point of the base of the distal phalanx of the hallux and the midpoint of the base of the mid-phalanx of the second toe was measured, using calibrated dorsal-plantar X-rays of the foot. The foot-posture index (FPI) was used to evaluate foot type (supinated foot (score <0); normal foot (score 0-5); pronated foot (score>5)).[127] Additionally, the American Orthopedic Foot Ankle Society (AOFAS) score for the first ray was used to clinically assess the foot, in which a higher score reflects a better outcome.[144,145]

Foot aesthetics

Foot aesthetics were evaluated with the use of 10-cm visual analogue scales (VAS) on four foot-specific domains: general foot appearance, toe size, nail appearance, and scar

appearance. The VAS ranged from "extremely ugly" (0) to "completely normal looking" (score of 100). Children were asked to assess their own foot/feet. Additionally, VAS scores were collected from a panel of lay persons (n=10), randomly recruited among author's acquaintances and with an age range from 9 to 59, and an expert panel, consisting of a congenital foot surgeon involved in the treatment (CvN) and a medical doctor with two years involvement in research on foot PPD (EB). Both laypersons and experts scored the feet using pictures.

Patient-reported outcome measures

To evaluate foot-specific quality of life and general health-related quality of life (HR-QoL), respectively, the Oxford Foot and Ankle Questionnaire for Children (OxAFQ-c)[131,146] and the PedsQL 4.0[132,147] were obtained. Outcome scores are calculated per domain on a scale from 0 to 100, a higher score reflecting a better outcome. Both questionnaires are especially developed for children and contain a child and parent version. In children under eight years, parents completed the questionnaires, as scores from questionnaires might be less reliable under the age of eight.[129]

Statistical analysis

Outcomes were compared between lateral and medial excision subgroups for Type IV and Type VI feet. Outliers in the plantar pressure outcomes were removed from peak pressure analyses. Given the small sample size (n= 2 to 8) per group, Mann-Whitney U tests were used for the continuous outcomes. The number of re-operations per excision group were compared with a Fisher's exact test. Plantar pressures, clinical and aesthetical outcomes were evaluated at individual foot level. Additional patient-reported outcome measures were evaluated at patient level.

RESULTS

Type IV (Proximal phalangeal duplication)

Eleven feet of eight children with Type IV foot PPD were included. In six feet, the medial ray was removed, in five feet the lateral ray (Table 1). The age at time of surgery ranged between 1.3 and 6.5 years, at time of clinical evaluation between 5.6 and 17.2 years. Only one foot needed revision surgery, because of lateral deviation of the preserved hallux. Preoperative and postoperative photographs of lateral and medial excision are shown in Figure 4.

The lateral excision group showed a significantly lower peak pressure at the first

metatarsal compared to the medial excision group (137 kPa vs 272 kPa, p=0.008), and a significantly higher hallux-to-1st metatarsal peak pressure ratio (1.02 versus 0.18, p=0.016) (Table 2). The lateral excision group also showed a significantly smaller forefoot circumference ratio in standing position compared to the medial excision group (0.94 versus 1.02, p=0.004), and a significantly larger medial hallux deviation (2.96 cm versus 1.72 cm, p=0.017).

Laypersons scored the appearance of the nail better after lateral excision than after medial excision (p=0.009) (Figure 5). The other factors concerning appearance in Type IV, like general foot size and hallux size were not significantly better between the two operation types. Patient-reported outcome measurements were not different between excision groups (Table 3).

Table 1. Patient characteristics of duplication type IV and duplication type VI, per excision side.

	TYPE IV duplication		**TYPE VI duplication**	
	Lateral excision	**Medial excision**	**Lateral excision**	**Medial excision**
N of feet	5	6	8	4
Sex (M / F)	0 / 4	3 / 1	1 / 3	0 / 2
Bilaterally affected (N of patients)	1	2	4	2
Median age at time of surgery, in years (range)	2.2 (1.3-6.5)	4.5 (2.3-6.4)	1.2 (0.7-1.8)	1.0 (0.9-1.1)
Median age at time of clinical evaluation, in years (range)	9.6 (8.6-10.3)	6.0 (5.6-17.2)	8.4 (5.2-11.0)	7.4 (4.4-10.4)
Median follow-up time, in months (range)	82 (46-96)	22 (14-178)	88 (48-119)	77 (41-113)
Reoperations (n per foot) #	0	1	5	1

 # The reason for the single re-operation in Type IV duplication was the presence of lateral deviation of the hallux. The reason in Type VI feet for the five re-operations after lateral excision was a recurrent medial hallux deviation; the reason for the single re-operation in the medial excision group was the presence of a symptomatic rest metatarsal.

Type VI (Metatarsal duplication)

Twelve feet of six children with Type VI foot PPD were included. In eight feet, the medial ray was removed and in four feet the lateral ray (Table 1). The age at time of surgery ranged between 0.7 and 1.8 years, at time of clinical evaluation between 4.4 and 11.0 years. Preoperative and postoperative photographs of lateral and medial excision are shown in Figure 6. Lateral excision was related to more revision surgery due to recurrent medial

deviation (5 vs 1, p=0.08).

The hallux and first metatarsal peak pressures, and the hallux-to-1st metatarsal peak pressure ratio were percentage-wise quite different but not significantly so between excision groups (Table 2). Medial hallux deviation was significantly larger in the lateral excision group (3.09 cm versus 1.37 cm, p=0.004). The FPI showed for both groups a pronated foot type, but significantly more pronation was found in the medial excision group (7 vs 10, p=0.048).

Children did not score foot aesthetics differently, between excision sides (Figure 7). Experts scored general foot appearance (p=0.048), toe size (p=0.048), and nail appearance (p=0.004) significantly better for the lateral excision group than the medial excision group. Laypersons rated scar appearance significantly better after medial excision (p=0.016), but rated the hallux size (p=0.016) and nail appearance (p=0.016) significantly better after lateral excision.

Children scored low on the footwear domain of the OxAFQ-c in both excision groups (Table 3).

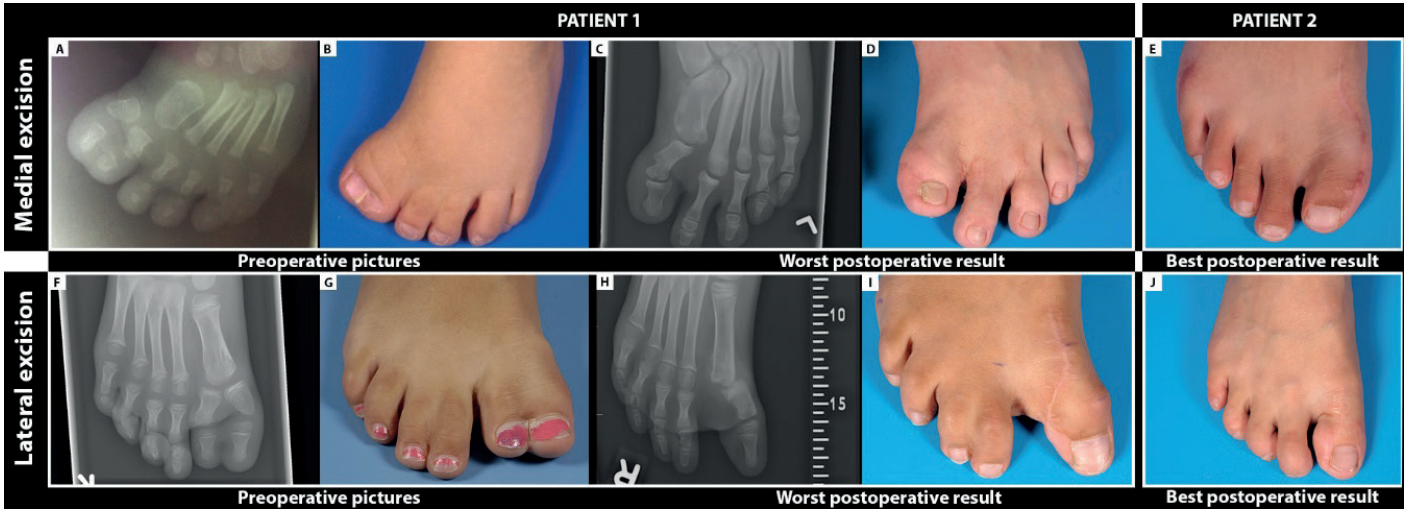

Figure 4. Pre-operative and post-operative photographs of medial and lateral excision in type IV duplication.

A+B) Pre-operative radiograph and clinical photograph of type IV duplication patient 1, in which the medial hallux will be removed. C+D) Post-operative radiograph and clinical photograph of type IV duplication in patient 1 (worst aesthetical outcome). E) Post-operative clinical photograph of type IV duplication in patient 2 (best aesthetical outcome) in which the medial hallux is removed.

F+G) Pre-operative radiograph and clinical photograph of type IV duplication in patient 1, in which the lateral hallux will be removed. H+I) Post-operative radiograph and clinical photograph of type IV duplication in patient 1 (worst aesthetical outcome). J) Post-operative clinical photograph of type IV duplication in patient 2 (best aesthetical outcome), in which the lateral hallux is removed.

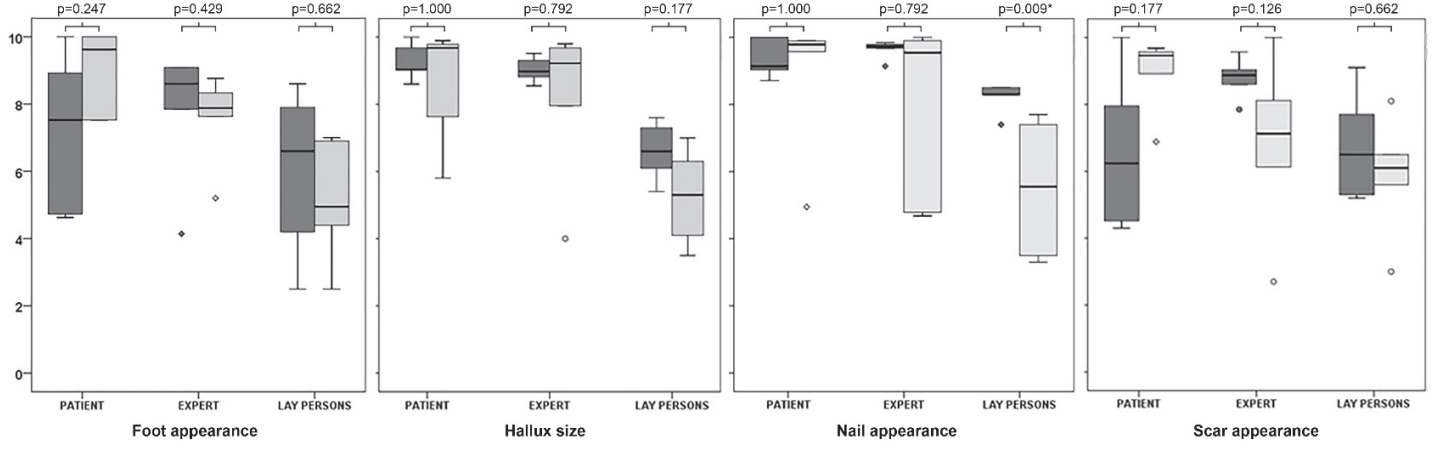

Figure 5. Foot aesthetics in duplication type IV per excision side.

Judged by the patient, an expert panel, and 10 laypersons, using 4 different visual analog scale scores (general foot appearance, hallux size, nail appearance, and scar appearance). Dark grey = lateral excision. Light grey = medial excision.

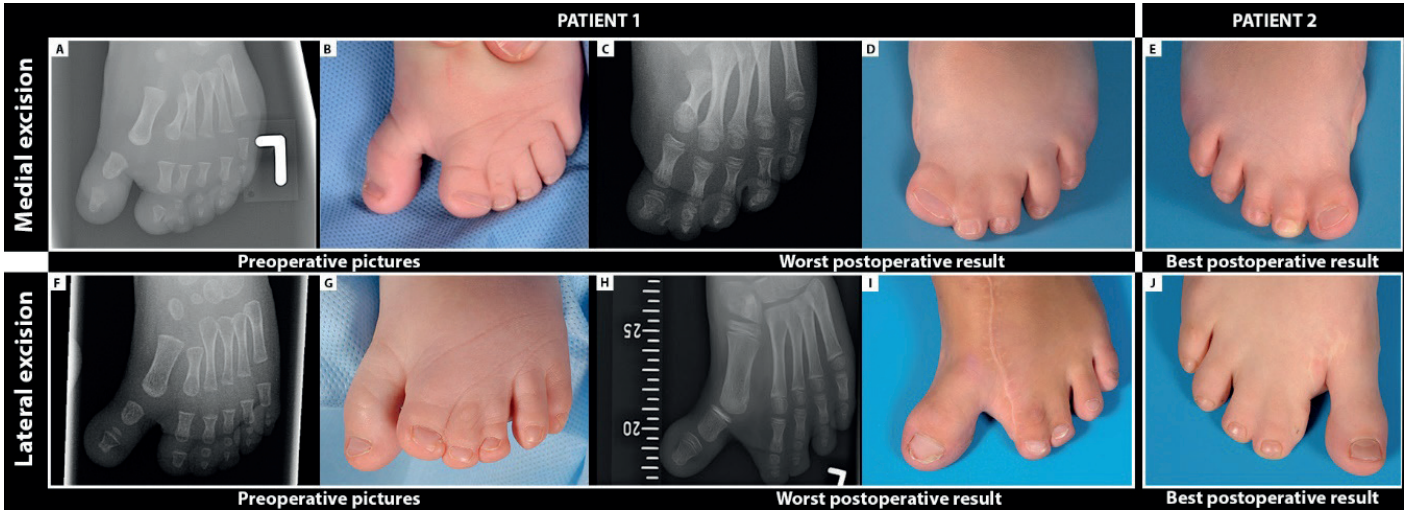

Figure 6. Pre-operative and post-operative photographs of medial and lateral excision in type VI duplication.

A+B) Pre-operative radiograph and clinical photograph of type VI duplication in patient 1, in which the medial hallux will be removed. C+D) Post-operative radiograph and clinical photograph of type VI duplication in patient 1 (worst aesthetical outcome). E) Post-operative clinical photograph of type VI duplication in patient 2 (best aesthetical outcome), in which the medial hallux is removed.

F+G) Pre-operative radiograph and clinical photograph of type VI duplication in patient 1, in which the lateral hallux will be removed. H+I) Post-operative radiograph and clinical photograph of type VI duplication in patient 1 (worst aesthetical outcome). J) Post-operative clinical photograph of type VI duplication in patient 2 (best aesthetical outcome), in which the lateral hallux is removed.

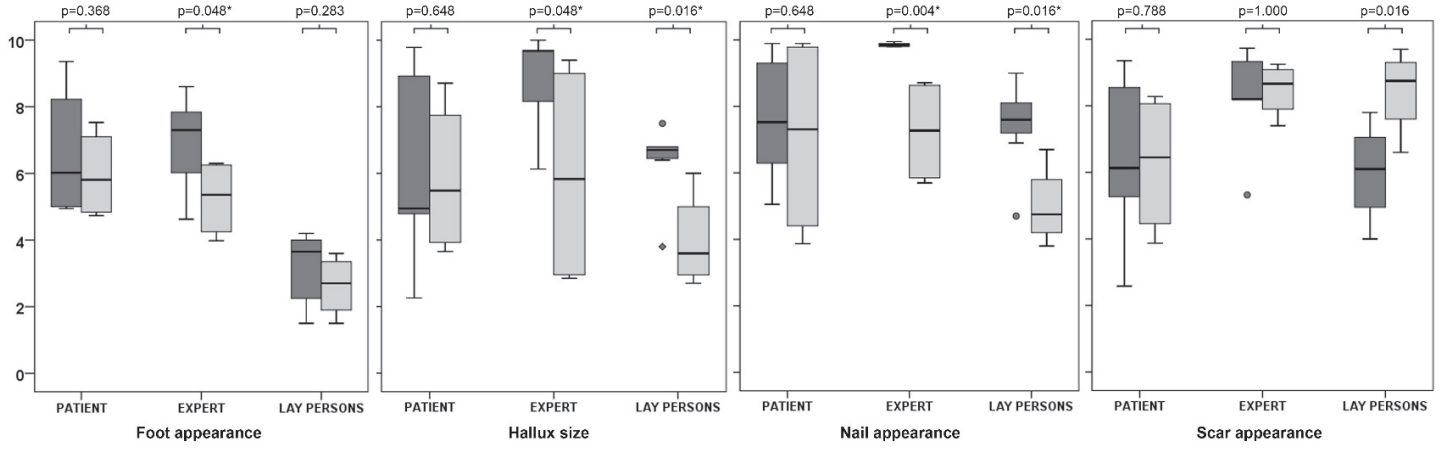

Figure 7. Foot aesthetics in duplication type VI per excision side

Judged by the patient, an expert panel, and 10 laypersons, using 4 different visual analog scale scores (general foot appearance, hallux size, nail appearance, and scar appearance). Dark grey = lateral excision. Light grey = medial excision.

Table 2. Dynamic foot function and clinical examination of the foot in duplication type IV and VI per excision side.

	TYPE IV duplication			TYPE VI duplication		
	Lateral excision N of feet = 5	**Medial excision N of feet = 5#**	**P-value**	**Lateral excision N of feet = 6#**	**Medial excision N of feet = 4**	**P-value**
Dynamic foot function						
	median (range)	*median (range)*		*median (range)*	*median (range)*	
Peak pressures (kPa)						
Total	320 (236-356)	386 (286-541)	0.222	409 (362-622)	329 (221-484)	0.352
Medial heel	191 (178-323)	263 (189-283)	0.421	386 (356-607)	230 (133-296)	0.010*
Lateral heel	179 (171-234)	232 (155-255)	0.841	318 (271-517)	207 (126-266)	0.010*
Medial midfoot	69 (43-88)	82 (49-116)	0.690	49 (0-86)	49 (36-59)	1.000
Lateral midfoot	84 (48-104)	74 (45-108)	0.841	56 (26-127)	59 (41-69)	1.000
1st metatarsal	137 (101-196)	272 (239-445)	0.008*	168 (108-322)	209 (98-314)	0.914
2nd metatarsal	219 (197-339)	153 (88-448)	0.222	257 (158-490)	298 (149-434)	1.000
3th-5th metatarsal	218 (201-251)	191 (84-521)	0.690	286 (129-308)	211 (133-291)	0.476
Hallux	114 (54-317)	44 (0-117)	0.095	239 (63-537)	138 (29-431)	0.476
2nd toe	146 (86-263)	94 (80-101)	0.095	94 (73-199)	55 (25-121)	0.114
Toes 3-5	137 (49-167)	60 (26-146)	0.222	119 (71-260)	53 (14-91)	0.038*
Hallux-to-1st metatarsal ratio	1.02 (0.29-1.73)	0.18 (0-0.36)	0.016*	1.64 (0.25-1.74)	1.03 (0.10-1.71)	0.476
Clinical examination of the foot						
	N of feet = 5	**N of feet = 6**		**N of feet = 8**	**N of feet = 4**	
AOFAS Hallux MTP-IP score	95 (83-100)	95 (83-100)	0.792	82 (73-93)	100 (75-100)	0.194
Foot posture index	0 (-1-4)	2 (2-2)	0.730	7 (4-10)	10 (9-11)	0.048*
Ratio circumference fore foot/length foot, standing (cm)	0.94 (0.65-0.98)	1.02 (0.99-1.04)	0.004*	0.95 (0.91-1.07)	0.96 (0.87-1.03)	0.933
Ratio length hallux/length foot (cm)	0.24 (0.19-0.26)	0.27 (0.23-0.30)	0.082	0.25 (0.22-0.27)	0.26 (0.23-0.27)	0.683
Medial deviation hallux (cm)	2.96 (2.58-3.61)	1.72 (1.54-2.77)	0.017*	3.09 (1.75-4.27)	1.37 (1.26-1.61)	0.004*
Plantar flexion 1st MTP joint (degrees)	30 (10-30)	30 (10-70)	0.629	35 (10-55)	38 (30-50)	1.000

	TYPE IV duplication			TYPE VI duplication		
	Lateral excision N of feet = 5	Medial excision N of feet = 5#	P-value	Lateral excision N of feet = 6#	Medial excision N of feet = 4	P-value
Dorsal flexion 1st MTP joint (degrees)	60 (35-70)	48 (40-55)	0.629	35 (15-60)	45 (15-55)	0.808
Plantar flexion 1st IP joint (degrees)	10 (5-15)	15 (5-30)	0.400	15 (10-20)	25 (10-30)	0.214
Dorsal flexion 1st IP joint (degrees)	15 (10-20)	10 (5-15)	0.229	15 (5-20)	18 (10-45)	0.283

AOFAS, American Orthopaedic Foot & Ankle Society; IP, interphalangeal; MTP, metatarsophalangeal.

** p<0.05*

 # Outlier analysis showed one outlier in the medial excision group of Type IV duplication and two outliers in the lateral excision group of Type VI duplication, which were removed from the plantar pressure analyses.

Table 3. Health-related quality of life in duplication type IV and type VI per excision side.

Parameters	TYPE IV duplication			TYPE VI duplication		
	Lateral excision (N of patients = 4)	Medial excision (N of patients = 4)	P-value	Lateral excision (N of patients = 4)	Medial excision (N of patients = 2)	P-value
	Median (range)	*Median (range)*		*Median (range)*	*Median (range)*	
Foot-related quality of life (OxAFQ-c)						
Physical domain	79 (50-100)	94 (58-100)	0.686	73 (58-88)	85 (75-96)	0.267
School & Play domain	100 (88-100)	100 (75-100)	0.886	97 (69-100)	94 (88-100)	1.000
Emotional domain	84 (56-100)	100 (63-100)	0.686	78 (63-94)	78 (56-100)	1.000
Footwear domain	100 (81-100)	75 (25-100)	0.486	63 (0-100)	50 (50-50)	0.800
General quality of life (PedsQL)						
Physical functioning	86 (75-100)	97 (75-100)	0.686	77 (75-100)	88 (78-97)	0.533
Emotional functioning	85 (75-100)	73 (60-100)	0.343	68 (50-100)	88 (75-100)	0.533
Social functioning	100 (95-100)	95 (90-100)	0.486	100 (55-100)	90 (85-95)	0.533
School functioning	90 (85-100)	93 (70-100)	1.000	90 (65-100)	83 (75-92)	0.800
Total score PedsQL	90 (81.5-100)	88 (85-94)	0.686	86 (64-91)	87 (78-96)	1.000

Outcome of foot-related quality of life and general quality of life measured per patient. In patients under eight years, a parent completed the questionnaire.

DISCUSSION

In foot PPD, the choice of medial or lateral excision in surgical treatment is largely based on expert-opinion.[40,41,44,56] We explored the differences in functional and aesthetic outcomes between lateral and medial excision in foot PPD patients with either proximal phalangeal or metatarsal duplication to help in clinical decision-making for these procedures.

Type IV (Proximal phalangeal duplication)

In proximal phalangeal duplication, the lateral excision group showed significantly lower first metatarsal peak pressures (137 kPa vs 272 kPa, p=0.008) and a better distributed peak pressure between hallux and first metatarsal (1.02 versus 0.18, p=0.016) compared with the medial excision group. While the small sample size did not allow establishing associations with other parameters that may explain this outcome, two clear differences between excision groups were present. First, in five of the six medial excision group cases, the remaining hallux was shorter than the second toe, while in three of the five lateral excision group cases the hallux was longer than the second toe. A shorter hallux might be used less effectively in foot progression and propulsion and may result in a decreased hallux and increased first metatarsal peak pressure as was found in the medial excision group. Secondly, the increased medial hallux deviation in the lateral excision group gives the hallux a more outward lever arm effect and possibly local pressure buildup, which would better distribute peak pressure across the first ray. While the significantly smaller medial hallux deviation in the medial excision group could be an advantage for shoe fitting, the significantly larger foot circumference at MTP level may work to a disadvantage in shoe fitting. Nevertheless, the OxAFQ-c revealed no statistically significant differences in problems with footwear between excision groups. Additionally, lateral or medial excision did not result in a clear difference in aesthetical appearance in this type, as judged by foot surgeons, lay persons, and patients.

Type VI (Metatarsal duplication)

In metatarsal duplication, relatively large but no statistical differences in peak pressures of the first metatarsal and hallux were observed. Furthermore, the ratio between these regions also did not reach statistical significance, although the median ratio showed a worse distribution in the lateral excision group, with a higher hallux pressure. As with type IV duplication, given the small group samples, associations with other parameters could not be determined; potentially, the significantly larger medial hallux deviation found in the lateral excision group may lead to higher hallux pressures; alternatively, syndactyly in the medial

excision group (i.e. presence of the soft tissue bridge between the hallux and the second toe) limits independent movement of the hallux, which may decrease hallux peak pressure.

Feet in the medial excision group were significantly more pronated than in the lateral excision group. This may be due to the preserved hypoplastic first metatarsal that is not able to provide enough strength to construct a strong foot arch. As a consequence, the potential need for special shoes may be higher in the medially excised children.

Experts and lay persons rated the general appearance of the foot, hallux size, and nail appearance as better in the lateral excision group, whereas children rated these aspects as equally appealing. Thus, while children may be less opinionated about preference for excision based on foot appearance, surgeons may use these aspects in clinical decision-making. It should be noted however, that children completing the questionnaires were not influenced by the results of other operated feet and only rated their own feet, which may possibly explain the difference between children and expert opinion.

Differences between duplication types

Separating the analyses based on duplication level revealed distinct findings in aesthetical and functional outcomes. Furthermore, Type VI feet needed more revision surgery than Type IV because of recurrent medial hallux deviation. Previous studies already showed that medial hallux deviation is a frequently returning problem in foot PPD. Venn-Watson reported in 50% of his patients with foot PPD medial hallux deviation and Phelps and Grogan in 14 out of 16 patients seen at follow-up.[19,40] The latter study suggested an association with the presence of a block metatarsal (short and broad metatarsal bone). We did not include cases with a block metatarsal, which indicates that also other factors should be considered in association with medial hallux deviation.

In both duplication types, the senior authors CvN and SH (both reconstructive surgeons) prefer to excise the most hypoplastic hallux. However, when both halluces are of the same length and development in Type IV feet, they prefer lateral excision, as functional outcome is better in lateral excision than in medial excision.

Strengths and limitations

Despite the fact that study assessments were done more than 24 months after the operation in most children, all children in the study are still maturing at time of analysis and therefore outcomes may change over time. The small sample sizes per duplication and excision group prevents drawing strong conclusions, which is the consequence of the very low prevalence

of foot PPD (0.4 per 10.000 living births[17]). Nevertheless, the Erasmus Medical Center is the national reference center for foot PPD, suggesting that larger study groups could not be established within a national study. Because of the small numbers in this study, statistical power of this study was reduced, possibly leading to overestimation of the effects. Therefore, the outcomes should be interpreted with some caution and this study must be seen as a first attempt to describe the effect of duplication type and excision side on outcome; other studies often combine duplication levels to increase sample size, which can lead to incorrect interpretations. [19,44,57]

Conclusion

In proximal phalangeal duplication (type IV), lateral excision gives a significantly better functional outcome regarding peak pressure distribution than medial excision, whereas in metatarsal duplication (type VI), only a small difference between excision groups exists. In both foot types, lateral excision gave more medial hallux deviation, which led to more re-operations in type VI feet. More foot pronation was found with medial excision in type VI feet. These differences in foot anatomy and function may affect shoe fit and the need for special shoes over time, although children themselves do not perceive their foot function as affected. The surgeons perceived a more normal-looking foot with excision of the lateral hallux in type VI and would prefer this intervention; children perceive foot aesthetics as not any different between lateral or medial excision.

These results may help in surgical decision-making although clear recommendations on lateral or medial excision in foot PPD cannot be given, because of the small sample sizes and variation in outcomes per excision side. Larger, multinational collaborative studies are needed, and this study should be seen as a first step in that direction.


6

CHAPTER 7

Long term follow-up and development of foot complaints in a surgically treated mirror foot –

A case report and review of literature

S.A. Lalé, E.B. Burger, J.H.J.M. Bessems, V. Pollet, C.A. van Nieuwenhoven

Foot and Ankle Surgery, December 2017

ABSTRACT

Mirror foot is a rare anomaly and limited long term follow-up information is available.

Seven years after operation a mirror foot patient returned with foot complaints and was evaluated using radiographs and clinical examination. A systematic literature search was conducted to study foot complaints in mirror feet.

Different origins of foot pain were considered in our patient; tibia length difference, deformed talus and accessory osseous structures in the tarsal region. Literature search resulted in 118 mirror feet. Based on cases reporting osseous structures, 74.2% showed tibia abnormalities and 94.5% an abnormal tarsal region. Only three cases mentioned a normal talus. Nine cases reported a follow-up period of more than five years.

Osseous abnormalities are not always visible at birth, but are often present. Therefore, detailed examination of the affected limb in mirror foot patients with foot pain is important, in order to localize the origin.

INTRODUCTION

Polydactyly of the foot is a limb malformation characterized by the presence of supernumerary digits.[44] The formation of fingers and toes during embryogenesis is controlled by sonic hedgehog (Shh). The number of digits and digit identity is influenced by Shh signalling patterns, which is regulated by the *Gli3* protein and could cause preaxial polydactyly.[148]

Mirror foot, a rare type of preaxial polydactyly, is characterized by mirror-image duplication around a midline axis with a recognizable hallux in the centre.[149] According to several authors, the definition of a mirror foot varies.[150,151] Literature shows an important variability in patterns.[151] Therefore, it is difficult to define the term mirror foot. According to Sudesh et al. less than thirty mirror foot cases have been reported in literature.[152] This number emphasizes the rarity of mirror foot cases in the general population, but exact prevalence is unknown.

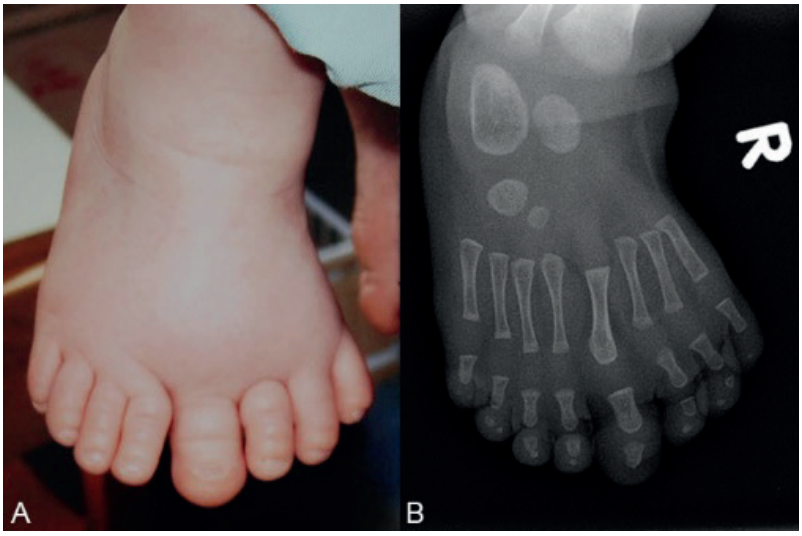

Figure 1. Preoperative view (a) and radiograph (b) of the right foot.

Treatment consists of excision of the extra rays to allow fitting of shoes. Despite a lot of case reports about treatment strategies and outcomes, long term follow-up data is often lacking. Little information is present about the foot problems that might occur later in life. In this case report, we present a patient who was operated on a right-sided mirror foot. Seven years after operation, the patient returned with right-sided foot complaints. The aim of this case report is to give more insights in different causes of foot complaints on the long term in

patients with surgically treated mirror foot. Furthermore, we performed a literature search in PubMed and Google Scholar for articles written in English or Dutch (Appendix 1), to evaluate the presence of these problems in other case reports to reflect on our results.

CASE REPORT

A boy, born without complications after a full-term pregnancy, was diagnosed with a right-sided mirror foot at birth. No other congenital abnormalities were present. The family history was negative for congenital anomalies. Examination of the right limb showed a mirror foot, with eight toes in total, including an identifiable hallux in the middle flanked by three toes on the medial site of the hallux and four normally developed toes on the lateral side of the hallux (Figure 1a). Radiographs of the right foot revealed eight metatarsal bones and their

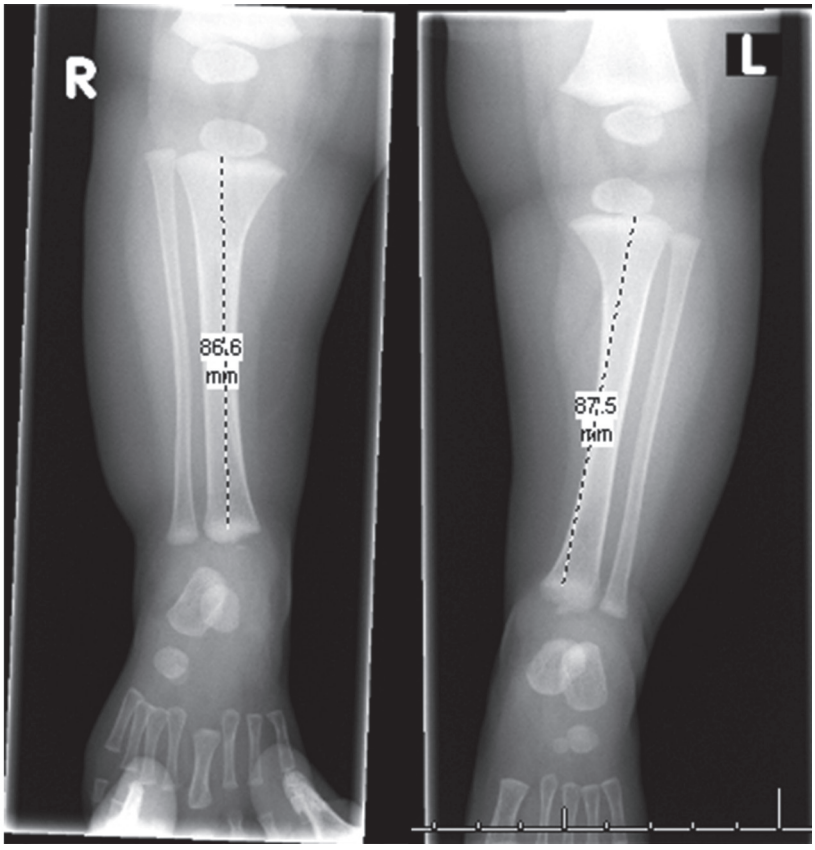

Figure 2. Radiograph of the left and right lower limb at the age of six months. A difference in tibial length of 0.9 cm is observed.

associated phalanges (Figure 1b). Furthermore, radiographs of both lower legs showed a tibial length difference of 0.9 cm in favour of the left leg (Figure 2). The left lower limb and foot showed no abnormalities. Excision of the three medial rays and reconstruction of the right foot was performed at the age of 11 months. Perioperative an additional extra cartilage tarsal structure was observed connected to the navicular bone and the caput tali. This structure was removed through the cartilage connection. No complications were reported.

At the age of eight years old, the patient returned to the outpatient clinic with pain complaints of his right foot, especially during activities such as running. The pain was located at the anterior part of his ankle. In addition, a mild not painful luxation of the proximal fibular head was present. Furthermore, a difference in the range of motion in dorsiflexion of 10° was observed (right 10°; left 20°). Radiographs of the right foot showed accessory osseous structures (Figure 3a) as well as a deformity of the talus (Figure 3b). We decided to treat the patient conservatively, with revision at the out-patient clinic within nine months. After nine months the patient returned for a limb length measurement (photo not shown), showing a 0.5 cm shorter femur on the left side and a 1.0 cm short lower leg on the right side.

The Ethics Committee at the Erasmus Medical Centre Rotterdam, the Netherlands provided approval for the study. Informed consent from parents was obtained.

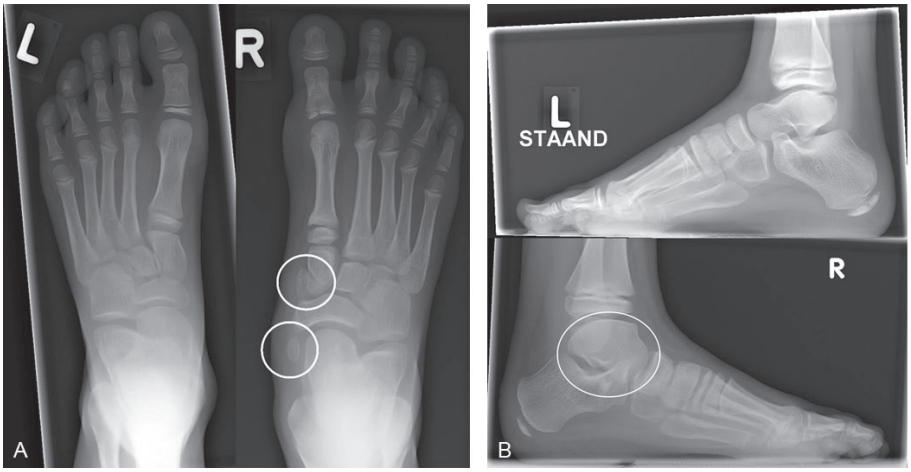

Figure 3. Radiograph of the lower limb at the age of eight years old.

The right foot shows accessory osseous structures (a) and talus deformity (b) when compared to the left foot.

DISCUSSION

Here we present a case of an operated right-sided mirror foot associated with pain complaints of the right leg and foot and impaired ankle dorsiflexion seven years after operation. After evaluation at the outpatient clinic, three different origins of pain can be proposed; presence of accessory osseous structures, dysplasia of the talus, and difference in length between the two legs. To study different causes for foot complaints in mirror feet, we conducted a systematic literature review.

During our search, we noticed that the definition of mirror foot is diverse, due to the variability in patterns. Also different terminologies are used to describe this specific type of foot duplication, the most common terms are diplopodia and mirror (-image) polydactyly. The precise definition of these terms depends on the author. We excluded cases not diagnosed with these terms, even though these cases showed similarities. In total 78 patients, with 118 mirror feet, were identified. All patients were sorted based on the type of tibial deficiency, talus abnormalities, abnormalities in the tarsal region and follow-up time.

In our patient we observed a minimal tibial length difference at birth. To investigate if this is common in mirror foot patients, we searched cases that showed tibial deficiencies and sorted them on type of deficiency (Figure 4). We identified 11 patients (13 feet)[150,153-159] with tibial hypoplasia, ranging from mild to severe, in combination with a mirror foot. A precise measurement of the tibial length was not always available and therefore these cases were difficult to compare with ours. Four case reports have measured that the affected limb was shorter compared to the unaffected limb. The length differences varied from 3.0 cm to 23.0 cm.[153-155] In 97 feet the tibial development was evaluated and in 74,2% of the cases it was abnormal. Information concerning pain symptoms in these patients was not available. One case report[160], showed a patient diagnosed with polydactyly and normal tibial development at birth. However, hypoplasia of both tibias was observed later in life.[160] This could suggest that tibial length difference is not always detectable at birth and could develop over time or that it was missed due to the minimal difference. Unfortunately, long term follow-up is lacking in this study. Although our patient did show a tibial length difference, when comparing the entire limb, there is only a difference of 0.5 cm in length. This suggests that pain in our patient is probably not caused by the difference in limb length.

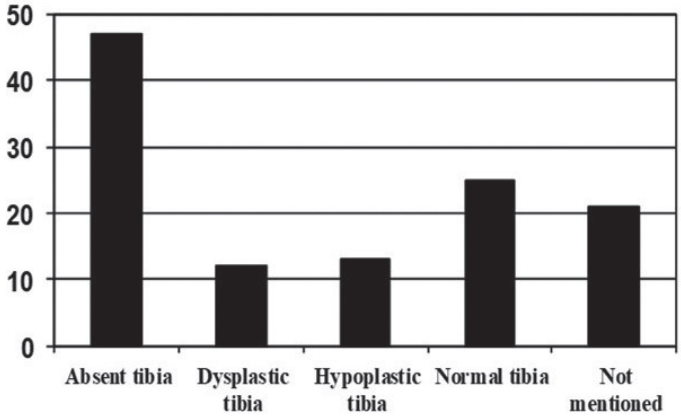

Figure 4. Number of feet sorted on type of tibial deficiency.

Absent tibia[150,152,155,158,159,161-178], *dysplastic tibia*[150,163,179-183], *hypoplastic tibia*[150,153-159], *normal tibia*[44,154,155,157,166,169,184-193], *and not mentioned*[151,172,188,194-199].

In our patient a talus deformity was also noticed. Specific information about the shape of the talus is lacking in most cases presented in literature. In three cases it is mentioned that the talus is normal.[154,184] In eight cases an abnormality of the talus was noticed. These were described as duplications[150,180], small in size[187], broad in shape[163], fused with the calcanei[164], and abnormally shaped[165]. In these cases pain symptoms were not evaluated. The deformed talus in our patient induces limited dorsiflexion of the ankle, which could be an explanation for the pain symptoms of the right foot.

The tarsal region of our patient also shows abnormalities. To verify the presence of abnormality of the tarsal region in literature, we classified all cases based on normal tarsal region, abnormal tarsal region or not mentioned (Figure 5). This highlights that abnormalities in the tarsal region are common. In 55 feet the tarsal region was evaluated and in 94,5% of these cases it showed abnormalities. For example, Buck-Gramcko[200] reported a child diagnosed with a complex left-sided partial duplicated foot (not diagnosed as mirror foot), with eight toes, additional tarsal bones and normal tibia. During operation, excision of the additional toes and partial excision of the tarsal bones was performed. After ten years of follow-up, radiographs showed that the tarsal bones had an unusual shape, with the presence of foot complaints after prolonged walking.[200] This is similar to our case, were abnormalities in the tarsal region, such as the dysplastic talus, can result in foot complaints.

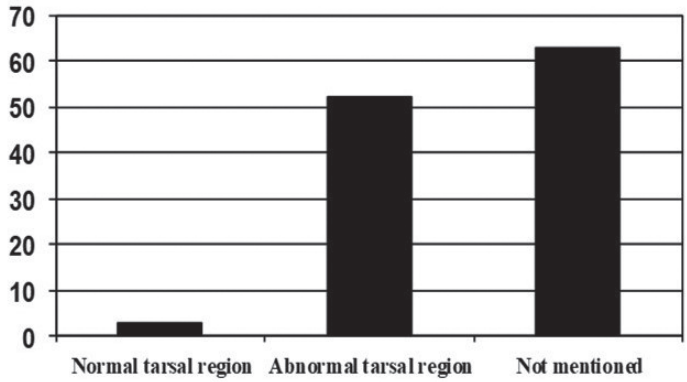

Figure 5. Number of feet sorted based on normal or abnormal tarsal region.

Normal tarsal region[150,154]*, abnormal tarsal region*[44,150-152,154-157,161-169,172,178-182,186,187,189,193,194,196]*, and not mentioned*[153,155,157-159,163,166,170-177,183-185,188,190-193,195,197-199].

We also noticed in our case the presence of accessory structures at the medial side of the foot, caused by incomplete removal of cartilage tissue, which cannot be confirmed on early radiographs. This is probably due to incomplete ossification at a young age, which lead to invisible accessory structures and abnormalities on early radiographs. Therefore, evaluating the tarsal region for abnormalities at a later age is important in order to recognize different shape and persisting structures in the tarsal region.

Few reports about long term follow-up results in patients with mirror foot are present in current literature. Out of the 78 patients only 32 reported their follow-up period, ranging from 4 months to 37 years.[44,150-153,155,159,163,165-167,180,187-191,194-196] Only nine cases had a follow-up period of more than five years. Out of the 118 feet, only four feet[185,188,193] evaluated foot complaints on the long term due to osseous abnormalities. This emphasizes the lack of long term results of mirror foot patients.

CONCLUSION

We present a patient with pain complaints of his foot seven years after operation on a right-sided mirror foot. After examination, the pain could be explained by a length difference of the limb, a talus deformity, and/or the presence of accessory structures at the medial side of the foot.

With our literature search we have shown that abnormal development of the

different osseous structures is present in patients with mirror foot, however also often not described. In evaluating our case, we think the talus deformity is the most likely cause of pain. Furthermore, we have shown that long-term follow-up data on mirror feet is minimal in current literature. With this case report we like to emphasise the importance of detailed examination of the osseous structures in the affected foot and lower leg at a later age, evaluating differences that might be a cause of pain developing during growth.

APPENDICES

Appendix 1. Search strategy.

Performed on 23-01-2016. Based on the reference list of the selected articles the following articles were included: Laurin et al 1994, Patil et al 2013 and Sandrow et al 1970.

Terms	PubMed		Google Scholar	
	Hits	***Articles selected***	***Hits***	***Articles selected***
Mirrorfoot	181 (1st search)	Bayram et al 1996, Belthur et al 2011, Bernardi et al 2010, Borg et al 1999, Fukazawa et al 2009, Hatchwell et al 1996, Hersh et al 1995, Kantaputra et al 2001, Khan et al 2008, Kim et al 1997, Kogekar et al 1993, Lohan et al 2014, Mariño-Enríquez et al 2008, Martin et al 1993, Martínez-Frías et al 1994, Mishra et al 2010, Pilkington et al 2000, Rivera et al 1999, Skoll et al 2000, Sudesh et al 2010, Urioste et al 1996, Verghese et al 2007, Viljoen et al 1990, Vlahovic et al 2015, Wechsler et al 2004.	173 (5th search)	Deshmukh et al 2015, Jose et al 2004, Omar et al 2014.
Mirrorpolydactyly	71 (2nd search)	Klopocki et al 2012, Martínez-Frías et al 1997, Nguyen et al 2014, Vanlerberghe et al 2015.	118 (6th search)	Pajkrt et al 2007, Vargas et al 1995.
Mirror-image polydactyly	24 (3th search)	Kjaer et al 2005, Salinas-Torres et al 2014.	996 (7th search)	Baines et al 2014
Diplopodia	27 (4th search)	Brower 2003, Ganey et al 2000, Hamanishi et al 1985, Hocaoğlu et al 2013, Kadir et al 2011, Karchinov 1973, Narang et al 1982.	386 (8th search)	Andersen et al 1971, Jones et al 1978, Olason et al 1988, Buck-Gramcko 2003

Appendix 2. Summary of literature search.

Abbreviations: Left (L) and right (R). Laurin-Sandrow syndrome (LSS)

Author	Case	Age of presentation	Diagnosis	Syndrome	Side	Tibia	Talus	Tarsal region	Toes	Pain	Follow -up
Belthur et al 2011		1.7 years	Mirror foot	-	R	R: normal	-	Accessory tarsals	R: 8	-	48 months
Verghese et al 2007	Case 1	All cases ranges from 9 months to 5 years	Preaxial mirror-image polydactyly	-	One sided	aplasia	-	Two calcaneus, two cuboid, two lateral cuneiform	8	-	9 months to 5 years
	Case 2		Preaxial mirror-image polydactyly	-	L/R	L/R: aplasia	-	L/R: 2 calcaneus, 2cuboid, 2 lateral cuneiform	L/R: 8	-	
	Case 3		Preaxial mirror-image polydactyly	-	One sided	aplasia	-	2 calcaneus, 2cuboid, 2 lateral cuneiform	8	-	
	Case 4		Preaxial mirror-image polydactyly	-	L/R	L/R: aplasia	-	L/R: no duplication	L/R: 7	-	
	Case 5		Preaxial mirror-image polydactyly	-	One sided	Dysplasia	Duplicated talus	no duplication	7	-	
	Case 6		Preaxial mirror-image polydactyly	-	One sided	Dysplasia	Duplicated talus	no duplication	7	-	
	Case 7		Preaxial mirror-image polydactyly	-	One sided	Dysplasia	Duplicated talus	no duplication	7	-	
	Case 8		Preaxial mirror-image polydactyly	-	One sided	Hypoplasia	-	no duplication	8	-	

Author	Case	Age of presentation	Diagnosis	Syndrome	Side	Tibia	Talus	Tarsal region	Toes	Pain	Follow -up
Vlahovic et al 2015		14 months	Mirror foot	-	R	-	-	R: supernumerary tarsal bone	R: 9	-	7,5 years
Sudesh et al 2010		6 years	Mirror foot	None	R	R: aplasia	-	R: duplicated calcaneus	R: 8	-	37 months
Hersch et al 1995		At birth	Mirror image duplication	Unknown syndrome	L/R	L/R: hypoplasia	-	-	-	-	17 months
Kadir et al 2011		15 years	Diplopodia	-	L/R	L: normal R: hypoplasia	-	L: duplicated R: normal	L: 7 R: 8	-	-
Karchinov 1973	Case1	13 months	Diplopodia	-	L/R	L/R: aplasia	-	L/R: duplications	L/R:8	-	-
	Case2	1 month (operation age)	Diplopodia	-	L/R	L: normal R: hypoplasia	-	L/R: additional tarsal bones	-	-	8 years
	Case3	2 years	Diplopodia	-	R	R: hypoplasia	-	-	R: 9	-	-
	Case4	18 months	Diplopodia	-	L	L: hypoplasia	-	L: duplicated	L: 8	-	-
	Case5	50 years	Diplopodia	-	R	R: severe hypoplasia	-	L: duplicated	R: 7	-	-
	Case6	1.5 month	Diplopodia	-	L	L: absent	-	-	L: 7	-	-
Marino-Enriquez et al 2008		33 weeks gestation	Mirror polysyndactyly	LSS	L/R	L/R: hypoplasia	-	L/R: a single anomalous tarsal bone	L: 11 R: 12	-	-
Martin et al 1993	Child	4 months	Mirror-image duplication	Mirror hands and feet with distinct nasal defect	L/R	L: normal R: hypoplasia	-	-	L/R: 10	-	-

Author	Case	Age of presentation	Diagnosis	Syndrome	Side	Tibia	Talus	Tarsal region	Toes	Pain	Follow -up
	Father		Mirror-image duplication	Mirror hands and feet with distinct nasal defect	L/R	L/R: normal	-	L: fusion of two cuneiforms R: accessory cuneiform	L/R: 8	-	-
Vanlerberghe et al 2015	Proband III-1	At birth	Mirror-image polydactyly	-	L/R	L: agnesia R: hypoplasia	-	-	L/R: 8	-	-
Wechsler et al 2004		10 months	L/R: Mirror image polydactyly	Unknown syndrome	L/R	L: hypoplasia R: aplasia	-	-	L: 7 R: 8	-	25 months
Andersen et al 1971		14 months	Diplopodia	-	L/R	L/R: "unidentifiable bones" (dysplasia)	-	L/R: 2 heel bones, 2 scaphoids, 3 unidentified tarsal bones	L/R:10	-	-
Bayram et al 1996		8 months	Mirror foot	None	R	R: aplasia	-	Duplicated calcaneus.	R: 8	-	-
Brower 2003		-	Diplopodia	-	L/ accessory foot	L: normal	L: normal	L: - accessory foot: duplications	L: 5 accessory foot: 4	-	-
Ganey et al 2000		3 years	Diplopodia	-	R	R: absent	-	R: duplicated calcaneus	R: 9	-	-
Nguyen et al 2014		2 years	Mirror club-foot	-	L/R	L/R: normal	-	-	L/R: 8	No	-
Omar et al 2014		40 years	Mirror foot	-	R	R: normal	-	R: five cuneiform bones	R: 9	-	-

Author	Case	Age of presentation	Diagnosis	Syndrome	Side	Tibia	Talus	Tarsal region	Toes	Pain	Follow -up
Sandrow 1970	Father	4 years (already been operated)	Mirror poly-syndactyly (unknown at that moment)	LSS (unknown at that moment)	L/R	-	-	L/R: duplicated calcaneus, four cuneiforms	-	-	At least till the birth of his first child
	Child	3 months	Mirror poly-syndactyly (unknown at that moment)	LSS (unknown at that moment)	L/R	-	-	L/R: duplicated calcaneus, four cuneiforms	-	-	-
Deshmukh et al 2015		15 months	Mirror foot	None	R	R: dysplasia	R: dupli-cated	-	R: 7	-	5 years
Hamanishi et al 1985		8 years	Diplopodia	None	L/lateral foot	L: normal	L: one small talus	L: accessory tarsal bones	L: 10	-	4 months
Kjaer et al 2005	Patient 1	At birth	Mirror image polydactyly	LSS	L/R	L/R: dysplasia	-	-	L/R: 9-10	-	37 years
	Patient 2	At birth	Mirror image polydactyly	LSS	L/R	L/R: absent	L/R: one broad talus	L/R: duplicated calcaneus	L/R: 9	-	8 years
Narang et al 1982		14 years	Diplopodia	-	R	R: absent	R: talus fused with the calca-neus	R: two calcanei, two cuboid, four cuneiform	R: 9	-	-
Rivera et al 1999		1 year (opera-tion age)	Diplopodia	-	R	R: absent	R: ab-normally shaped talus	R: duplicated calcaneus	R: 8	-	6 months
Fukazawa et al 2009	Case 1	4 months 14 months (operation age)	Mirror foot	-	R	R: absent	-	-	R: 8	-	6 months

Author	Case	Age of presentation	Diagnosis	Syndrome	Side	Tibia	Talus	Tarsal region	Toes	Pain	Follow -up
	Case2	4 months 11 months (operation age)	Mirror foot	-	R	R : normal	-	R : extra cuneiform	R : 8	-	-
	Case 3	1 month 25 months (operation age)	Mirror foot	-	R	R: normal	-	R: calcaneus and the cuboid are duplicated	R: 7	No	9 years
Hatchwell et al 1996		At birth	Mirror foot	LSS	L/R	L: "less differentiated"(?) R: normal	-	-	L: 7 R: 8	-	20 months
Hocaglu et al 2013		4 days old 10 month (operation age)	Diplopodia	-	L	L: normal	-	L: duplicated	L: 9	-	5 months
Kogekar et al 1993		At birth	Mirror polydactyly	LSS	L/R	L/R: "shortness of both tibiae" (?)	-	-	L/R: 8	-	9 months
Laurin et al 1994		1 year (operation age)	Mirror foot	LSS (unknown at that moment)	L/R	L/R: absent	-	L/R: duplicated calcaneus	-	-	6 years
Martinez –Frias et al 1994		At birth	Mirror polysyndactyly	LSS	L/R	L/R: normal	-	-	L: 8	-	9 months
Olason et al 1988		2 years 3 years (operation age)	Diplopodia	-	R	-	-	R: additional tarsal bones	R: 8	-	6 years

Author	Case	Age of presentation	Diagnosis	Syndrome	Side	Tibia	Talus	Tarsal region	Toes	Pain	Follow -up
Pilkington et al 2000		At birth 6 months (operation age)	Mirror foot	LSS	L/R	L/R: normal	-	-	L: 7 R: 8	-	6 years
Bernardi et al 2010		7 months	Mirror poly-dactyly	VACTERL association	L	L: absent	-	Duplicated tarsal bones	L: 7	-	-
Borg 1999		9 years	Mirror-image polydactyly	None	L/R	L: normal R: aplasia	-	L: two supernu-merary cuneiform bones R: abnormal tarsal bones and supernumerary cuneiform bones	L: 8 R: 7	-	-
Jones et al 1978	Case 11	-	Diplopodia	-	L	L: aplasia	-	-	-	-	-
	Case 12	-	Diplopodia	-	L/R	L/R: aplasia	-	-	-	-	-
	Case 13	-	Diplopodia	-	L/R	L/R: aplasia	-	-	-	-	-
	Case 16	-	Diplopodia	-	L/R	L/R: aplasia	-	-	-	-	-
	Case 18	-	Diplopodia	-	R	R: absent	-	-	-	-	-
Khan et al 2008		4 months	Diplopodia	-	L	L: absent	-	-	L: 7	-	-
Martinez –Frias et al 1997	Case 1	34 weeks gestation	Mirror-image polydactyly	-	L/R	L/R: absent	-	L/R: tarsal dupli-cation	-	-	-
	Case 2	30 weeks gestation	Mirror poly-dactyly	-	L	L: "Left leg is short" (?)	-	-	L: 7	-	-
Pajkrt et al 2007		At birth	Mirror-poly-dactyly	None	L/R	L/R: agnesia	-	-	L: 9 R: 8	-	-

Author	Case	Age of presentation	Diagnosis	Syndrome	Side	Tibia	Talus	Tarsal region	Toes	Pain	Follow -up
Patil et al 2013		31 months	Mirror-image polydactyly	LSS	L/R	L/R: absent	-	-	L: 10 R: 12	-	-
Salinas-Torres et al 2014	Patient 1	55 years	Mirror polysyndactyly	LSS	L/R	L/R: absent	-	-	L: 8 R: 9	-	-
	Patient 2	2 weeks	Mirror polysyndactyly	LSS	L/R	L/R: absent	-	-	L: 8 R: 9	-	-
Urioste et al 1996	Patient 1	At birth	Mirror polydactyly	-	L/R	L/R: aplasia	-	-	L/R: 6	-	-
Vargas et al 1995	Patient 1	1 month	Mirror-image polydactyly	Werner syndrome	L/R	L/R: absent	-	-	L: 8 R: 9	-	-
Viljoen 1990		11 months	Mirror polydactyly	-	L	L: aplasia	-	Duplication of calcaneus	L: 7	-	-
Kantaputra 2001		54 years	Mirror-image polydactyly	LSS	L/R	L/R: "thick and short tibia" (dysplasia)	-	L/R: tarsal bones severely malformed and supernumerary cuneiform	L: 9 R: 9	-	-
Skoll et al 1999		2 months	Mirror foot	-	R	R: "short, broad and bowed" (dysplasia)	-	R: enlarged first cuneifrom	R: 8	-	-
Jose et al 2004		18 months	Mirror foot	-	L	R: normal L: "short and broad" (dysplasia)	-	-	R: 8	-	-
Kim et al 1997		4 months	Mirror image polydactyly	None	L/R	L/R: normal	-	-	L/R: 8	-	-
Mishra et al 2010	Case 1	6 months 12 months (operation age)	Mirror foot	-	R	R: normal	-	-	R: 8	Yes	3 years

Author	Case	Age of presentation	Diagnosis	Syndrome	Side	Tibia	Talus	Tarsal region	Toes	Pain	Follow -up
	Case 2	7 months (operation age)	Mirror foot	-	L	L: normal	-	-	L: 8	-	5 years
	Case 3	12 months 16 months (operation age)	Mirror foot	-	R	R: normal	-	R: single broad cuneiform	R: 7	-	3 years
Baines et al 2014		-	Mirror-image polydactyly	LSS	L/R	-	-	-	L/R: to-gether 17	-	-
Kloppocki et al 2012	Case 1	34 weeks gestation	Mirror image polydactyly	-	L/R	-	-	-	L/R: 8	-	-
	Case 2	15 weeks gestation	Mirror-image polydactyly	-	R	-	-	-	-	-	-
Lohan et al 2014	Family 4 (father)	-	Mirror-image polydactyly	LSS	L/R	-	-	-	-	-	-
	Family 4 (daugh-ter 1)	-	Mirror-image polydactyly	LSS	L/R	-	-	-	-	-	-
	Family 4 (daugh-ter 2)	-	Mirror-image polydactyly	LSS	L/R	-	-	-	-	-	-


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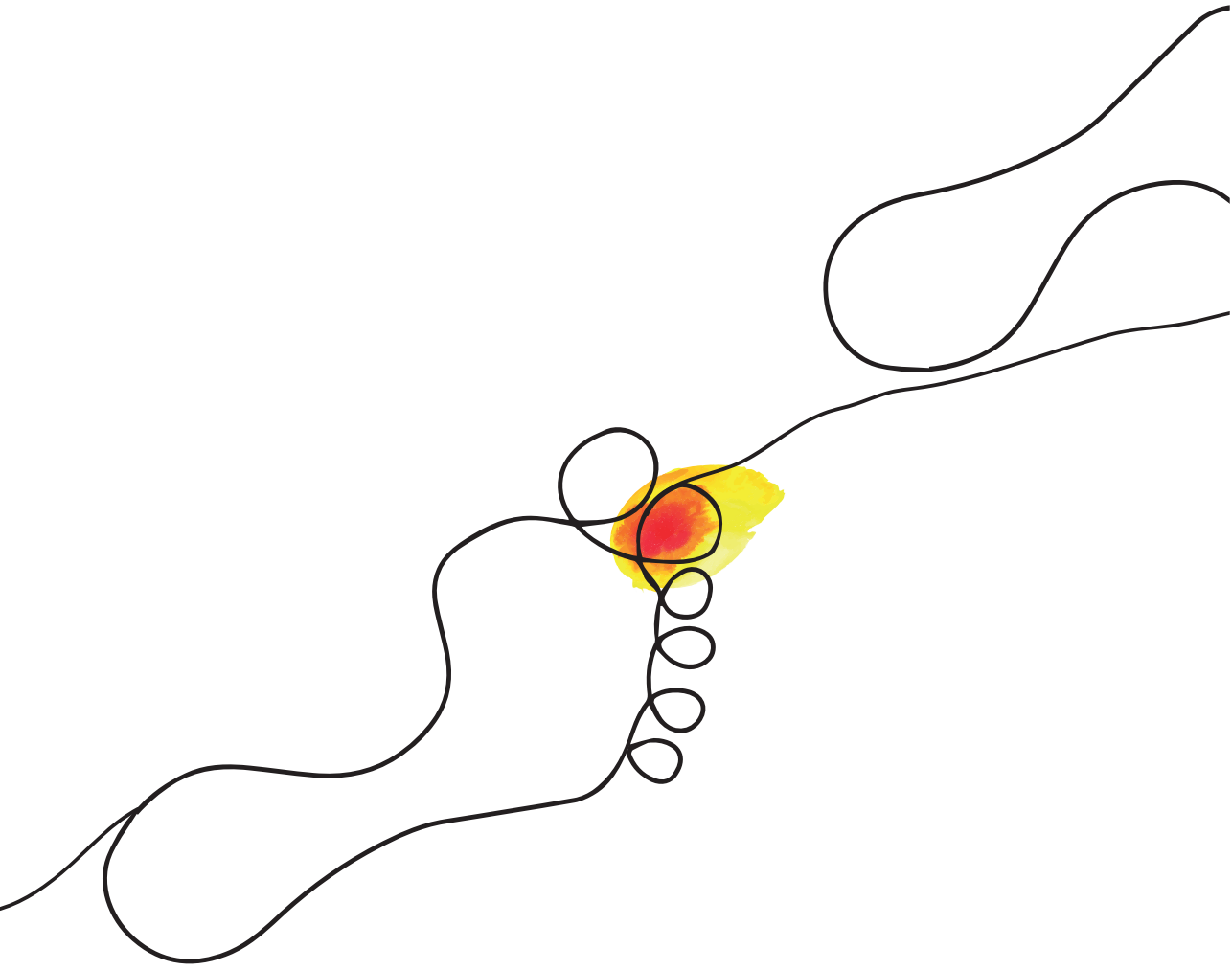

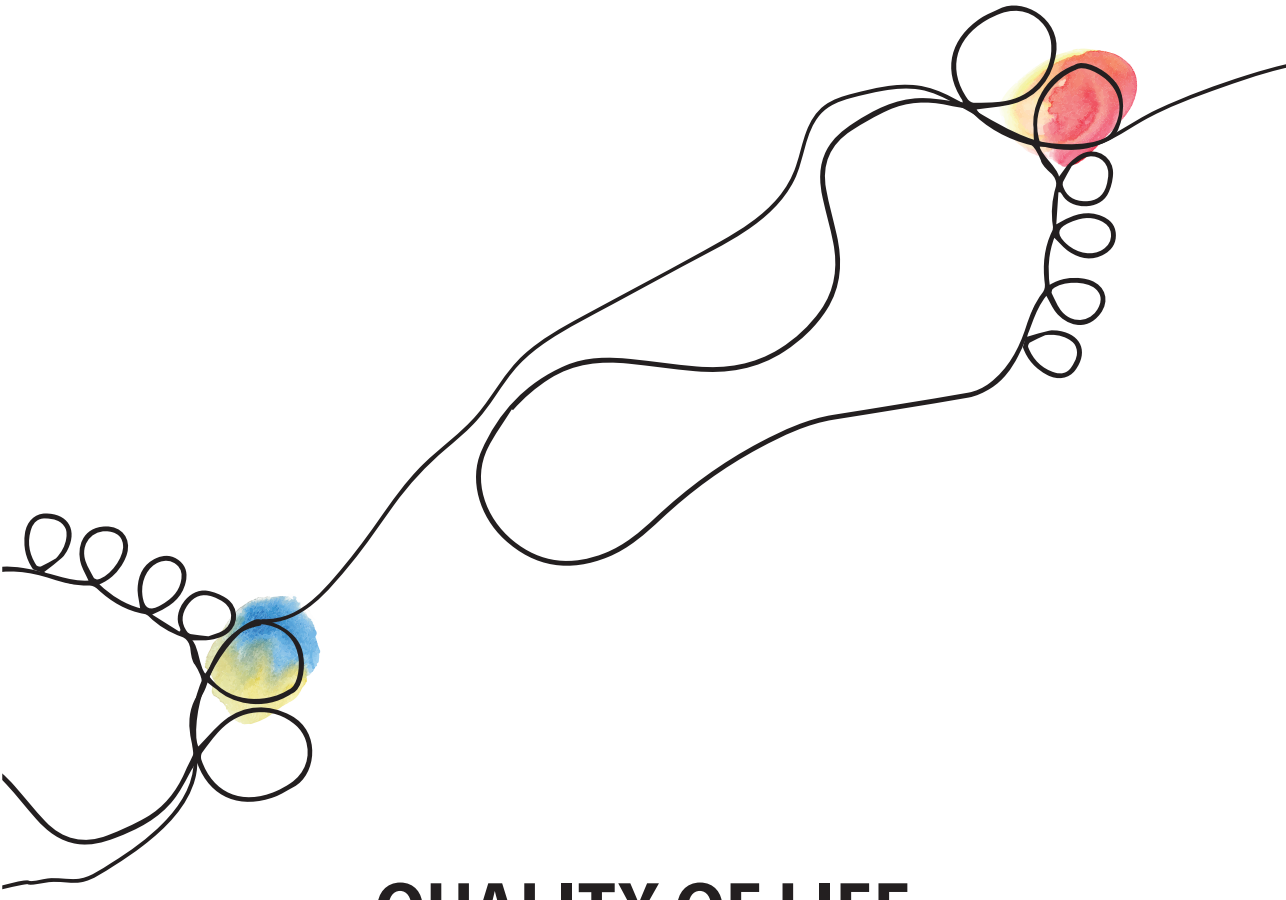

QUALITY OF LIFE

CHAPTER 8

The Dutch version of the Oxford Ankle and Foot Questionnaire for Children: Useful for evaluation of pediatric foot problems in groups

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Foot and Ankle Surgery, April 2019

ABSTRACT

The purpose of this study is to develop a Dutch version of the Oxford Ankle and Foot Questionnaire for Children (OxAFQ-c) to allow evaluation of pediatric foot care.

The OxAFQ-c was translated into Dutch, according to the ISPOR-guidelines. Children with different foot and ankle complaints completed the OxAFQ-c at baseline, after two weeks, and after 4-6 months. Measurement properties were assessed in terms of reliability, responsiveness, and construct validity.

Test-retest reliability showed moderate intraclass correlation coefficients. Bland-Altman plots showed wide limits of agreement. After 4-6 months, the group that experienced improvement also showed improved questionnaire outcomes, indicating responsiveness. Moderate correlation between the OxAFQ-c and the Kidscreen and foot-specific VAS-scores were observed, indicating moderate construct validity.

The Dutch OxAFQ-c showed moderate to good measurement properties. However, because we observed limited sensitivity to changes and wide limits of agreement in individual patients, we think the questionnaire should only be used in groups.

INTRODUCTION

Health-related quality of life questionnaires and patient-reported outcome measures (PROMs) are of increasing interest in clinical research, allowing the opportunity to assess patients' perspective in clinical care.[201] In contrast to provider-focused assessment methods, such as physical examination and clinician-centered rating scales, PROMs can be used to verify subjective experiences of patients. Currently, a distinction is made between generic PROMs and specific PROMs.[201] Generic PROMs are suitable to measure general aspects of health in a broad population, whereas specific PROMs can be targeted for specific populations, diseases, and body regions.[202]

Several region-specific PROMs for foot and ankle problems have been developed.[203,204] Nevertheless, most PROMs for foot and ankle problems are developed and validated for adults.[204] Given the differences between the daily activities of children and adults, these PROMs for adults may be less applicable in children with foot and ankle problems. In 2008, Morris et al. developed the first questionnaire for children with foot and ankle problems, the Oxford Ankle and Foot Questionnaire for Children (OxAFQ-c).[130,146,205] This questionnaire is developed for all foot and ankle problems in children and it measures the effect of foot or ankle problems in three domains: 1) physical, 2) school&play, and 3) emotional. Moreover, an extra question about foot wear is included. The questionnaire contains two versions: the OxAFQ-c for 5 to 17 year old patients and a parent-proxy version.

Unfortunately, the OxAFQ-c is developed in English and is currently not available in the Dutch language. A Dutch version of the OxAFQ-c will contribute to Dutch pediatric ankle and foot care and will give more insights in the children's and parents' perspective of functioning in daily life. However, translated questionnaires should first be validated, otherwise outcomes could lead to invalid conclusions.[206] A good validation procedure consists of the assessment of reliability, validity, and responsiveness, in order to ascertain that the translated questionnaire measures reliable and valid outcomes. In 2015, two validation studies of an Italian and a Danish version of the OxAFQ-c were performed, showing good validity and feasibility.[207,208] In order to obtain a validated Dutch version of the OxAFQ-c, we performed in this study a Dutch translation and validation of the OxAFQ-c.

PATIENTS AND METHODS

Translation

The linguistic translation of the OxAFQ-c contained a forward and backward translation performed according to the ISPOR guidelines for translation.[209] After translation a consensus

meeting was planned with the forward translators and principal investigator to establish a first version of the Dutch child and proxy questionnaires. Comprehensibility of these questionnaires was tested at the orthopedic outpatient clinic of the Sophia Children's hospital. patients with foot and ankle problems and their parents were asked to complete the translated questionnaire. Comments on difficulties in this translated questionnaire were incorporated in the final version of the Dutch OxAFQ-c.

Validation process

Patient selection

Prior to the inclusion of patients, the study was approved by the Institutional Review Board of the Erasmus Medical Centre, Rotterdam (MEC-2014-669). Children between the age of 5 and 17 years old with all kinds of foot or ankle complaints and their parents were recruited at the orthopedic outpatient clinic and the orthopedic operation department of the Sophia Children's hospital, Rotterdam. The included population consisted of patients that were waiting for surgery, were already treated and came for a clinical control appointment, or were newly admitted to the outpatient clinic. Informed consent was signed by parents of children that participated in this study. Children above the age of 12 years old also signed informed consent.

Measurements

All included patients and their parents were asked to complete the OxAFQ-c three times; the first time at the outpatient clinic or before surgery, the second time two weeks after the first questionnaire, and the third time four to six months after the first questionnaire. Two weeks was considered as sufficient time to assume patients could not remember their answers, but also no change in foot complaints occurred. Four to six months was considered as sufficient time to show improvement of the complaints. The second and third questionnaires were sent by mail to all participants. When no response was received, patients were called for a reminder.

The OxAFQ-c is a questionnaire for children with foot and ankle problems and contains 15 questions in four different domains: physical (6 questions), school&play (4 questions), emotional (4 questions), and footwear (1 question).[130] The questionnaire is available in a child-version and proxy-version. All questions have five answer options, scoring from zero (always) to four (never). Per domain a score can be calculated by dividing the total amount of points by the maximal amount of points in that domain. A high score represents a better outcome.[130]

Reliability

Reliability is defined by the COSMIN panel as 'the degree to which the measurement is free from measurement error' [206], and was analyzed by test-retest reliability and internal consistency. Test-retest reliability was evaluated by comparing the first and second scoring of the questionnaire, assuming no difference between foot and ankle function between these two moments. Patients who already received treatment at the second measurement were excluded from analysis. As it is suggested that questionnaires in younger children are less reliable [130], we additionally analyzed the effect of age on measurement error by excluding children below the age of eight. Internal consistency was used to evaluate if each question in one domain measured the same construct. To do so, correlation between questions in every domain was studied, testing for sufficiently strong relations between the items to assume that they measure the same construct.

Responsiveness

Responsiveness is defined by the COSMIN panel as 'the ability of an instrument to detect change over time in the construct to be measured'.[206] Therefore, all patients that completed the third OxAFQ-c were also asked if foot complaints became worse, better, or stayed the same compared to the first measurement time. Differences in domain outcomes between the first and third OxAFQ-c were compared between the three complaint groups in order to evaluate if the OxAFQ-c was able to detect change over time in those patients that reported a change.

Construct validity

Construct validity is defined by the COSMIN panel as 'the degree to which the scores of a measurement instrument are consistent with hypotheses (regarding internal relationships, relationships with scores of other instruments or differences between relevant groups)'.[206] To test construct validity, seven hypotheses were formulated about the relationship between the OxAFQ-c and two additional questionnaires; the Kidscreen and foot-specific VAS-scores. All questionnaires were completed at baseline.

The Kidscreen is a generic health related quality of life questionnaires, which is validated in the Dutch language.[210] Because the developers have used the 27-item questionnaire for the development of the OxAFQ-c to test construct validity, we chose to use this questionnaire in our validation study. All questions have five answer options, scoring from zero (never) to four (always). According to the questionnaire manual, the domain scores were recalculated in a way that higher scores indicate higher quality of life.

Additionally, four different VAS-scores for foot pain, foot function, foot appearance, and influence of foot complaints on daily life were scored by children and parents. These VAS-scores were included to be able to formulate a sufficient amount of hypotheses to test construct validity.[206] In the VAS, zero was equal to absence of pain, perfect function, maximal satisfaction about appearance, and no problems in daily life, ten was equal to maximal pain, no function, no satisfaction about appearance, and always problems in daily life. The seven hypotheses about the relationship between the OxAFQ-c and the additional questionnaires were:

- A higher score in the physical domain of the OxAFQ-c correlates with a higher score in the physical domain of the Kidscreen;
- A higher score in the school&play domain of the OxAFQ-c correlates with a higher score in the peers and social support domain of the Kidscreen;
- A higher score in the emotional domain of the OxAFQ-c correlates with a higher score in the psychological well-being domain of the Kidscreen;
- A higher score in the physical domain of the OxAFQ-c correlates with a lower VAS-score on foot function;
- A higher score in the physical domain of the OxAFQ-c correlates with a lower VAS-score on pain;
- A higher score in the school&play domain of the OxAFQ-c correlates with a lower VAS-score on daily life;
- A higher score in the emotional domain of the OxAFQ-c correlates with a lower VAS-score on appearance;

Statistical analysis

Domain scores of the OxAFQ-c were treated as continuous data. Normal distribution of domain scores and VAS-scores were tested by histograms and Kolmogorov-Smirnov tests. All tests were two-tailed and statistical significance was assumed at $p<0.05$. A missing data-analysis was performed after collection of all questionnaires. Percentage of missing questions were calculated and Little's tests was used to test for missing completely at random (MCAR). The imputation method was determined based on these outcomes. Statistical analyses were performed using IBM SPSS 22.0.

Reliability

Test-retest reliability was analyzed with use of intra-class correlation coefficients (ICC) and Bland-Altman plots per domain of the OxAFQ-c.[211] ICCs for all test-retest analyses were calculated with a two-way random effect model, absolute agreement. ICCs above 0.7 were considered good.[211] Mean scores of the first and second measurement were plotted against the difference between these two measurements to obtain Bland-Altman plots.[212] Systematic and random measurement error were assessed with use of respectively the mean difference and limits of agreement. Limits of agreement were calculated as the mean difference plus or minus 1.96x the standard deviation of the mean difference. Because we expected no changes in foot and ankle complaints between the two measurements, the mean difference should be close to zero combined with a small interval between the limits of agreement.[212]

Internal consistency per domain was tested with Cronbach's alfa.[213] Cronbach's alpha's between 0.7 and 0.9 were considered good.[211]

Responsiveness

Differences in domain score between the first and third questionnaire were calculated and plotted per complaint group. We expected a difference above zero in the group with improved foot and ankle complaints and no difference of domain score in the group without improvement.

Construct validity

Correlation between the OxAFQ-c, the Kidscreen and VAS-scores was calculated with the Spearman correlation coefficient (r). Values were rated as: r<0.3= low correlation, r=0.3-0.49 = medium correlation, and r>0.50= high correlation.[130]

RESULTS

Translation

Forward and backward translations did not lead to differences in the most crucial words of the questionnaire. The English questionnaire used different verb tenses than the Dutch questionnaire. Therefore, at the consensus meeting we decided to change the verbs to create a more similar meaning of the questions. At the test phase, seven children and their parents completed the questionnaires. They did not report problems in understanding the questionnaire.

Table 1. Patient characteristics

Characteristics	Baseline (SD)	Second questionnaire (SD)	Third Questionnaire (SD)
N of patients	64	41	36
Gender (M / F)	37 / 27	22 / 19	24/12
Age (SD) (in years)	10.8 (3.4)	11.1 (3.0)	11.1 (3.0)
Diagnosis (n of patients)			
Congenital talipes equinovarus	18	11	14
Idiopathic toe-walker	5	1	2
Pes planus / pes planovalgus	5	4	3
Trauma	8	5	4
Tarsal coalition	6	6	1
Pes cavovarus (due to HMSN, CP, sacral Ewing sarcoma)	7	5	4
Toe deformities (hallux valgus, macrodactyly, M. Freiberg)	6	3	5
Tumor or exostoses (lipoma, tarsal bossing, multiple hereditary exostoses)	3	3	1
Other (osteochondritis dissecans talus, idiopathic pain, pes transversus, pes equinus, cleft foot)	6	3	2
	Mean domain scores at baseline (range)	**Mean domain scores 2nd questionnaire (range)**	**Mean domain scores 3rd questionnaire (range)**
OxAFQ – Child			
Physical	52.2 (0-100)	43.1 (0-100)	52.3 (0-100)
School & Play	76.7 (0-100)	61.3 (0-100)	71.2 (12.5-100)
Emotional	78.5 (31.3-100)	74.1 (18.8-100)	74.7 (6.3-100)
Foot wear	58.6 (0-100)	49.4 (0-100)	52.8 (0-100)
OxAFQ – Parent			
Physical	48.0 (0-100)	50.4 (0-100)	55.5 (0-100)
School & Play	70.0 (6.3-100)	69.2 (0-100)	75.4 (31.5-100)
Emotional	74.1 (37.5-100)	74.8 (25-100)	73.4 (0-100)
Foot wear	55.1 (0-100)	60.4 (0-100)	59.0 (0-100)

Validation process

Patient selection

Sixty-four patients and their parents completed the first questionnaire. Twenty-seven girls and 37 boys were included with a mean age of 10.8 (SD = 3.4) and a variety of foot and ankle disorders (Table 1). The second questionnaire was completed by 41 patients and their parents (response rate: 64%). The third questionnaire was completed by 36 patients (response rate: 56%). No differences in age and gender were seen between baseline, the second group (gender: p=0.676; age: p=0.555) and the third group (gender: p=0.595; age: p=0.384).

Missing data

Fifteen questions of the OxAFQ-c (0.7%) were missing in the completed children questionnaires at all three time points, ten questions (0.5%) were missing in the parent questionnaires. Missing data was equally distributed among the questions. Little's test showed that data were MCAR (p=0.801). Together with the small proportion of missing data, we decided to perform single imputation of the domain scores using the expectation maximization algorithm. This type of imputation provides unbiased estimates and improves statistical power of analyses.[214]

Table 2. Mean differences, limits of agreement and ICCs between the first and second questionnaire in children aged 8 years and older.

Children > 7 years (n=24)		Mean difference (SD difference)	Limits of agreement	ICC (95% CI)
Child	Physical	-0.3 (11.3)	-22.4-21.8	0.884 (0.750-0.948)
	School & Play	-2.1 (21.5)	-44.2-40.0	0.579 (0.233-0.794)
	Emotional	1.8 (15.5)	-28.6-32.2	0.714 (0.444-0.865)
	Foot wear	-11.5 (30.4)	-71.1-48.1	0.538 (0.194-0.767)
Parent	Physical	-0.02 (16.0)	-31.4-31.3	0.764 (0.524-0.891)
	School & Play	0.3 (13.5)	-26.2-26.8	0.831 (0.647-0.923)
	Emotional	-1.0 (13.0)	-26.5-24.5	0.797 (0.585-0.907)
	Foot wear	3.1 (20.0)	-36.1-42.3	0.818 (0.626-0.917)

Reliability

The four different domains showed moderate to good ICCs between the first and second questionnaire. However, Bland-Altman plots showed an extensive random variability indicated by vast limits of agreement (Figure 1). Because ten patients already received

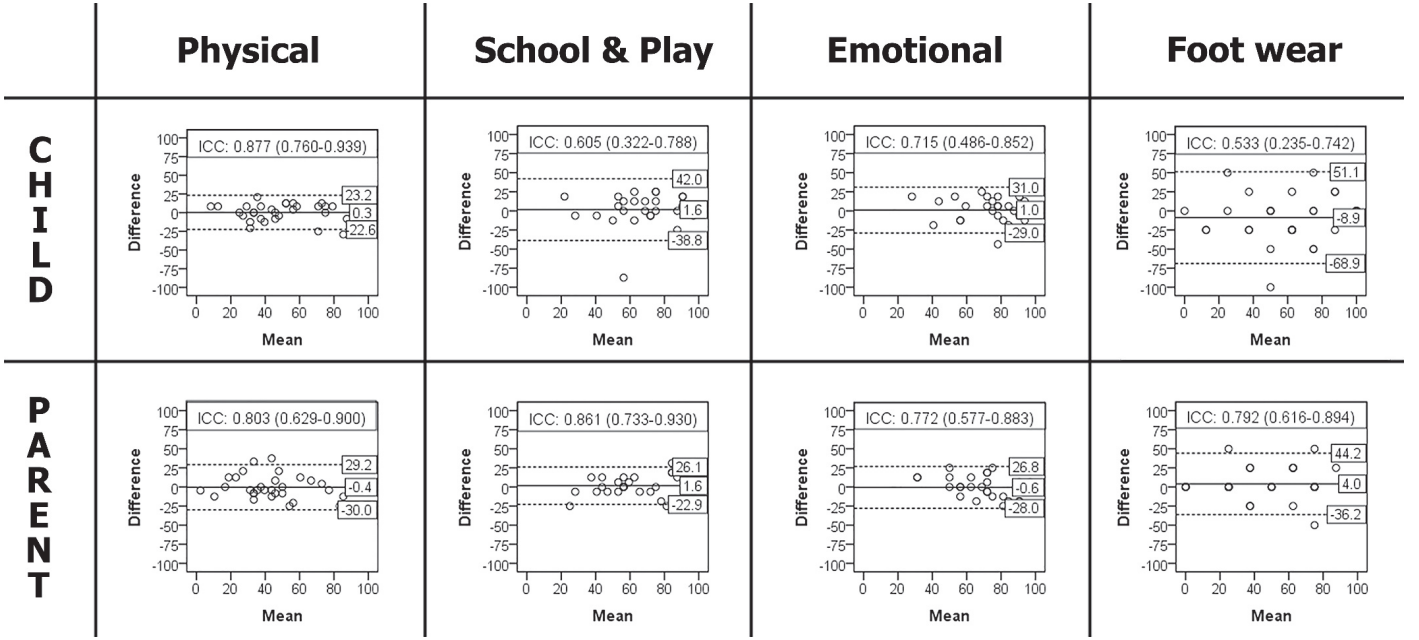

Figure 1. Bland Altman plots and ICCs per domain of the parent and child version of the OxAFQ-c in children between the age of 5 and 17 years.

Solid lines represent mean differences; dotted lines represent limits of agreement.

treatment at the time of the second questionnaire, 31 patients were included in this reliability analysis. Excluding younger patients did not improve the test-retest reliability (Table 2).

Cronbach's alpha of both parent and child versions of the physical and school&play domains were above 0.7 (Table 3). The emotional domain had an alpha lower than 0.7, caused by the question about walking pattern. Exclusion of this question led to an alpha above 0.7 in both versions.

Table 3. Internal consistency between questions per OxAFQ-c domain, evaluated with Cronbach's alpha.

Version		Cronbach's alpha
Child	Physical	0.826
	School & Play	0.858
	Emotional	0.602
	Foot wear	-
Parent	Physical	0.915
	School & Play	0.906
	Emotional	0.671
	Foot wear	-

Values below 0.7 indicate that one or more questions in that domain do not measure the same construct.

Responsiveness

Mean differences of the group that experienced improvement of foot and ankle complaints were above zero in all domains (Figure 2), indicating that domain scores increased between the first and third questionnaire. The group that experienced no change in foot and ankle complaints showed in all domains a score around zero and was in all domains lower than the improved group.

Construct validity

Six of the seven hypothesis showed medium to high correlations. All lower VAS-scores were correlated with a higher OxAFQ-c domain score (Table 4). The correlation between the school&play domain of the OxAFQ-c and the peers and social support domain of the Kidscreen showed a non-significant correlation.

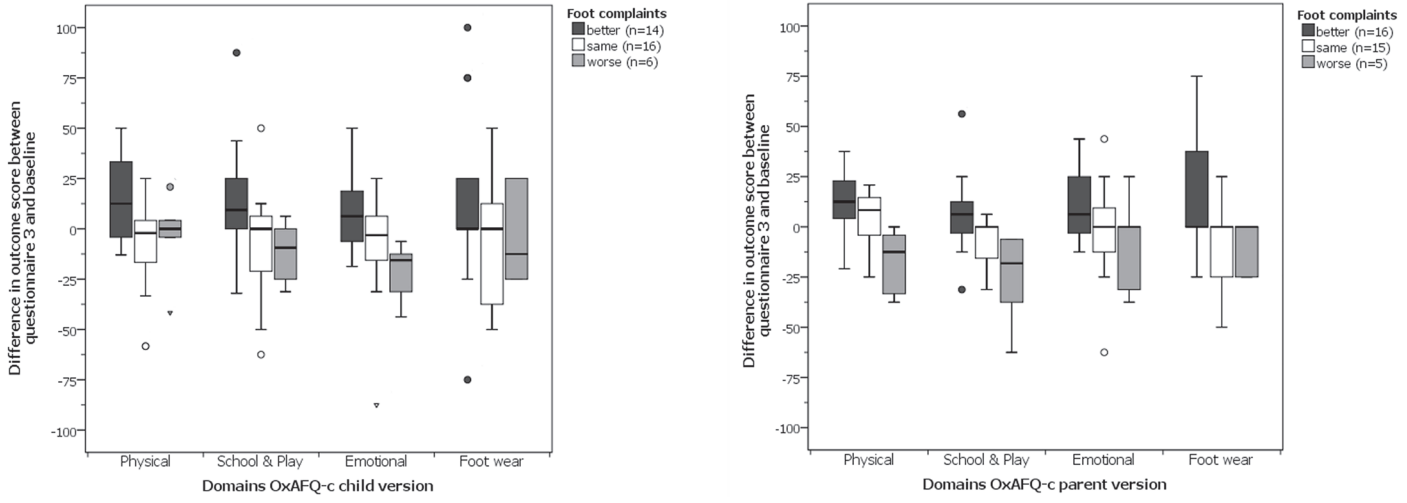

Figure 2. Mean difference between the third questionnaire and the baseline questionnaire in different foot complaints groups per domain of the child version (a) and parent version (b) of the OxAFQ-c.

Table 4. Spearman's correlation of the seven pre-formulated hypotheses regarding the relationships between domain scores of the OxAFQ-c and the Kidscreen

and VAS-scores.

Version	Hypothesis	Spearman correlation coefficient	P-value	Hypothesis confirmed
Child	A higher score in the physical domain of the OxAFQ correlates with a higher score in the physical domain of the Kidscreen.	0.578	<0.001	√
	A higher score in the emotional domain of the OxAFQ correlates with a higher score in the psychological well-being domain of the Kidscreen.	0.381	0.002	√
	A higher score in the school and play domain of the OxAFQ correlates with a higher score in the peers and social support domain of the Kidscreen.	-0.025	0.846	
	A higher score in the physical domain of the OxAFQ-c correlates with a lower VAS-score on foot function.	-0.526	<0.001	√
	A higher score in the physical domain of the OxAFQ-c correlates with a lower VAS-score on pain.	-0.596	<0.001	√
	A higher score in the school and play domain of the OxAFQ-c correlates with a lower VAS-score on daily life	-0.382	<0.001	√
	A higher score in the emotional domain of the OxAFQ-c correlates with a lower VAS-score on appearance	-0.375	0.002	√
Parent	A higher score in the physical domain of the OxAFQ correlates with a higher score in the physical domain of the Kidscreen.	0.543	<0.001	√
	A higher score in the emotional domain of the OxAFQ correlates with a higher score in the psychological well-being domain of the Kidscreen.	0.390	0.001	√
	A higher score in the school and play domain of the OxAFQ correlates with a higher score in the peers and social support domain of the Kidscreen.	-0.041	0.747	
	A higher score in the physical domain of the OxAFQ-c correlates with a lower VAS-score on foot function.	-0.558	<0.001	√
	A higher score in the physical domain of the OxAFQ-c correlates with a lower VAS-score on pain.	0.667	<0.001	√
	A higher score in the school and play domain of the OxAFQ-c correlates with a lower VAS-score on daily life	-0.614	0.002	√
	A higher score in the emotional domain of the OxAFQ-c correlates with a lower VAS-score on appearance	-0.484	<0.001	√

DISCUSSION

To develop a Dutch questionnaire for children with foot and ankle complaints, we translated the English OxAFQ-c into the Dutch language and validated this new questionnaire. To validate the questionnaire, we tested reliability, responsiveness, and construct validity. Test-retest reliability was assessed by comparing the baseline OxAFQ-c with the OxAFQ-c completed after two weeks. Outcomes showed ICC's above 0.7, indicating a good test-retest reliability. When comparing baseline outcomes of the OxAFQ-c with outcomes after 4-6 months, we found a clear difference in outcomes in patients that reported improvement and patients that reported no difference in foot or ankle complaints, indicating responsiveness to change of the questionnaire. Construct validity was assessed by testing seven hypotheses regarding the relationships between the OxAFQ-c and other questionnaires, showing a significant correlation in six of the seven hypotheses. Altogether, measurement properties of the Dutch version of the OxAFQ-c were moderate to good and we therefore concluded that the questionnaire is useful for evaluation of foot and ankle problems in pediatric patient groups.

The Dutch translation showed good test-retest reliability, reflected by ICC's above 0.7 in most domains. However, analysis with Bland-Altman plots showed vast limits of agreement, indicating that domain scores can differ more than 25 points in one patient, without changes in foot and ankle complaints. This suggests that the questionnaire will not be very sensitive or even incapable of evaluating improvement of foot and ankle complaints in individual patients, since changes up to around 25 points may be attributed to change.[212] This finding is not new, although it was never specifically underlined. For example, the Danish translation of the OxAFQ-c showed comparable results, with limits of agreement as large as -1.69 to 1.99 on a scale of -4 to 4.[207] Unfortunately, comparison with the results from the original developers is not possible, because they did not report Bland-Altman plots or Smallest Detectable Changes (SDC).[130] Nevertheless, the good ICCs, absence of systematic errors, and the mean differences around zero in the Dutch questionnaire suggest that the questionnaire is useful for evaluation of foot and ankle complaints in pediatric patient groups. Notably, practical application of the Dutch OxAFQ-c in its current form is limited to the assessment of general function or treatment outcomes at the population level. Its use at the individual patient level is hampered by the wide limits of agreement, which might therefore introduce measurement error. This is likely true of a myriad of patient-reported outcome measures.

Internal consistency showed three alpha's outside the proposed interval of 0.7 to 0.9. In the emotional domain an alpha below 0.7 was observed, caused by the question

about walking pattern. Exclusion of this question resulted in an alpha above 0.7, which might indicate that this question does not measure the same construct as the rest of the questions in this domain. The physical and school&play domain of the parent version had both an alpha slightly above 0.9, indicating that questions in the specific domains are very related and may not have an additional contribution to the domain score. Because other translations studies did not show comparable results in their populations [207,208] and higher alpha's up to 0.95 are also accepted in literature [215], we did not remove these questions.

Evaluation of responsiveness showed that the group with improvement of their foot and ankle complaints, as measured with a single question about improvement, had higher domain scores in the third measurement compared to the group that reported similar foot and ankle complaints. This indicates that the questionnaire is capable of detecting improvement of the foot and ankle complaints, which is in line with the conclusions of the other translations of the OxAFQ-c.[207,208] Nevertheless, differences between the groups were small and should be interpreted with caution since reliability analysis showed that large differences in domain scores in individual patients may occur without changes in complaints.

The Dutch version of the OxAFQ-c is a comprehensible questionnaire, also for young children. Exclusion of children below the age of eight did not result in better reliability. Furthermore, only small differences in domain scores between parents and children were observed, which suggests that children understand the questionnaire. Although the direction and magnitude of the relationship between the domain scores of children and their parents is unknown, Ardon et al. showed in congenital hand differences that mean group scores of parents and children did not differ a lot, which is similar to our results.[216]

To reduce the burden to participate in the study, administration of the questionnaires took place in both the hospital and at home, which may have influenced the outcomes. The first questionnaire was often completed in the hospital, where focusing on the foot or ankle problem during the visit could have led to a systematical lower score on the OxAFQ-c. The second and third questionnaire were completed at home, without the additional focus on the foot or ankle problem, leading to a possible higher outcome. Despite this potential effect, mean differences between the first and second questionnaire were two-sided, showing both positive and negative differences in different domains. This indicates no consistent pattern in reporting higher or lower scores at a specific administration moment.

Unfortunately, during the study we experienced a lower response rate than anticipated, which resulted in a smaller sample sizes at the second and third measurement moment than expected. Furthermore, sample size of the second measurement was decreased due to the fact that some patients received treatment within two weeks after the first questionnaire.

Nevertheless, the results of the test-retest analysis show that comparing outcomes of individual patients might introduce measurement error. Inclusion of more patients would not have changed the outcomes of the Bland-Altman plots in a way that the questionnaire will be useful for comparing individual patients.

CONCLUSIONS

We translated and validated the first questionnaire for children with foot and ankle problems into the Dutch language. Comparable with previous studies, analysis of test-retest reliability indicates that the OxAFQ-c is not very sensitive to observe changes in individual patients and therefore should carefully be used in individual children with foot and ankle problems. Nevertheless, we think the OxAFQ-c has sufficient measurement properties to compare outcomes or identify foot and ankle problems in pediatric patient groups, allowing evaluation of patient's perspective in Dutch pediatric foot and ankle care.

Availability of the questionnaire

For more information about the Dutch Oxford Ankle and Foot Questionnaire for children go to: https://innovation.ox.ac.uk/clinical-outcomes/patient-reported-outcome-measures/. For license applications go to: https://process.innovation.ox.ac.uk/.

Acknowledgments

We are grateful to the children and parents who took part in the study and to Monique den Hollander-Ardon and Daphne Zoutendijk who helped us with the translation of the questionnaire. Also we would like to thank the people from Isis Innovation Ltd. for answering all our questions on the translation process and licensing.


8

CHAPTER 9

Quality of life in children with preaxial polydactyly of the foot in comparison to adults, postaxial polydactyly and healthy controls

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In submission

ABSTRACT

The effect of preaxial polydactyly of the foot on health-related quality of life (HR-QoL) has not been investigated in current literature. To improve counseling, we investigated HR-QoL in this patient group.

A patient-control study was performed with children with preaxial polydactyly (n=20), adults with preaxial polydactyly (n=15), children with postaxial polydactyly (n=15), and healthy controls (n=62). The primary outcome was the difference in foot-specific quality of life (FS-QoL) between children with preaxial polydactyly and adults with preaxial polydactyly, children with postaxial polydactyly, and healthy controls, using the Oxford Ankle and Foot Questionnaire (OxAFQ-c) and five foot-specific visual analogue scales (VAS). The secondary outcome was the difference in general HR-QoL between the groups, using the PedsQL. Outcomes were compared with the Mann-Whitney-U test.

Comparison between children with preaxial polydactyly and healthy peers and postaxial polydactyly showed worse outcomes in all domains of the OxAFQ-c. The VAS score on pain, foot function, daily life, foot appearance, and scar appearance were significantly worse in children with preaxial polydactyly compared to postaxial polydactyly and healthy controls. No difference in VAS was seen between children and adults with preaxial polydactyly. Only the physical domain of the PedsQL showed a lower outcome in children with preaxial polydactyly than in postaxial polydactyly and healthy controls. Children and adults with preaxial polydactyly scored the same in all domains**.**

The FS-QoL and the physical domain of the general QoL questionnaire showed significant worse outcomes in children with preaxial polydactyly compared to healthy peers and postaxial polydactyly. However, large variation was observed in children and adults with preaxial polydactyly, suggesting large differences between patients. In both children and adults, the foot and scar appearance seems to be the biggest problem, while diminished foot function seems less of an issue.

INTRODUCTION

Preaxial polydactyly of the foot is a congenital malformation characterized by an extra hallux. Patients with preaxial polydactyly of the foot are often surgically treated in the first two or three years of their life in order to improve shoe fitting, foot function, and foot appearance.[40,44] Previously, we have studied the effect of surgical treatment on foot function and patient satisfaction in children, which showed a different dynamic function of the foot compared to healthy feet.[217] Despite this different dynamic function, children did not experience a clear function deficit in their daily life after surgery. However, comparison with a healthy control group is not performed and it is unclear if patients with preaxial foot polydactyly experience a lower quality of life than healthy controls. Furthermore, preaxial polydactyly of the foot receives a lot of attention during the first years of a child's life in order to resolve the problems experienced by the malformation. After reaching adulthood, evaluation of perceived problems is often not standardized in current health care and the evolution of problems after the age of 18 years is never studied.

In other congenital malformations, such as club feet, studies show that patients report problems with footwear and have a lower health-related quality of life (HR-QoL) than healthy controls.[141,218] Also in children with less severe foot problems, for example flat feet, foot-specific quality of life (FS-QoL) was significantly lower than FS-QoL in children with neutral feet.[142] On the other hand, in patients with congenital hand malformations no reduction in HR-QoL was observed.[219]

In current health care, HR-QoL is of increasing importance, as it is used to assess patients perspectives in a disease and its treatment.[220] The definition of HR-QoL is the extent to which one's usual or expected physical, emotional, and social well-being are affected by a medical condition or its treatment.[220] Patient-reported outcome measures (PROMs) are widely used in clinical research in order to define HR-QoL and to enhance traditional clinician-centered outcome measures with patient experiences.[201]

The goal of this study is to examine quality of life in preaxial polydactyly patients, children and adults, using different questionnaires for FS-QoL and general HR-QoL. First, the difference in quality of life between healthy children and children with preaxial polydactyly was studied. Additionally, by comparing outcomes of a children and parent group, we evaluate foot problems in preaxial foot polydactyly in different periods of life. Finally, we compare children with preaxial foot polydactyly with children with postaxial polydactyly, to find out the impact of two different forefoot malformation on quality of life.

PATIENTS & METHODS

Patient selection

Before recruitment of participants, the medical ethic committee of the Erasmus Medical Center, Rotterdam, approved the study (MEC-2016-488 / MEC-2015-679). All children aged between 8 and 18 years with preaxial and postaxial polydactyly treated by the Children's Hand Team of the Sophia Children's Hospital were included in our study. The Children's Hand Team is often consulted for children with preaxial and postaxial polydactyly of the foot, because these malformations frequently present together with congenital hand malformations. The team consists of a plastic surgeon specialized in congenital malformations of the hand and fore foot, a rehabilitation physician, and a hand therapist. Information about medical history, operation date, syndrome diagnosis, and other malformations were collected from the hospital database.

For the control group, we recruited healthy children without foot problems between the age of 8 and 18 years old randomly in daily life and at a sport club. Controls were considered healthy if they did not see a doctor on regular basis and never received foot surgery.

We chose to include patients between 8 and 18 years old, because these children are able to understand and complete the questionnaires themselves.[128,129] Furthermore, children in this age become increasingly self-conscious and compare themselves with their peers.[221]

Questionnaires

All participants were asked to complete the Dutch versions of the Oxford Ankle and Foot Questionnaire (OxAFQ-c)[222], five foot-specific visual analogue scales (VAS), and the PedsQL[132]. We used a paper version and a digital version of the questionnaire to collect the data. The questionnaires were completed at home or in the hospital and returned by mail or email. A reminder was send to those participants who did not respond within three to six weeks, to ensure a higher response rate.

The OxAFQ-c is a validated 15-item questionnaire focusing on foot problems with four different domains: physical, school & play, emotional, and footwear. Each question has a 5-point Likert scale from 0 (always) to 4 (never).[146,222] Every domain is reported with a score between 0 and 100. A higher score indicates a better HR-QoL regarding foot function.

Because the OxAFQ-c is a questionnaire to evaluate foot problems specifically in children, the Foot Function Index (FFI) was used in the adult preaxial polydactyly group, which is an adult-focused foot-specific questionnaire.[223] This questionnaire consist of two

domains: Pain and Disability. Every domain is reported with a score between 0 and 100. A lower score indicates a better HR-QoL regarding foot function. Because no questions about emotional experience and footwear were included in the FFI, we decided to use these specific domains of the OxAFQ-c to get a global idea in adults, despite the fact that the questionnaire is not validated for this patient group.

To further specify the foot-problems in the different groups, five foot-specific VAS-scores on pain, function, daily life, appearance, and the scar were also added. A lower score indicates less foot pain, better foot function, less problems in daily life, better appearance of the foot, and a better looking scar.

To evaluate generic HR-QoL, the PedsQL was used, which is a validated questionnaire with 23 questions for children with the age of 2 to 18.[132,147] It contains four different domains: physical health, emotional functioning, social functioning, and school functioning. A specific adult version is also available, even though not yet validated. Each question has a 5-point Likert scale from never (0) to always (4). The total score is recalculated in a linear 0-100 scale, in which a higher score represents a better HR-QoL.

Outcomes

The primary goal of this study was to compare the FS-QoL of children with preaxial polydactyly with their healthy peers, adults with preaxial polydactyly, and children with postaxial polydactyly. Our secondary goal was to compare generic HR-QoL, between children with preaxial polydactyly and their healthy peers, adults with preaxial polydactyly, and children with postaxial polydactyly.

Sample size and statistical analysis

Due to the rarity of preaxial foot polydactyly [17], no sample size was calculated and all patients in the correct age range, willing to participate, were included in the study. Beforehand, we decided to include approximately three times more control patients than children with preaxial polydactyly in order to produce more precise effect measures for the control group.

The outcomes of the OxAFQ-c, VAS-scores, and PedsQL of the preaxial polydactyly patient group were compared with the adult preaxial polydactyly group, the postaxial polydactyly group, and the healthy control group. Because of the small amount of patients in each group, the median and interquartile range (IQR) was reported. The Mann-Whitney U test was used to test significance.

RESULTS

Patient characteristics

Twenty children with a median age of 11 years old (IQR: 9-14.8) were included in the child preaxial polydactyly group (Table 1). Most children were bilaterally affected (14 vs 6). The median follow up time after surgery was 9 years (IQR: 7-13). The median age at surgery and median time after surgery in the postaxial group was comparable with the preaxial group (17 months (IQR: 13-28) vs 17.5 months (IQR:12.3-37.5)). In the adult group with preaxial polydactyly, the median age at foot surgery was little higher (22.5 months (IQR 10.8-50.8)). The follow-up time was 28.5 years (IQR: 19.8-43.5) in this group. In the control group, 62 participants were included, with a median age of 12.5 (IQR:10-14).

Table 1. Patient characteristics

	Children preaxial polydactyly (8-18y)	**Controls (8-18y)**	**Adults preaxial polydactyly (>18y)**	**Children postaxial polydactyly (8-18y)**
N of patients	20	62	15	15
Gender *(m/f)*	5 / 15	28 / 34	5 / 10	11 / 4
Age *(years; median, (IQR))*	11 (9-14.8)	12.5 (10-14)	36 (25-46)	12 (10-13)
Affected side *(uni / bilateral)*	6 / 14	-	3 / 12	5 / 10
Age at foot surgery *(months)*	17 (13-28)	-	22.5 (10.8-50.8)	17.5 (12.3-37.5)
Follow up time after surgery *(years; median, (IQR))*	9 (7-13)	-	28.5 (19.8-43.5)	9 (7.8-12.3)

Missing data

Limited amount of missing data was observed in our study, due to the use of digital questionnaires with mandatory answer options in a lot of participants. The OxAFQ was completed by all participants in all groups, without missing data. In the child preaxial polydactyly group, two children did not complete the emotional domain of the PedsQL. In the adult group one participant did not complete the PedsQL. All children with postaxial polydactyly and all healthy controls completed the PedsQL. All VAS scores were completed in the affected feet in the different polydactyly groups and in all feet in the control group. The VAS about the appearance of the scar was not completed, if no scar was present.

Information about the date of surgery was missing in one child in the preaxial polydactyly group and one child in the postaxial polydactyly group. In the adult group, the

age at time of surgery was used, because in most cases no exact date of surgery could be recalled by the participants. Because of the small amount of missing data, we decided to perform a complete case analysis.

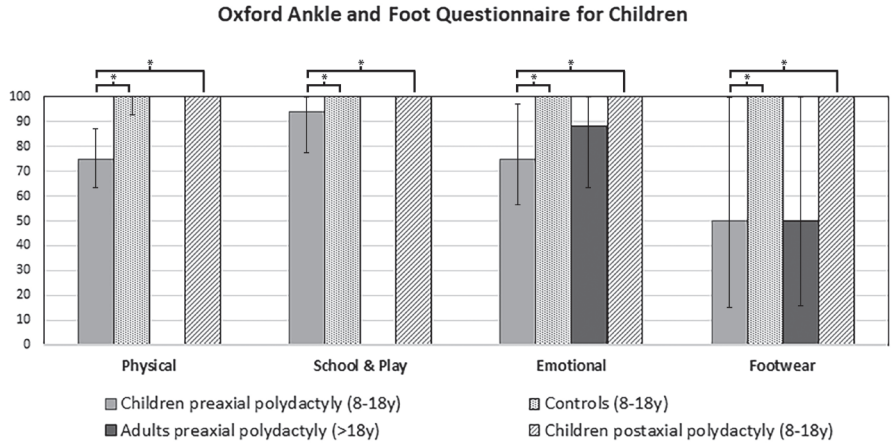

Figure 1. Median outcome scores of the Oxford Ankle and Foot Questionnaire for Children in children and adults with preaxial polydactyly, lateral polydactyly, and healthy peers. ** = p < 0.05 ; error bars represent interquartile ranges.*

Comparison between preaxial polydactyly and healthy peers showed significant differences in physical: p<0.001; school & play: p<0.001; emotional: p<0.001; footwear: p<0.001.

Comparison between preaxial polydactyly and postaxial polydactyly showed significant differences in physical: p<0.001; school & play: p=0.021; emotional: p=0.003; footwear: p=0.013.

Comparison between preaxial polydactyly children and adults showed no significant differences in emotional: p=0.438; footwear: p=0.564.

Foot-specific quality of life

Children with preaxial polydactyly scored significantly lower than patients with postaxial polydactyly and healthy controls, in all four domains of the OxAFQ-c (Figure 1). Adults and children with preaxial polydactyly both scored the same in the emotional (p=0.438) and footwear domain (p=0.564). Adults scored in the FFI, a score of 11 (IQR: 0-21) in the pain domain, and a score of 3 (IQR: 0-6) in the disability domain.

Foot-specific VAS-scores

The VAS score on pain was significantly higher in children with preaxial polydactyly than in patients with postaxial polydactyly and healthy controls, for both the right and the left foot (Figure 2). The same holds for the other VAS scores on foot function, daily life, foot appearance, and the appearance of the scar. No difference in VAS were seen between children with preaxial polydactyly and adults with preaxial polydactyly in all domains.

General health-related quality of life

The physical domain of the PedsQL showed a lower outcome in children with preaxial polydactyly than in children with postaxial polydactyly ($p=<0.001$) and healthy controls ($p<0.001$) (Figure 3). Other domains did not show significant differences between these groups. Also, the total score of the PedsQL was comparable between the groups. No significant differences were observed in all domains of the PedsQL questionnaire between children and adults with preaxial polydactyly**.**

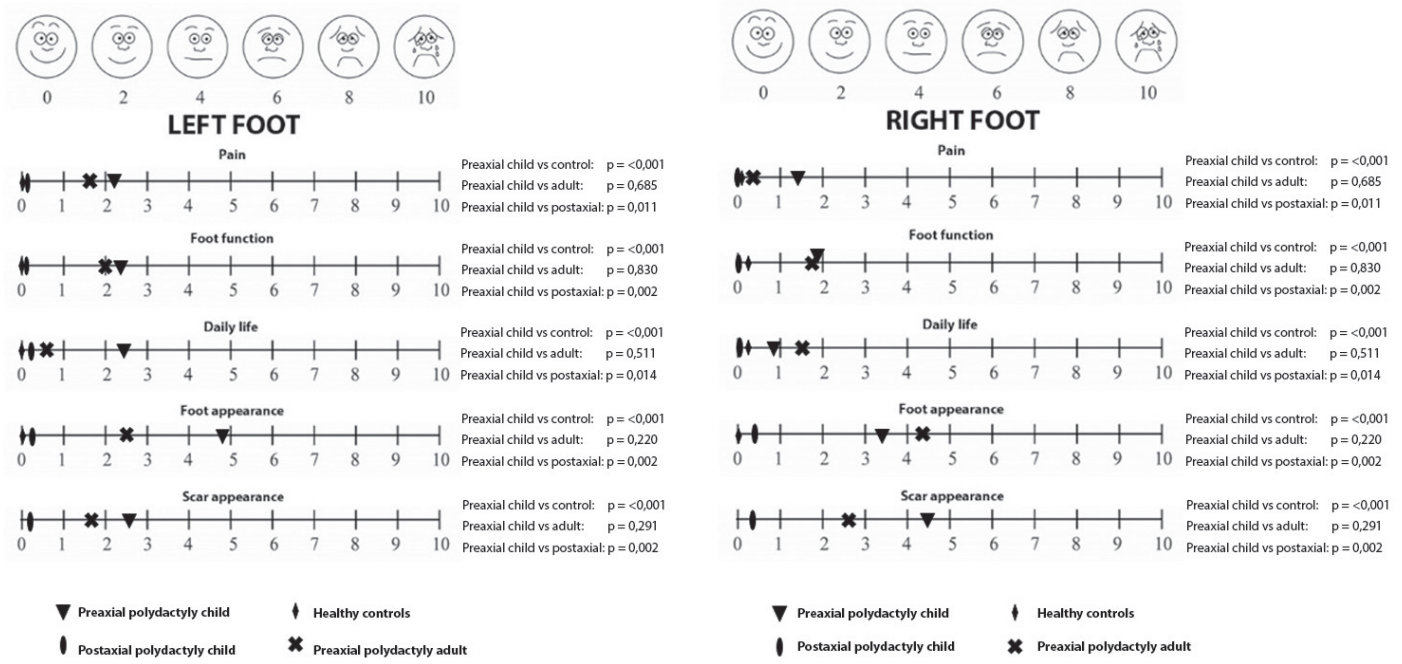

Figure 2. VAS-scores of both feet

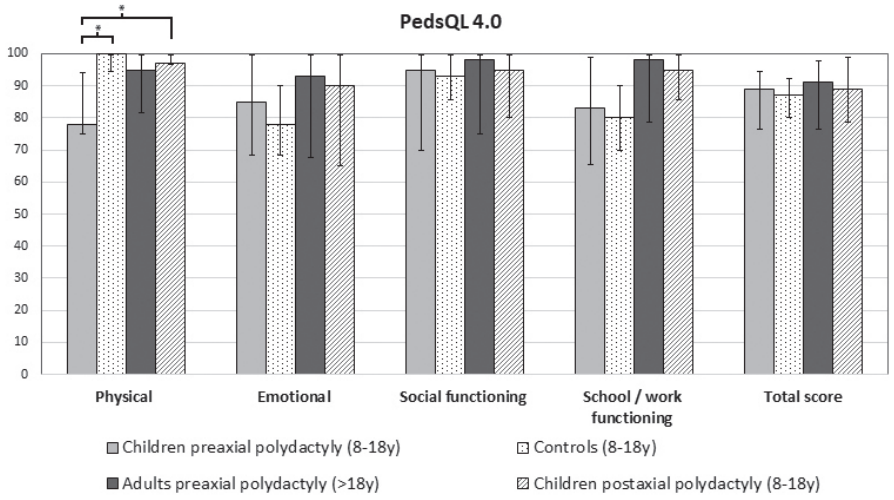

Figure 3. Median outcome scores of the PedsQL 4.0 in children and adults with preaxial polydactyly, lateral polydactyly, and healthy peers. ** = p < 0.05 ; error bars represent interquartile ranges.*

Comparison between preaxial polydactyly and healthy peers showed significant differences in the physical domain p<0.001. The other domains showed no significant differences (emotional: p=0.314; social functioning: p=0.893; school / work functioning: p=0.807; total score: p=0.945).

Comparison between preaxial polydactyly children and adults showed no significant differences in all domains (physical: p=0.083; emotional: p=0.985; social functioning: p=0.823; school / work functioning: p=0.104; total score: p=0.398).

Comparison between preaxial polydactyly and postaxial polydactyly showed significant differences in the physical domain: p<0.001. The other domains showed no significant differences (emotional: p=0.873; social functioning: p=0.780; school / work functioning: p=0.093; total score: p=0.290).

DISCUSSION

In this study, we investigated the HR-QoL in children and adults with preaxial polydactyly of the foot. No difference was seen between children and adults with preaxial polydactyly of the foot in FS-QoL and general HR-QoL. However, results show that children with preaxial polydactyly score lower than healthy children in all four investigated domains of the OxAFQ-c (physical, school&play, emotional, and footwear). Moreover, healthy children score maximal scores in all four domains. Also children with postaxial polydactyly score maximal scores, and thus significantly better than preaxial polydactyly children. Adults and children with preaxial polydactyly score the same in the emotional and footwear domain. In general quality of life, only a significant lower score in the physical domain was observed in children

with preaxial polydactyly than in healthy and postaxial polydactyly children. In all other domains and in the total score, children with preaxial polydactyly score the same compared to healthy children and to children with postaxial polydactyly. Adults and children with preaxial polydactyly score the same in all domains.

With the use of five foot-specific VAS scores we obtained more insights in the type of foot problems occurring in preaxial polydactyly. In both children and adults, the appearance of the foot scored the lowest, while pain and problems in daily life scored the best. This indicates that especially the appearance of the foot is bothering people with preaxial polydactyly and that foot function is less of a problem. However, all VAS scores (pain, function, daily life, appearance, and scar) were significantly worse in children with preaxial polydactyly compared to postaxial polydactyly and healthy feet, showing that children with preaxial polydactyly still experience more problems with all aspects of their feet than healthy peers.

Because the FFI is used for the adult group, comparison with the children group is difficult. In the study of Schneider et al., data of normative patient groups were reported and outcomes were split per age group and gender.[224] This study showed a mean score of 9.7 (3.5-15.9) in women and 5.2 (0.9-9.5) in men in the Pain domain, and a mean score of 10.1 (2.4-17.8) in women and 2.5 (0.1-4.9) in men in the Difficulty domain.[224] Comparing the outcome scores of adults with preaxial polydactyly of the foot with the normative groups indicate no reduced FS-QoL in the adult group.

A large variation in outcome scores of the OxAFQ-c and VAS was observed in the children and adult group with preaxial polydactyly, which suggests large variation between individual subjects. This can be caused by the inclusion of different types of preaxial polydactyly in the children and adult group, showing various malformations of the foot and all receiving personalized treatment. Because of the rarity of preaxial polydactyly of the foot, the inclusion of all these types is inevitable, as otherwise patient groups became too small to draw conclusions. Additionally, information about foot types of the adult population was not available, as patient information is only saved 15 years after the age of 18 in The Netherlands, making classification in different foot types impossible. Lumping the preaxial polydactyly foot types together is giving a first idea about the problems patients experience, but larger patients groups are needed to correlate this with the severity of the malformation.

Comparison of foot-specific HR-QoL of preaxial polydactyly with foot-specific HR-QoL of other foot disorders, such as flatfeet [142], clubfeet [141], and juvenile idiopathic arthritis (JIA)[140], show that preaxial polydactyly has average scores on all OxAFQ-c domains compared to the other disorders. Flat feet show comparable scores in the physical domain and school&play

domain, but show better scores in the emotional domain and the footwear domain.[142] In clubfeet, surgery and the Ponseti method both show better scores in all domains.[141] JIA have the worst outcome scores of all foot problems.[140] Although the outcomes scores in this study were not reported in percentages, distinct lower outcome scores could be observed in the JIA patients compared to preaxial polydactyly.

Quality of life studies have also been performed in other congenital malformations, with various outcomes. For example, in congenital hand malformations, children report similar health-related quality of life as their healthy peers.[219] The number of affected digits, bilaterally involvement of the malformations and age all influence the score of quality of life, but do not all have, as one would expect, a reducing effect. Additionally, in cleft lip patients quality of life is also not necessary lower than in healthy peers.[225-227] Possible reason for the comparable quality of life between cleft patients and healthy peers might be the effective coping strategy of the children, provided by the extensive support system and the available psychological interventions in cleft health care.

The main limitation of this study is the cross-sectional design. Due to this design, children in different ages and at different follow-up times after surgery are included, still growing up and possibly experiencing different problems. Nonetheless, the included children in all study groups have a median age around 11 or 12 and an interquartile range smaller than 5 years, which shows that variation between groups is little. The reason to choose for a cross-sectional design is the lack of a large patient population, due to the rarity of preaxial polydactyly of the foot, with a prevalence of only 0.4 per 10,000 births in the Netherlands. Therefore, it is difficult to obtain larger patient groups without international collaborations. In order to design a prospective study where disease course can be studied with sufficient patient amounts, an international database should be set up.

Altogether, this study is the first that investigated the quality of life in preaxial polydactyly of the foot and showed significant lower foot-specific quality of life in children with preaxial polydactyly of the foot compared to healthy controls and children with postaxial polydactyly. Especially foot and scar appearance experience children with preaxial polydactyly worse than their healthy peers. Overall effect of preaxial polydactyly of the foot on general health-related quality of life appear to be minimal. This information can be useful for physicians that counsel (future) parents about the influence of preaxial polydactyly of the foot on daily life during childhood and in adulthood.

APPENDIX

Appendix 1. VAS-scores of both feet

	Children preaxial polydactyly (8-18y)	**Controls (8-18y)**		**Adults preaxial polydactyly (>18y)**		**Children postaxial polydactyly (8-18y)**	
	Outcome (0-100) *Median (IQR)*	***Outcome (0-100)*** *Median (IQR)*	***p-value***	***Outcome (0-100)*** *Median (IQR)*	***p-value***	***Outcome (0-100)*** *Median (IQR)*	***p-value***
Right							
Pain	14 (2-47)	0 (0-2)	<0.001	3 (1-35)	0.192	0 (0-4)	0.002
Function	19 (1-53)	1 (0-2)	<0.001	19 (3-32)	0.877	0 (0-4)	0.011
Daily life	9 (0-26)	1 (0-3)	0.001	16 (1-51)	0.436	0 (0-3)	0.007
Appearance	34 (25-55)	0 (0-4)	<0.001	43 (9-76)	0.666	3 (0-33)	0.004
Scar	45 (31-65)	-	-	26 (2-53)	0.084	3 (0-21)	<0.001
Left							
Pain	21 (4-41)	0 (0-2)	<0.001	16 (1-46)	0.685	0 (0-4)	0.011
Function	23 (15-32)	0 (0-2)	<0.001	20 (3-35)	0.830	0 (0-2)	0.002
Daily life	24 (6-38)	0 (0-2)	<0.001	6 (1-38)	0.511	1 (0-4)	0.014
Appearance	48 (23-61)	0 (0-2)	<0.001	25 (5-73)	0.220	1 (0-25)	0.002
Scar	26 (17-60)	-	-	17 (3-52)	0.291	1 (0-10)	0.002

CHAPTER 10

General discussion

Preaxial polydactyly of the foot is a congenital malformation characterized by duplication of the hallux.[42,44] The low prevalence of 0.4 per 10,000 births[17] can cause problems in recognition of the accompanied malformations and syndromes, and treatment choices are still based on expert opinion, due to the diverse anatomic presentation. This thesis aimed to provide more clarity about the clinical and genetic presentation of this rare malformation in order to improve the recognition of associated anomalies and syndromes and to facilitate easy communication about different foot types. Furthermore, surgical treatment of preaxial polydactyly of the foot was studied in order to expand the knowledge on treatment strategies and its effects on foot function, aesthetic appearance, and quality of life.

PART 1: GENOTYPE AND PHENOTYPE OF PREAXIAL POLYDACTYLY OF THE FOOT

By describing the phenotypic and genotypic characteristics of our own patient group with preaxial foot polydactyly, in combination with data from genetic databases, we were able to give an overview of the additional anomalies presenting together with preaxial polydactyly of the foot in **Chapter 2**. Our study demonstrated that twenty-one different disease entities were associated with preaxial polydactyly of the foot according to genetic databases, of which nine entities were included in our own population. This finding clearly illustrates the importance of combining genetic databases with clinical practice. With the introduction of genetic databases, such as the human phenotype ontology database, the extensiveness of the description of congenital anomalies, the related syndromes, and genetic mutations increased tremendously.[62] However, while these databases try to provide a complete picture of malformations and disorders, they do not give a realistic picture of the number of anomalies and syndromes seen in clinical practice. Therefore, the combination of genetic databases and observations in large patient populations would be better to manage expectations about probabilities of rare anomalies and disorders in clinical practice.[63]

Unfortunately, also in our study, it is impossible to compose prevalence or incidence numbers when birth numbers are unknown. For example, our study is performed in a specialized center for congenital limb malformations, where referral is possibly dependent on severity of the malformation. This could have given an overestimation of the amount of certain disease entities. Therefore, large population studies are still needed to give exact prevalence numbers of different disease entities in congenital anomalies. Ultimately, combining prevalence numbers with genetic databases will present the best overview of congenital malformations in clinical practice.

The presence of a malformation does not immediately lead to the diagnosis of a specific disease or syndrome. Seventeen percent of the included patients with preaxial polydactyly

of the foot had multiple malformations, but no disease or syndrome could be diagnosed after regular genetic testing. Moreover, in patients with isolated preaxial polydactyly of the foot, with or without polydactyly of the hand, no specific gene mutation could be found in 26%. With the recent development of next-generation genome sequencing (NGS) and the declining costs of this technique (<€2500), a big step is made in the world of genetic testing and confirmation of rare diseases.[228,229] NGS is used to perform large-scale genomic analyses and in the last ten years it also became increasingly useful as diagnostic tool in clinical practice in patients with rare or atypical presentations of diseases.[230,231] Disadvantages of NGS also exist, such as the identification of many possible disease-causing variants without clinical meaning and the large amount of data obtained from NGS giving rise to misinterpretation. Because identification of a causative gene mutation is easier using data of other patients or family members with similar malformations, the search for disease-causing mutations will be more successful in patients with several malformations or several affected family members. In isolated preaxial polydactyly of the foot, searching for disease-causing mutations using NGS is more difficult and the additional value debatable.[230,232]

In our population of preaxial polydactyly patients, 36% of the patients presented with a mutation in the GLI-Kruppel family member 3 (*GLI3*) gene. DNA variants in this gene are known to cause different polydactyly related syndromes, such as Pallister Hall and Greig. The presentation of these syndromes is different and the phenotypes within the different syndromes are highly variable. Therefore, some authors suggest that the *GLI3*-syndromes are a spectrum of syndromes, rather than separate entities. In **Chapter 4,** we investigated the phenotype-genotype correlation in *GLI3*-mediated polydactyly syndromes, in order to clarify the function of *GLI3* in the development of polydactyly of the hand and foot. Earlier studies on the phenotype-genotype correlation in *GLI3* used definitions of the syndromes Greig and Pallister Hall to classify patients, rather than objective phenotypes.[30,81] This has led to the problem that many patients did not fulfill the exact syndrome diagnosis, leading to various definitions and terms, such as sub-Greig and sub-Pallister Hall. By using the specific hand, foot, and craniofacial malformations, instead of the syndrome diagnosis, we tried to prevent misclassification of patients. Strictly classifying the objective phenotypes presented in *GLI3*-mediated polydactyly syndromes, enabled us to identify two different phenotypes based on the type and location of the mutation: (1) anterior anomalies (preaxial polydactyly of the hand and foot), and (2) posterior anomalies (postaxial polydactyly of the hand and foot).

The outcomes of this study support the importance of classifying congenital limb anomalies, as it can be a first step in understanding the genetic background and etiology of these anomalies. In hand anomalies, the OMT-classification of Oberg et al.[34] is

developed, which uses the etiology of the limb anomaly as framework. Whereas the earlier developed Swanson classification mixed the descriptive and etiological categories, the OMT-classification only uses developmental biology to classify the anomalies. It divides the different anomalies in malformations (abnormal formation), deformations (occurs after normal formation), and dysplasia's (abnormality in size, shape, and organization of cells). Our study on *GLI3*-mediated polydactyly syndromes has shown that correct phenotypic description of an anomaly can contribute to expanding the knowledge on the etiology of a limb anomaly. Therefore, classification systems are essential in congenital anomalies. Not only, as often mentioned, to provide easy communication between clinicians and to predict treatment outcomes, but also to further elucidate the underlying genetic substrate behind the congenital anomaly. In order to make an all comprising classification of preaxial polydactyly of the foot possible, we developed a new classification system in **Chapter 3**, the Rotterdam foot classification. The primary objective was to describe the most important characteristics of the malformation, but eventually also with the aim to link phenotypic presentation with genetic findings and to predict treatment outcomes in the future. An always returning question in classification systems for rare congenital malformations is whether it is better to lump or split patient groups based on anatomic variations, because lumping may result in a non-specific description of the malformation without predictive value, while splitting might lead to small groups, which are too small to predict or conclude anything.

Based on this thesis and our former experiences with classification systems, we conclude that predictive classification systems in preaxial polydactyly are unrealistic without international registration of malformations, because patient groups of a single center are too small, even when splitting is minimized. These international databases should be uniform, centrally controlled, and the registration should be part of common practice, instead of merely for scientific purposes. The Rotterdam foot classification can be useful in starting this database, as it enables a uniform description of the foot malformations in preaxial polydactyly. However, the external validity of the classification system is not yet confirmed, because we used this classification system only to describe our own patient population. By performing a literature review on the existing foot types beforehand, we have tried to overcome the problem of unclassifiable feet. Nevertheless, the first step should be to confirm the usability of the Rotterdam foot classification system in other patient populations, before using it as a classification in an international database.

Further development of the Rotterdam foot classification should be towards a more predictive classification. From the Rotterdam hand classification[72], which describes the anomalies in preaxial polydactyly of the hand, we have learned that specific definitions

of categories related to the surgical implications are helpful.[233] For example, which hallux deviation leads to an impaired foot function and which hypoplastic configuration will need difficult surgical techniques? In preaxial polydactyly of the foot, often duplication level is mentioned as an important predictive factor for treatment outcomes by experts. However, in our comparative study between children with preaxial polydactyly of the foot and healthy children, no effect of duplication level was observed between the two groups on foot function and aesthetic appearance (**Chapter 5**). Also in a large multi-centered outcome study on preaxial polydactyly of the hand, no differences were seen in outcome between different duplication types.[234] When comparing treatment outcomes of proximal phalangeal and metatarsal duplication (**Chapter 6**), we did find a small effect of duplication level on outcome, as metatarsal duplication resulted in more re-operations compared to proximal phalangeal duplication. These two studies are a first start in finding predictive characteristics. Nevertheless, as mentioned before, small patient numbers make definite conclusions on the predictive value of anatomic characteristics impossible. Therefore, international collaboration and the setup of databases are needed to further improve classification systems.

Future clinical and research perspectives

- The number of preaxial polydactyly of the foot-related syndromes and diseases is still expanding and the development of next generation sequencing may lead to more known genetic mutations in the human genome that are linked to this congenital malformation. With this technique it might be possible to find genetic mutations, where normal genetic testing did not reveal abnormalities in the genome. The combination of the improvement of genetic testing and descriptive classification systems of polydactyly, might eventually lead to more insights in the signaling pathway and embryology of polydactyly.
- The development of the new Rotterdam foot classification is the first step towards a specific classification system for preaxial polydactyly of the foot that is more than an anatomic description of the malformation. The next step will be to set up an international database using the Rotterdam foot classification to increase patient numbers in order to further investigate predictive characteristics in preaxial polydactyly of the foot.

PART 2: TREATMENT OF PREAXIAL POLYDACTYLY OF THE FOOT

For decades, excision of one of the extra halluces is the standard surgical procedure in preaxial polydactyly of the foot.[40] Important reasons for surgical treatment are the different

appearance of the foot and the perceived problems with shoe fitting, leading to pressure points and pain. In the current literature, no other functional shortcomings are described in patients that did not receive surgical treatment. However, only a few untreated patients are described and also our own patient population contain only a small number of untreated patients.[40,44] Because most patients are treated during childhood and non-surgical conservative treatment is almost never advised, it is difficult to answer the question whether or not surgery is the best treatment for preaxial polydactyly of the foot. Additionally, it is likely that untreated patients without any foot problems will never visit a doctor, because they do not experience problems with the extra hallux.

In order to study the effects of surgical treatment on biomechanical, functional, and aesthetic outcome in preaxial polydactyly of the foot, we compared surgically treated patients with healthy controls in **Chapter 5** and we compared lateral hallux excision with medial hallux excision in **Chapter 6.** Both studies show that patients experience only few problems with their feet on functional and aesthetic level, while biomechanical function differed between surgically treated feet and healthy feet, and between lateral and medial hallux excision. The exact reason for this change cannot be identified based on the results of both studies, due to the small numbers of patients and the execution of only static measurements to map the structure of the feet, instead of measurement of foot structure during walking. In both studies, several suggestions for the different pressure loading results are mentioned, such as the effect of the medial hallux deviation, a more proximal position of the first metatarsal phalangeal joint, a shorter hallux, the inability of independent movement of the hallux due to syndactyly, or even psychological factors. In **Chapter 5,** no correlation was found between medial hallux deviation and peak pressures in the hallux or first metatarsal regions. Nevertheless, in **Chapter 6** we found higher peak pressures under the hallux and lower peak pressures under the first metatarsal in feet with a larger medial hallux deviation (the lateral excision groups). Possibly this is because the hallux can be used as support point in feet with a larger medial hallux deviation. The other suggested causes may also have an effect on the ability to use the hallux as support point. Therefore, it can be suggested that the better the pressure can be transferred towards the hallux during propulsion, the higher the peak pressure under the hallux will be.

Gait analyses using a three-dimensional dynamic foot model would contribute to the understanding of the effect of different first ray anatomy on pressure loading. A dynamic foot model is able to recognize the position and movement of joints and foot structures during walking.[235] For example, in a study that investigated the foot dynamics after first metatarsophalangeal arthrodesis, a difference in forefoot and hindfoot dynamics between

patients with an arthrodesis and healthy controls was found, in combination with a similar foot loading pattern as we found in our patient group.[236] A difficulty in the use of a three-dimensional gait model in children might be the relatively difficult placement of markers on the hallux due to foot size, resulting in less reliable outcomes. However, these kinds of problems were not described by others while using such models in children.[237,238]

The choice of which hallux should be removed, is often easy, because one of the halluces is underdeveloped. However, in some feet, maturation of both the lateral and medial hallux is comparable or the preservation of the best developed hallux needs an extensive correction of the preserved hallux, leading to a more difficult choice. Due to the rarity of preaxial polydactyly of the foot, no treatment guidelines exist, and the diverse presentation of the malformation results often in an individual treatment plan for every patient. Additionally, the amount of surgeries per surgeon is small and operation techniques are altered based on former experiences of the surgeon, leading to different opinions about the best treatment strategies. For example, Masada suggested that lateral excision was the best treatment option in metatarsal duplications, while Venn-Watson advises to excise the medial hallux in all duplication types.[40,41] In our study, we looked at preferred excision side in proximal phalangeal duplication and metatarsal duplication (**Chapter 6**). Both medial and lateral excision have pros and cons and different arguments exist to choose for a specific treatment method. Whether the type of surgery rather than the pre-existent anatomic malformation have the largest influence on the final functional outcome is unclear. In a proportion of patients, several re-operations are performed due to recurrent medial hallux deviation, despite extensive correction of the deviation in the first operation. If this recurrent deviation is due to failure of the operation or due to structural anatomic differences remains indistinct. Furthermore, it is described that block metatarsals are more difficult to treat due to underdevelopment of the first metatarsal which results in altered maturation and reduced length of the first ray, influencing the function of the first ray.[40,44] The differences in anatomic presentation also influence the complexity of the operation techniques. For example, in proximal and distal phalangeal duplication the first metatarsal bone is often not involved in the malformation and the foot arch is not altered during surgery. In metatarsal duplications, the lateral or medial first metatarsal must be excised which affects the strength of the foot arch and thereby possibly influencing the need for special shoes. Ultimately, no strict guidelines could be formulated and several unsolved problems in the treatment of preaxial polydactyly remain after this thesis, which is especially caused by the small patient groups and the cross-sectional character of the performed studies. Nevertheless, a first step is made to study the effects of surgical treatment on a more extensive level. A second step

would be to study this patient group in a prospective manner, to be able to better assess the development of foot complaints over the years in relation to pre-operative foot type and treatment strategy.

Future clinical and research perspectives

- We made a first step to further elucidate the effect of surgery on dynamic foot function with the use of plantar pressure measurements. In the future, the use of three-dimensional gait models of the foot might be useful to explain the different foot loading patterns during walking in children surgically treated for preaxial polydactyly of the foot.
- We studied the largest available single-centered patient population, but still experienced difficulties with inclusion of patients, leading to underpowered studies. To improve the quality of data about treatment outcomes in preaxial polydactyly of the foot it is recommended to start international collaborations in order to increase the number of patients that can be included. A first step can be the inclusion of thorough descriptions of patients and their malformations (using the Rotterdam classification) and the used treatments.
- A prospective study is necessary to corroborate the causal relationships between preoperative foot anatomy and postoperative results, and between foot characteristics and dynamic foot loading. At the moment, only descriptive cross-sectional retrospective studies are performed in children with preaxial polydactyly. Prospective data and follow-up of patients will lead to more reliable data about treatment outcomes and the effects of different determinants. Nevertheless, unless we are able to include enough patients, the additional value of a prospective study is marginal.

PART 3: QUALITY OF LIFE IN PREAXIAL POLYDACTYLY

In the last part of this thesis, we studied the quality of life in patients with preaxial polydactyly of the foot. In current health care, patient perspectives on their health and quality of life are of increasing importance. Clinicians are rated by the patient judgement and health costs are not only reimbursed based on clinical outcomes, but also on patient experiences. To measure patient perspectives, the development of measurement instruments increased enormously in the last 30 years, leading to an immense amount of patients questionnaires measuring quality of life. The proliferation of patient questionnaires resulted in more than one questionnaire for the same disorder or patient group, all promoting their superiority.

Consequently, investigators choose different questionnaires to answer the same questions and the comparability of study outcomes diminished. In order to resolve this problem, the International Consortium for Health Outcomes Measurements (ICHOM) was founded in 2012 to standardize measurements and reports of patient outcomes.[239] With standard sets of questions for specific conditions, they hope to overcome the problem of incomparability between study results and try to stimulate an uniform approach in disorders and patient groups. At the moment, no standard set for (congenital) foot/lower limb conditions exist and development of such a set by ICHOM would be a good next step to improve the evaluation of quality of life in patients with congenital foot malformations.

We used the Dutch version of the OxAFQ-c to study quality of life in patients with preaxial polydactyly of the foot to shed more light on the problems these patients experience using their feet (**Chapter 9**). From this study it became clear that these patients especially experienced problems with shoe fitting and the appearance of their feet and to a lesser extent with function of the foot or participation in daily life. In the OxAFQ-c, only one question focusses on footwear and no elucidating questions about foot appearance are included, which made it hard to determine the reason for the complaints about foot appearance in these children. Is the scar the problem, the size of the hallux, or something else? Where research in congenital hand malformations is suffering from an overload of patient questionnaires, congenital foot malformations might suffer from the lack of patient questionnaires, leading to the use of general questionnaires, resulting in unspecific outcomes. In 2008, the first general questionnaire for children with foot problems was developed, the Oxford Ankle and Foot Questionnaire for Children, and no other general foot questionnaire for children is developed ever since.[146] Only two foot disorder-specific child questionnaires for club feet and juvenile idiopathic arthritis exist.[240,241] Looking at our questionnaire outcomes in preaxial polydactyly, we think it is useful to develop a new sub-part of the OxAFQ-c questionnaire, which focuses more on the specific problems of congenital foot malformations, in order to clarify the specific problems experienced in this patient group. This should not be a complete new questionnaire but can be internalized within the existing OxAFQ-c in order to reduce the developmental effort and to overcome the problem of 'another' questionnaire in the already existing spectrum of foot questionnaires.

Future clinical and research perspectives

- To stimulate international collaboration on congenital foot malformations and to improve the quality and comparability of the gathered data on patient-reported outcome, it is recommended to produce a standard set of measures to evaluate outcome in congenital foot malformations. Using the approach and network of ICHOM, this standardized set can easily be developed in an efficient manner with inclusion of the opinions of patients and clinical experts. The usage of a standardized set for congenital foot malformations will improve health care quality, support informed decision-making, and eventually reduce health care costs.
- In order to provide more detailed and specific information on patient perspectives in different congenital foot malformations, one specific sub-questionnaire for congenital foot malformations should be developed, that includes specific difficulties that patients with different congenital foot malformations experience. Of course, the psychometric properties, such as reliability, responsiveness, and validity should be tested in a larger population to confirm the usefulness of the questionnaire.

CONCLUSION

This thesis studied the genetic background, the presentation, and treatment options of preaxial polydactyly of the foot in order to improve our understanding of this rare and complex condition and to give better guidance to clinicians treating this condition. Classification of patients with preaxial polydactyly was performed, showing that preaxial polydactyly of the foot is a diverse malformation with more than 14 different foot types and 21 disease entities. Because of the large variety of presentation, classification of preaxial polydactyly of the foot is a first helpful step towards more insights in the etiology of this anomaly and might contribute to the development of treatment guidelines. How classification of preaxial polydactyly of the foot can guide treatment remains to be investigated. Ideally, classification would lead to clarity concerning the subtype of the malformation and the use of these subgroups in intervention studies could lead to evidence-based treatment recommendations. Nevertheless, as in all congenital anomalies, the diverse presentation and rarity of these anomalies often results in patient-specific surgical interventions based on expert-opinion. We have shown in this thesis that surgical intervention in preaxial polydactyly of the foot often leads to good functional outcomes, despite an altered plantar loading of the foot. Whether lateral hallux excision or medial hallux excision is the better treatment choice, is still unclear, as functional and aesthetic outcomes do not show clear preferences for either one. In the future, international collaborations and the setup of larger

databases with outcomes of surgical interventions in all congenital limb anomalies will likely help improve health care and surgical decision making in congenital limb malformations and specifically in preaxial polydactyly of the foot. Currently, clinicians and surgeons are advised to become familiar with the different presentations of preaxial polydactyly of the foot and the existing treatment options for different foot types, so to provide the patient the best possible counselling and treatment.

CHAPTER 11

Summary

Preaxial polydactyly of the foot is a congenital malformation defined by the duplication of the hallux. This thesis aimed to improve the recognition and description of preaxial polydactyly of the foot and focused on expanding the current knowledge on presentation and the effects of surgical treatment on foot function, aesthetical appearance, and quality of life.

PART 1: GENOTYPE AND PHENOTYPE OF PREAXIAL POLYDACTYLY OF THE FOOT

The first part of this thesis focused on the phenotypic presentation of patients with preaxial polydactyly of the foot, the anatomic variations of their feet, and the link with the genetic background of the different phenotypes.

In rare diseases, a correct description of the malformations is the starting point to understand the disorder. In **Chapter 2** we used the CulaPhen protocol, developed by our group, to give a clear overview of the organ systems that are often affected in patients with preaxial polydactyly of the foot, grouped per corresponding disease entity. This new method showed that 21 disease entities with preaxial polydactyly of the foot are described at the moment and frequently present with hand, foot, and/or craniofacial malformations. In clinical practice, this information gives a first direction to search for other anomalies when a patient with preaxial polydactyly of the foot presents at the outpatient clinic. Furthermore, we formulated clinical guidelines for referral to a clinical geneticist for genetic testing:

1. *Isolated preaxial polydactyly of the foot.*
   The detection rate of gene mutations is very low and therefore referral to a clinical geneticist is not mandatory. When it is familial or when it presents bilateral, detection rate increases and genetic testing can be considered.
2. *Preaxial polydactyly of the foot in combination with other hand and foot malformation.*
   Genetic testing is recommended, in order to verify the presence of genetic mutations and sometimes confirm a syndromic diagnosis.
3. *Preaxial polydactyly of the foot in combination with anomalies in other parts of the body.*
   Genetic testing is recommended, in order to verify the presence of genetic mutations and sometimes confirm a syndromic diagnosis.

We described the anatomic variation of the feet in **Chapter 3**, by developing a new classification system for preaxial polydactyly of the foot. Based on literature review and our own patient population and clinical experience, we developed a new classification system, the Rotterdam foot classification. In this classification system, we included four different

categories that were mentioned by other authors as most important factors in decision-making: duplication level, the presence of a hypoplastic ray, syndactyly, and deviation of the hallux. Classification of our population showed a variety of different foot types, but also showed frequently returning foot types. To verify reliability of the Rotterdam foot classification, we studied intrarater and interrater agreement, which showed moderate to good reliability. Using this new classification system, communication between clinicians may improve and evaluation of treatment results will become more comparable between study groups.

In **Chapter 4**, we focused on a specific group of patients, namely patients with GLI-Kruppel family member 3 (GLI3) -mediated polydactyly syndromes. GLI3 encodes for a zinc finger transcription factor which plays a key role in the sonic hedgehog (SHH) signaling pathway essential in both limb and craniofacial development. Location and type of mutations were correlated with phenotypes of patients from our own patient database and from literature. Using a latent class analysis, two different classes could be distinguished:

1. A posterior phenotype, which presents in 96% of the cases with postaxial polydactyly of the hand and in 69% of the cases with postaxial polydactyly of the foot;
2. An anterior phenotype, which presents with presents in 53% of the cases with preaxial polydactyly of the hand and in 96% of the cases with preaxial polydactyly of the foot.

Combining these results with the existing literature of genetic experiments with GLI3 models, we were able to formulate a new hypothesis on the effects of the different mutations in GLI3: Variants that cause haplo-insufficiency of GLI3 (only one allele is coding for a normal protein instead of both alleles, resulting in a reduction of 50% of gene function leading to an abnormal phenotype) produce anterior anomalies of the hand, whereas variants with abnormal truncation of the activator domain of GLI3 (resulting in overexpression of GLI3-repressor) produce more posterior anomalies.

PART 2: TREATMENT OF PREAXIAL POLYDACTYLY OF THE FOOT

The second part of the thesis studied the effects of surgical treatment of preaxial polydactyly of the foot on foot function, foot appearance, and patient-reported outcomes.

In **Chapter 5**, we studied foot function of children that are surgically treated for preaxial polydactyly of the foot and compared functional and aesthetic outcomes with healthy feet. Using plantar pressure measurements this study contributes to our understanding of pressure loading, as foot structures might change during walking. We showed that patients

had a 54% lower peak pressure underneath the hallux and a 31-33% higher peak pressure underneath the metatarsals. This outcome suggests a diminished use of the hallux and a more lateral pressure loading in patients with preaxial polydactyly of the foot compared to controls. Explanation for this difference could not be found in the medial deviation of the hallux. Other possible reasons for the diminished pressure load underneath the hallux could be a stiffer metatarsal phalangeal joint, a shorter hallux, or a floating position of the hallux, causing different kinematics of the hallux. However, we were unable to identify reasons for the different foot kinematics in our study. Fortunately, the different foot loading patterns in patients with preaxial polydactyly of the foot did not result in low scores on patient-reported outcome questionnaires on foot function and general health-related quality of life.

After the comparison with healthy feet, we studied the outcomes of different types of preaxial polydactyly of the foot and different treatment strategies in **Chapter 6**. The choice for excision of the lateral or medial hallux can be difficult when no clear preference for excision side exist, due to similar development of the lateral and medial hallux or severe deviation of the medial hallux. Therefore, we compared treatment results after lateral or medial excision in proximal phalangeal and metatarsal duplication using biomechanical, functional, and aesthetic outcomes. In proximal phalangeal duplication (duplication Type IV according to the Rotterdam classification), plantar pressure measurements showed a better pressure distribution in the lateral excision group, with a significantly lower peak pressure at the first metatarsal. Aesthetic appearance of lateral and medial excised halluces were judged the same by patients, surgeons, and lay persons. In metatarsal duplication (duplication Type VI according to the Rotterdam classification), pressure distribution did not show significant differences between lateral or medial excision in the hallux and first metatarsal region, but this was probably due to the low number of patients. Lateral excision resulted in a more normal looking foot and hallux judged by surgeons and lay persons, but often resulted in an extensively deviated hallux, frequently opting for revision surgery. Medial excision results in a heavily pronated foot with an unattractive appearance judged by surgeons and lay persons, but without extensive medial deviation of the hallux. Overall, both excision sides in proximal phalangeal and metatarsal duplication types have pros and cons and this study showed that different arguments exist to choose for a specific treatment method.

In **Chapter 7**, we described the long-term outcome of a patient with a special type of preaxial polydactyly of the foot, the mirror foot, and studied the additional deformities frequently presenting with mirror feet. We showed with a literature review that tibial and tarsal malformations are present in many patients with mirror feet. Also our patient had an abnormal talus and several accessory osseous structures at the medial side of his foot.

PART 3: QUALITY OF LIFE IN PREAXIAL POLYDACTYLY OF THE FOOT

In the third part of this thesis, we focused on the development of a Dutch questionnaire for children with foot problems and used this questionnaire to further elucidate the complaints and experiences of children with preaxial polydactyly of the foot.

In **Chapter 8**, we translated and validated the English version of the Oxford Ankle and Foot Questionnaire for Children (OxAFQ-c) into the Dutch language. This questionnaire consists of a child and parent version and measures foot function in four different domains: Physical, School & Play, Emotional, and Footwear. After forward and backward translation, comprehensibility of both the child and parent version was tested in seven children and their parents. Afterwards, sixty-four patients were included to test validity and reliability. Test-retest reliability showed moderate to good intra-class correlation coefficients in every domain, ranging from 0.533 to 0.877. However, Bland-Altman plots showed wide limits of agreement, meaning a large random variability in outcomes of individual patients. Therefore, it is recommended to use this questionnaire only in patient groups and not in individual patients. Analysis of responsiveness showed that the questionnaire is capable of detecting improvement of foot and ankle complaints, but also only in groups of patients. By developing this questionnaire, we hope that the evaluation of pediatric foot problems in general will improve in The Netherlands, as it enables clinicians to include patient experiences in the analysis of treatment outcomes.

The Dutch version of the OxAFQ-c was used to evaluate quality of life in children with preaxial polydactyly compared to lateral polydactyly and healthy controls in **Chapter 9**. Children with preaxial polydactyly scored significantly lower than children with postaxial polydactyly and healthy controls, in all four domains of the OxAFQ-c, and significantly lower in the physical domain of the PedsQL. Adults and children with preaxial polydactyly both scored the same in the emotional and footwear domain of the OxAFQ-c and no significant differences were observed between children and adults with preaxial polydactyly of the foot. These outcomes illustrate that children with preaxial polydactyly of the foot have a lower quality of life than healthy children and children with a less severe foot malformation (postaxial polydactyly). Moreover, the malformation influences (foot) functioning in daily life, not only in childhood, but during their entire life.

CHAPTER 12

Nederlandse samenvatting

Preaxiale polydactylie van de voet is een aangeboren voetafwijking, waarbij er sprake is van een verdubbeling van de grote teen, de hallux. Dit proefschrift heeft als doel om de herkenning en beschrijving van preaxiale polydactylie van de voet te verbeteren en de kennis over de effecten van de chirurgische behandeling op voetfunctie, uiterlijk van de voet en kwaliteit van leven te vergroten..

DEEL 1: GENOTYPE EN FENOTYPE VAN PREAXIALE POLYDACTYLIE VAN DE VOET

Het eerste deel van dit proefschrift richt zich op de fenotypische presentatie van patiënten met preaxiale polydactylie, de anatomische variaties van de voeten en de genetische achtergrond van de verschillende fenotypes.

Bij zeldzame ziektes is een correcte beschrijving van de afwijking een startpunt om de ziekte beter te begrijpen. Om herkenning van de afwijking te verbeteren, hebben we in **Hoofdstuk 2** een overzicht gegeven van de afwijkingen die samen met preaxiale polydactylie voorkomen. Dit overzicht laat zien dat er 21 aandoeningen voorkomen die zich presenteren met preaxiale polydactylie van de voet. Deze aandoeningen presenteren zich vaak samen met andere hand-, voet- en/of aangezichtsafwijkingen. In de klinische praktijk zorgt dit onderzoek voor meer duidelijkheid over de manier waarop patiënten met preaxiale polydactylie zich kunnen presenteren in het ziekenhuis. Daarnaast hebben we ook klinische richtlijnen geformuleerd wanneer kinderen met preaxiale polydactylie genetisch zouden moeten worden onderzocht:

1. *Geïsoleerde preaxiale polydactylie van de voet.*
   Detectiegraad van gen mutaties is laag en verwijzing naar een klinisch geneticus is niet verplicht. Wanneer de afwijking familiair of bilateraal is, wordt de detectie graad hoger en genetisch testen kan in deze groepen worden overwogen.
2. *Preaxiale polydactylie van de voet in combinatie met een andere hand- of voetafwijkingen.*
   Verwijzing naar een klinisch geneticus is aanbevolen, om genetische afwijkingen en eventueel een syndroom diagnose vast te stellen.
3. *Preaxiale polydactylie van de voet in combinatie met afwijkingen van andere delen van het lichaam.*
   Verwijzing naar een klinisch geneticus is aanbevolen, om genetische afwijkingen en eventueel een syndroom diagnose vast te stellen.

In **Hoofdstuk 3** hebben we de anatomisch variatie van preaxiale polydactylie beschreven, door een nieuw classificatie systeem te ontwikkelen. Met behulp van literatuur onderzoek en onze eigen patiëntenpopulatie, ontwikkelde we een nieuw classificatiesysteem, de Rotterdam voet classificatie. Dit classificatiesysteem bevat 4 verschillende categorieën: duplicatie level, aanwezigheid van een hypoplastische straal, syndactylie en deviatie van de hallux. Om de betrouwbaarheid van de Rotterdam voet classificatie te testen, hebben we de intrarater and interrater agreement onderzocht, die een gemiddelde tot goede betrouwbaarheid liet zien. Door dit nieuwe classificatiesysteem te gebruiken, is het mogelijk om communicatie tussen artsen te verbeteren en behandelresultaten tussen verschillende groepen makkelijker te vergelijken.

In **Hoofdstuk 4** hebben we een specifieke patiënten groep met preaxiale polydactylie onderzocht, namelijk patiënten met het GLI-Kruppel family member 3 (GLI3) gemedieerde polydactylie syndroom. GLI3 is een gen wat codeert voor een 'zinc finger' transcriptie factor dat een grote rol speelt in de 'sonic hedgehoc' (SHH) pathway, essentieel in ontwikkeling van aangezicht en extremiteiten. Locatie en type mutaties worden in dit hoofdstuk gecorreleerd met fenotypes van patiënten, om een verklaring te vinden voor de verschillen tussen patiënten. Van hieruit kunnen twee verschillende groepen worden gedefineerd:

1. Een posterieur fenotype, met in 96% postaxiale polydactylie van de hand en in 69% postaxiale polydactylie van de voet.
2. Een anterieur phenotype, met in 53% preaxiale polydactylie van de hand en in 96% preaxiale polydactylie van de voet.

Door deze resultaten te koppelen aan de bestaande literatuur over experimentele GLI3 modellen werd een nieuwe hypothese geformuleerd over de fenotypische presentatie: varianten die zorgen voor haplo-insufficiëntie van GLI3 resulteren in anterieure afwijkingen, terwijl varianten met een abnormale verkorting van het activatiedomein van GLI3 resulteren in posterieure afwijkingen.

DEEL 2: BEHANDELING VAN PREAXIALE POLYDACTYLIE VAN DE VOET

In het tweede deel van dit proefschrift zijn de effecten van de chirurgische behandeling van preaxiale polydactylie van de voet bekeken. Hierbij is gekeken naar voetfunctie, uiterlijk van de voet en patiënt-gerapporteerde uitkomsten.

De voetfunctie en het voetuiterlijk van kinderen die chirurgisch behandeld zijn voor preaxiale polydactylie werd vergeleken met kinderen met gezonde voeten in **Hoofdstuk 5.** In deze studie hebben we de dynamische voetfunctie onderzocht met behulp van voetdrukmetingen, om zo meer duidelijkheid te krijgen over de drukverdeling tijdens het lopen. Patiënten hadden een 54% lagere piekdruk onder de hallux en een 31-33% hogere piek druk onder de metatarsalia, dan kinderen met een gezonde voet. Deze uitkomsten suggereren dat de hallux minder wordt gebruikt en dat er sprake is van een meer laterale drukverdeling bij patiënten met preaxiale polydactylie van de voet. Een verklaring kon niet worden gevonden in deze studie, maar mogelijke oorzaken zouden een kortere hallux, een stijver metatarsophalangeaal gewricht of een omhoog staande hallux kunnen zijn, die voor een andere beweging van de hallux zorgt. Ondanks deze verschillen in voetdruk tussen patiënten met preaxiale polydactylie en gezonde controles, resulteerde de veranderde voetdruk niet in lage scores in voet-gerelateerde kwaliteit van leven en algemene kwaliteit van leven.

Na de vergelijking met gezonde voeten, hebben we in **Hoofdstuk 6** gekeken naar de behandeluitkomsten per voet type en per behandelstrategie. Bij duplicatie van de proximale falanx (duplicatie type IV volgens de Rotterdam classificatie), liet de drukmeting een betere drukverdeling in de laterale excisie groep zien met een lagere piekdruk onder de eerste metatarsaal. Het uiterlijk van de voet werd door zowel patiënten, chirurgen, als vrijwilligers in beide groepen vergelijkbaar beoordeelt. Bij duplicatie van de metatarsaal (duplicatie Type VI volgens de Rotterdam classificatie), liet de drukverdeling onder de voet geen verschil zien tussen de twee groepen, maar wel was er sprake van een sterk gedevieerde hallux in de laterale excisiegroep, wat resulteerde in meer re-operaties. Het uiterlijk van de voet werd in deze laterale excisiegroep als meer normaal beoordeelt door chirurgen en vrijwilligers, in vergelijking met de mediale excisiegroep. Concluderend kan worden gesteld dat zowel het verwijderen van de mediale, als de laterale hallux voor- en nadelen heeft en dat er verschillende redenen zijn om voor een specifiek behandelmethoden.

In **Hoofdstuk 7** wordt een specifieke preaxiale polydactylie casus beschreven van een patiënt met een 'mirror voet'. Met behulp van een literatuurstudie hebben we aangetoond dat patiënten met een mirror voet vaak ook afwijkingen van de tibia en/of de tarsalia hebben. Ook bij de besproken casus bleek dat er sprake was van een afwijkende talus en verschillende accessoire ossale structuren aan de mediale zijde van de voet.

DEEL 3: KWALITEIT VAN LEVEN IN PREAXIALE POLYDACTYLIE VAN DE VOET

Het derde deel van dit proefschrift focust zich op de ontwikkeling van een Nederlandse vragenlijst voor kinderen met voetproblemen, waarmee we uiteindelijk de kwaliteit van leven in preaxiale polydactylie van de voet hebben onderzocht.

De Engelse versie van de Oxford Ankle and Foot questionnaire for Children (OxAFQ-c) hebben we vertaald en gevalideerd in het Nederlands in **Hoofdstuk 8**. Deze vragenlijst bestaat uit een kind- en ouderversie en bevat vier verschillende domeinen om de voet-gerelateerde kwaliteit van leven vast te stellen: Fysiek, School en Spelen, Emotioneel, Schoeisel. Na een voorwaartse en achterwaartse vertaling werd de validiteit en betrouwbaarheid getest in 64 patiënten. Hieruit kwam naar voren dat de vragenlijst vooral betrouwbaar is voor groepen, maar minder betrouwbaar in individuele patiënten. Met de ontwikkeling van deze vragenlijst hopen we dat de evaluatie van kinderen met voetproblemen wordt verbeterd en dat patiëntervaringen vaker kunnen worden meegenomen in de analyse van behandeluitkomsten.

In **Hoofdstuk 9** hebben we de Nederlandse versie van de OxAFQ-c gebruikt om de kwaliteit van leven te evalueren bij kinderen met preaxiale polydactylie. De uitkomsten hebben we vergeleken met gezonde kinderen en met kinderen met laterale polydactylie van de voet. Tevens hebben we gekeken naar de kwaliteit van leven bij volwassenen met preaxiale polydactylie. Kinderen met preaxiale polydactylie scoorden lager dan gezonde kinderen en kinderen met postaxiale polydactylie in alle vier domeinen van de OxAFQ-c. Ook scoorde ze lager in het fysieke domein van de algemene kwaliteit van leven vragenlijst, de PedsQL. Volwassenen met preaxiale polydactylie scoorden vergelijkbaar met kinderen met preaxiale polydactylie op de domeinen Emotioneel en Schoeisel. In vergelijking met andere volwassenen met voetafwijkingen scoorde ze vergelijkbaar of beter. Uitkomsten van deze studie laten zien dat kinderen met polydactylie een lagere kwaliteit van leven hebben dan gezonde kinderen en dat de voetafwijking het hele leven van invloed kan zijn op het dagelijks functioneren.

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APPENDICES

List of publications

PhD Portfolio

Curriculum Vitae

Dankwoord

List of publications

Lateral versus medial hallux excision in preaxial polydactyly of the foot.
Burger EB, Bus SA, Hovius SER, van Nieuwenhoven CA.
Foot Ankle Int. 2020 Dec;41(12):1553-1562

Variant type and position predict two distinct limb phenotypes in patients with GLI3-mediated polydactyly syndromes.
Burger EB, Baas M, van den Ouweland AMW, Hovius SER, de Klein A, van Nieuwenhoven CA, Galjaard RJH.
J Med Genet. 2021 Jun;58(6):362-368.

Foot Function in Patients With Surgically Treated Preaxial Polydactyly of the Foot Compared With Age- And Sex-Matched Healthy Controls
Burger EB, Lalé SA, Hovius SER, van Nieuwenhoven CA, Bus SA.
Foot Ankle Int. 2019 Apr;40(4):414-421.

The Dutch version of the Oxford Ankle and Foot Questionnaire for Children: Useful for evaluation of pediatric foot problems in groups.
Burger EB, Selles RW, van Nieuwkasteele S, Bessems JHJM, Pollet V, Hovius SER, van Nieuwenhoven CA.
Foot Ankle Surg. 2019 Apr;25(2):204-210.

Controversies in Poland Syndrome: Alternative Diagnoses in Patients With Congenital Pectoral Muscle Deficiency.
Baas M, **Burger EB**, Sneiders D, Galjaard RH, Hovius SER, van Nieuwenhoven CA.
J Hand Surg Am. 2018 Feb;43(2):186.e1-186.e16.

Preaxial polydactyly of the foot - Clinical and genetic implications for the orthopedic practice based on a literature review and 76 patients.
Burger EB, Baas M, Hovius SER, Hoogeboom AJM, van Nieuwenhoven CA.
Acta Orthop. 2018 Feb;89(1):113-118.

Long term follow-up and development of foot complaints in a surgically treated mirror foot – A case report and review of literature.
Lalé SA, **Burger EB**, Bessems JHJM, Pollet V, van Nieuwenhoven CA.
Foot Ankle Surg. 2017 Dec;23(4):e9-e13.

The Rotterdam foot classification. A classification system for medial polydactyly of the foot.
Burger EB, Hovius SER, Burger BJ, van Nieuwenhoven CA.
J Bone Joint Surg Am. 2016 Aug 3;98(15):1298-306.

Netwerkrichtlijn kindermishandeling en huiselijk geweld in Limburg. Aanpak binnen de acute zorgketen.
Burger EB, Hermans BCM, van Zeben-van der Aa DCMB.
Tijdschrift voor Kindergeneeskunde. 2014 Apr;82(2):64-69.

PhD Portfolio

Name PhD student: Elise Bette Burger

Erasmus MC Department: Plastic, Reconstructive, and Hand Surgery

PhD period: 2014 - 2020

Promotor(s): Em. prof. dr. S.E.R. Hovius

Supervisor: dr. C.A. van Nieuwenhoven, dr. S.A. Bus

1. PhD training

	Year	Workload
Courses in methodology and statistics		
NIHES Master of Clinical Epidemiology	2014-2016	70 ECTS
Courses in didactic skills, research integrity, and scientific communication		
BROK course ('Basiscursus Regelgeving Klinisch	2015	1 ECTS
Onderzoek')	2015	10 hours
Presentation workshop	2015	3 hours
Poster workshop	2016	3 ECTS
Biomedical English Writing and Communication	2016	0.3 ECTS
Research Integrity	2016-2017	0.9 ECTS
Didactic skills (deel-BKO)		
- Teach the Teacher Module I	*2016*	*15 hours*
- Giving a lecture	*2017*	*4 hours*
- Individual supervision	*2017*	*3 hours*
- Interaction with difficult groups	*2017*	*4 hours*

(Inter)national conferences and seminars		
Presentations		
NVVH, *oral presentation*	2014	20 hours
MOSA conference, *poster presentation*	2014	20 hours
World Symposium on Congenital Hand malformations, *oral presentation*	2015	20 hours
European Pediatric Orthopedic Symposium, *oral presentation*	2016	20 hours
European Foot and Ankle Symposium, *oral presentation*	2016	20 hours
NVPC najaarsvergadering, *oral presentation (2x)*	2016	40 hours
FESSH, *oral presentation (3x)*	2017	40 hours
European Pediatric Hand Symposium, *oral presentation (4x)*	2017	30 hours
Attendance		
Esser course 'On your nerves'	2014	8 hours
Esser course 'Ins and Outs of Nose Surgery'	2014	8 hours
Esser course 'What's New in Breast Reconstruction'	2014	8 hours
Bi-annual Symposium of the Dutch Society of Plastic Surgery	2014-2017	32 hours
Kortjakje	2015-2018	12 hours
All hands on deck – farewell symposium Steven Hovius	2016	8 hours
The Big Hand Event	2017	8 hours
Esser course 'Oncoplastic breast surgery'	2017	8 hours
Skillslab training		
Microsurgery	2014-2017	250 hours
Local flaps in plastic surgery	2015	4 hours
Tendon repair	2015	4 hours
Basic nerve reconstruction	2016	4 hours
Seminars and workshops		
CPO mini-course	2014	8 hours
Workshop 'Onderhandelen'	2017	3 hours

Grants and funding		
Esser foundation research grant	2014	n.a.
Johanna Kinderfonds research grant (€20.000)	2016	40 hours
Trustfonds travel grant (€150)	2016	10 hours

2. Teaching

	Year	**Workload**
Lecturing		
2nd year medical students course: Anatomy of the hand	2015-2016	4 hours
2nd year anatomy course	2015-2018	30 hours
3rd year anatomy course	2015-2017	20 hours
Skills		
Coach tendon suturing 3rd year medical students	2015	8 hours
Coach international course in microsurgery	2015-2017	40 hours
Coach basic suturing techniques for OR-assistants	2015	8 hours
Supervising medical reviews and Master thesis		
Supervising review 2nd year medical students:		
- Overview of medial polydactyly	2015	10 hours
Supervising review 3rd year medical students:		
- Treatment of Dupuytren's disease	2015	10 hours
- Treatment of pediatric fingertip injuries	2016	10 hours
Master Thesis:		
- Shaktie Lale	2015	60 hours
- Judith 't Hart	2016	60 hours

3. Other activities

	Year	**Workload**
Organizing activities		
10th world symposium on congenital hand	2014-2015	150 hours
All hands on deck – farewell symposium Steven Hovius	2016	200 hours
Board memberships		
Secretary of the resident society Erasmus MC (AAV)	2015-2017	250 hours

Curriculum Vitae

Elise Bette Burger was born on April 2nd, 1988 in Amsterdam, the Netherlands. After graduating from the Petrus Canisius College in 2006, she studied Biomedical Sciences at Utrecht University. In 2010, she graduated for her Bachelor degree and started with the special 4-year medicine track at the University of Maastricht.

After graduating in 2014, she started with her PhD project resulting in this thesis at the Department of Plastic and Reconstructive Surgery and Hand Surgery at the Erasmus MC University Medical Center in Rotterdam (Prof. dr. Steven Hovius). During her PhD research period, Elise Bette also completed the NIHES research master Clinical Epidemiology.

After working as a house officer in the winter of 2017-2018, she was admitted into the plastic surgery training program at the Erasmus MC University Medical Center in Rotterdam (Dr. Teun Luijsterburg). In October 2018, she started with her 2-year general surgerytraining at the Maasstad Hospital in Rotterdam, the Netherlands (Dr. René Klaassen). In November 2020 she returned to the Department of Plastic and Reconstructive Surgery and Hand Surgery to continue her plastic surgery training.