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RAPID COMMUNICATION

TGDS pathogenic variants cause Catel-Manzke syndrome without hyperphalangy

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Abstract

Catel-Manzke syndrome, also known as micrognathia-digital-syndrome, is a rare autosomal recessive disorder characterized by the combination of the two cardinal features Pierre-Robin sequence and bilateral hyperphalangy leading to ulnar clinodactyly (ulnar curvature of the phalanges) and radial deviation (radial angulation at the metacarpophalangeal joint) of the index fingers. Individuals without one of these major hallmarks or with additional hand malformations have been described as atypical or Catel-Manzke-like syndrome. Biallelic *TGDS* pathogenic variants have thus far been detected in eight individuals with typical Catel-Manzke syndrome and in one fetus with additional features. Here we report on two individuals with *TGDS* pathogenic variants who presented with mild radial deviation and ulnar clinodactyly of the index fingers but without radiologic signs of hyperphalangy. Furthermore, both individuals have disproportionate short stature, a feature that has not yet been associated with Catel-Manzke syndrome. Our data broaden the phenotypic spectrum of *TGDS*-associated Catel-Manzke syndrome and expand the indication for diagnostic testing.

KEYWORDS

Catel-Manzke syndrome, hyperphalangy, Manzke dysostosis, Pierre-Robin sequence, short stature, TGDS

1 | INTRODUCTION

Catel-Manzke syndrome, also known as micrognathia-digital-syndrome (MIM:616145), is characterized by the combination of the two cardinal features Pierre-Robin sequence (with or without cleft palate) and bilateral hyperphalangy leading to ulnar clinodactyly (ulnar curvature of the phalanges), radial deviation (radial angulation at the metacarpophalangeal joint), and shortening of the index finger (Catel & Heintzen, 1963). Hyperphalangy (also referred to as Manzke dysostosis) is caused by an accessory ossification center between the proximal phalanx and metacarpal (Manzke, 1966). The supernumerary phalanx coalesces with the proximal phalanx with age. Additional congenital abnormalities comprise congenital heart defects, joint hypermobility, mild facial dysmorphism, pectus deformities, short halluces, and fifth finger clinodactyly (Manzke, Lehmann, Klopocki, & Caliebe, 2008). Pierre-Robin sequence and congenital heart defects can lead to postnatal failure to thrive and cause severe morbidity and an increased mortality. Biallelic pathogenic variants in *TGDS* have been described in nine individuals including one fetus with Catel-Manzke syndrome (Ehmke et al., 2014; Pferdehirt, Jain, Blazo, Lee, & Burrage, 2015; Schoner et al., 2017). Individuals without one of the two major hallmarks or with

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additional hand malformations have been described as atypical or Catel-Manzke-like syndrome (Manzke et al., 2008). Although *TGDS* pathogenic variants were detected in a fetus with additional shortening of the middle fingers (Schoner et al., 2017), and *IMPAD1* pathogenic variants were detected in two other individuals with Catel-Manzke-like syndrome (Nizon, Alanay, et al., 2012), the genetic cause remains unknown in the majority of atypical cases.

We report on two individuals with known *TGDS* pathogenic variants who presented with mild bilateral radial deviation and ulnar clinodactyly of the index fingers but without radiological signs of hyperphalangy. In addition, both individuals have disproportionate short stature, which extends the known phenotypic spectrum.

2 | MATERIAL AND METHODS

The parents gave their written consent for genetic testing and the publication of clinical information and photographs. Trio exome sequencing for both individuals was performed at GenomeScan (Leiden, The Netherlands) as described previously (Popov et al., 2019).

3 | RESULTS

3.1 | Clinical report

Individual 1 was born at term as the second child of non-consanguineous Dutch parents with an unremarkable family history with a birth weight of 3,680 g (+0.38 *SD*), a length of 48 cm (−1.78 *SD*), and a HC of 35 cm (−0.02 *SD*). On prenatal ultrasound, short limbs were seen as well as retrognathia for which amniocentesis was performed. Karyotyping did not show any abnormalities. Shortly after birth, Pierre-Robin sequence with cleft palate, radial deviation and ulnar clinodactyly of both index fingers was noted. Six weeks postpartum her body length was 51.8 cm (−2 *SD*). She developed a more pronounced pectus excavatum deformity during her first year of life and joint laxity became apparent. At the age of 13 months, surgery for correction of her cleft palate was performed, and she received exercise treatment for her phalangeal deformities. However, she developed a bilateral hip dysplasia for which she received bilateral femoral osteotomy at the age of 9 years. Her psychomotor development progressed normally. Her sitting height to height ratio at the age of 10 years was 0.575 (+4.6 *SD*). At last physical examination at the age of 13 years her height was 131 cm (−4.4 *SD*). Parental heights were 182.2 and 169.6 cm for her father and mother, respectively, therefore deciding her target height at 169.7 cm. She also presented with craniofacial features including thin arched eyebrows, mild hypertelorism, proptosis, low-set posteriorly rotated ears, full cheeks, and small mouth. Hand radiographs taken over the years showed no signs of hyperphalangy (Figure 1f–h). Extensive genetic testing single nucleotide polymorphism (SNP) array, NGS panel including Stickler syndrome associated genes because of her joint hypermobility and cleft palate, and next generation sequencing (NGS) panel including genes associated with connective tissue disorders due to her hypermobility) did not show any abnormalities.

Individual 2 is the first child of healthy, non-consanguineous parents with an unremarkable family history. Parents had a previous history of two first-trimester miscarriages at 5 and 6 weeks of gestation prior to this pregnancy. Prenatal ultrasound showed a short femur, and chromosome analysis after amniocentesis revealed a 46,XY karyotype. The boy was delivered in the 41st week of pregnancy with a birth weight of 3,610 g (−0.21 *SD*) and a length of 47 cm (−2.58 *SD*). Postnatal he was noted to have retrognathia, low-set ears, ptosis, short neck, thin eyebrows (Figure 1a), and bilateral hand abnormalities. During the first months of life, he had chronic lung problems due to paralysis of the right-side diaphragm. No abnormalities were detected on cardiac ultrasound. Over the years, he developed progressive short stature (Figure 1b) for which extensive endocrine labs, genetic evaluation (SNP array, sequencing and mulitplex ligation-dependent probe amplification (MLPA) analysis of *SHOX*) and skeletal surveys were performed, but no causal diagnosis was ever made. He was otherwise healthy with normal neurodevelopment, milestones and above-average school performances. He did undergo corrective surgery for positional deformity of his knees (genu valgus) and was frequently seen by an orthodontist due to malar crowding and retrognathia. When last seen in clinic at the age of 15 years, he had short stature with a height of 154 cm (−2.7 *SD*) with a mid-parental height of −0.5 *SD*. His weight for height was normal (+1.0 *SD*), as were his head circumference of 53.5 cm (−1.4 *SD*) and arm span of 157 cm. He did have disproportionately short legs with a sitting height to height ratio of 0.552 (+3.8 *SD*). On physical exam, he was noted to have retrognathia, low-set ears, high palate, and a bifid uvula (Figure 1c,d). Mild radial deviation and ulnar clinodactyly of both index fingers was present (Figure 1i). In addition, he had remarkable muscularity of both upper legs and calves without a history of frequent weight training. Tanner stage was V with testicular volume of 20 ml bilateral. Hand radiographs performed over the years showed mild ulnar clinodactyly and radial deviation of the index finger but no hyperphalangy (Figure 1j–l).

Clinical features of the two individuals and all previously reported individuals with confirmed *TGDS* pathogenic variants are summarized in Table 1.

3.2 | Genotype

Trio exome sequencing of Individual 1 and her parents showed the homozygous missense variant c.700T>C, p.(Tyr234His) in exon 9 of *TGDS* (chr13[GRCh37]:g.95230384A>G; NM_014305.3). We also detected a *de novo* heterozygous 1-bp duplication in *HYDIN* (NM_001270974.2; c.13228_13229dup, p.(Thr4411fs)). Biallelic *HYDIN* pathogenic variants cause primary ciliary disease (PCD). A second variant in *HYDIN* was not found and the individual does not have any features of PCD. Therefore, she is most likely a carrier of PCD. In addition, we found a maternally inherited known pathogenic variant in *IMPG2* (NM_016247.3; c.2716C>T, p.(Arg906*)). Biallelic

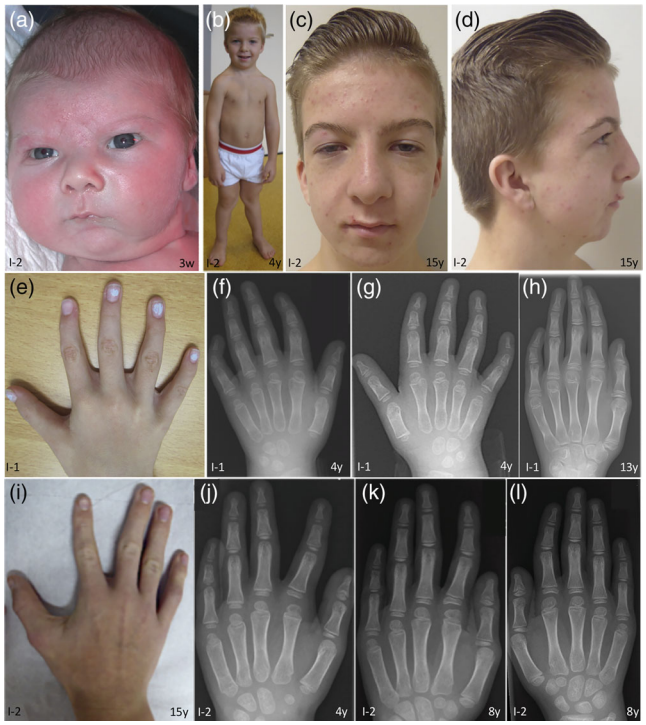

FIGURE 1 Clinical manifestations of Individual 1 (I-1) and 2 (I-2). (a–d) Clinical photographs of Individual 2 showing thin eyebrows, ptosis, mild hypertelorism, low-set posteriorly rotated ears, micro −/retrognathia, short neck, and disproportionately short legs. (e–h) Clinical photograph and hand radiographs of Individual 1 showing clinodactyly of digits II, IV, and IV. No radiologic sign of an additional ossification center is visible. (i–l) Clinical photograph and hand radiographs of Individual 2 showing bilateral mild radial deviation and clinodactyly of the index fingers but no sign of Manzke dysostosis [Color figure can be viewed at wileyonlinelibrary.com]

IMPG2 pathogenic variants cause Retinitis Pigmentosa (RP), which has not been reported in the maternal family. A second variant in *IMPG2* was not found and the individual does not have any features of RP. Therefore, she is most likely a carrier of RP.

Trio exome sequencing of Individual 2 and his parents showed compound heterozygosity for the paternally inherited variant c.700T>C, p.(Tyr234His) in exon 9 of *TGDS* (chr13[GRCh37]:g.95230384A>G) and the maternally inherited variant c.298G>T, p.(Ala100Ser) in exon 4 of *TGDS* (chr13[GRCh37]:g.95243122C>A).

In both individuals, no other variants in genes associated with short stature were identified.

4 | DISCUSSION

The two individuals described here are the first with confirmed *TGDS* pathogenic variants who present with almost normal hand radiographs and therefore do not show one of the clinical hallmarks of Catel-Manzke syndrome, that is, Manzke dysostosis (Manzke, 1966). Until now, nine individuals (including one fetus) with biallelic *TGDS* pathogenic variants have been reported (Ehmke et al., 2014; Pferdehirt et al., 2015; Schoner et al., 2017). All individuals presented with Pierre-Robin sequence and hyperphalangy; only in the fetus shortening of the proximal second and third phalangeal bone was detected but no hyperphalangy, which could be due to the early time point of imaging (22nd week of gestation) (Schoner et al., 2017). Both individuals presented in this study have mild bilateral radial deviation and ulnar clinodactyly of the index fingers (Figure 1e,i), despite the absence of hyperphalangy or shortening of the proximal phalanx on hand radiographs. In Individual 1, an additional clinodactyly of the digits and V is visible (Figure 1e). Thus, our findings demonstrate that the clinical manifestation of the "digital" phenotype varies greatly (i.e., bilateral hyperphalangy of the second fingers, shortening of the second and third fingers, or no signs of hyperphalangy or shortening on radiographs). Likewise, not all individuals show the full spectrum of Pierre-Robin sequence (i.e., micro−/retrognathia, glossoptosis, and cleft palate). Until now, the presence of the two main hallmarks micro-/retrognathia and hyperphalangy provided the basis for the phenotypic classification of individuals into typical (classic Catel-Manzke syndrome) and atypical (Catel-Manzke-like syndrome). It can be discussed whether this clinical categorization is still reasonable or whether a molecular genetic classification appears more appropriate (i.e., *TGDS*-associated Catel-Manzke syndrome).

TGDS encodes the enzyme thymidine diphosphate (TDP) glucose-4,5-dehydratase whose function in mammals is still unknown. So far, seven different pathogenic variants in *TGDS* have been published (Ehmke et al., 2014; Pferdehirt et al., 2015; Schoner et al., 2017). Individual 1 is homozygous for the variant c.700T>C, p.(Tyr234His), which has been reported in compound heterozygous state in another Dutch family (Ehmke et al., 2014; Kant et al., 1998). She presented with retrognathia and cleft palate, and her facial appearance is similar to the Individual 2 reported by Ehmke et al. (2014) and the individual reported by Pferdehirt et al. (2015). Individual 2 in this report carries the above mentioned variant c.700T>C, p.(Tyr234His) and the most common variant c.298G>A, p.(Ala100Ser). He has retrognathia and dysmorphic facial features including low-set ears, thin eyebrows, mild hypertelorism, and ptosis, all features that have been described in previously reported individuals. The detection of already known variants in the here reported individuals despite the nonoccurrence of hyperphalangy on hand radiographs indicates that there is no clear genotype–phenotype correlation. Furthermore, both individuals in this report have disproportionate short stature (Individual 1: −4.4 *SD* for height with a +4.6 *SD* sitting height to height ratio, Individual 2: −2.7 *SD* for height with a +3.8 *SD* sitting height to height ratio; Figure 1b). Shortening of the femur was detected in both individuals on prenatal ultrasound. Four of the previously reported individuals with confirmed *TGDS* pathogenic variants had short stature but our findings show that more severe, disproportionate short stature are clinical features of *TGDS*-associated Catel-Manzke syndrome. Once again, the phenotypic overlap with the following conditions Desbuquois dysplasia 1 (DBQD1, MIM:251450) caused by pathogenic variants in *CANT1* (MIM:613165), Temtamy preaxial brachydactyly syndrome (MIM:605282) caused by pathogenic variants in *CHSY1* (MIM:601882) and chondrodysplasia with joint dislocations

TABLE 1 Clinical features and molecular data of the two reported individuals and individuals with *TGDS* pathogenic variants previously described

	This study		Ehmke et al. (2014)[a]							Pferdehirt et al. (2015)	Schoner et al. (2017)	Summary
	I-1	I-2	I-1	I-2	I-3	I-4	I-5	I-6	I-7	I-1	Fetus	11
Sex	Female	Male	Male	Female	Female	Female	Male	Female	Female	Male	Female	Four male/ seven female
Ethnicity	Dutch	Dutch	Cameroon	British/South American	German	German	German	Dutch	French	German/Czech	Russia	
Consanguinity	No	No	No	No	No	No	No	No	No	No	No	
Age at last exam	13 years	15 years	18 months	2.5 year	16 months	19 year	52 year	17 year	28 year	1 year	21 + 2 weeks of gestation	
TGDS pathogenic variants (*NM_014305.3*)												
First variant	c.700T>C, p.(Tyr234His)	c.298G>A, p.(Ala100Ser)	c.892A>G, p.Asn298Asp)	c.298G>A, p.(Ala100Ser)	c.298G>A, p.(Ala100Ser)	c.298G>A, p.(Ala100Ser)	c.298G>A, p.(Ala100Ser)	c.298G>A, p.(Ala100Ser)	c.298G>A, p.(Ala100Ser)	c.298G>A, p.(Ala100Ser)	c.298G>T p.(Ala100Ser)	
Second variant	–	c.700T>C, p.(Tyr234His)	c.270_271del, (p.Lys91Asn*fs**22)	c.294T>G (p.Phe98Leu)	–	–	–	c.700T>C, p.(Tyr234His)	c.269A>G (p.Glu90Gly)	–	c.895G>A p.(Asp299Asn)	
Type	Homozygous	Compound heterozygous	Compound heterozygous	Compound heterozygous	Homozygous	Homozygous	Homozygous	Compound heterozygous	Compound heterozygous	Homozygous	Compound heterozygous	
Clinical manifestations												
Manzke dysostosis (HP:0009495)	–	–	+	+	+	+	+	+	+	+	(+)	9/11
Pierre-Robin sequence (HP:0000201)	+	+ Bifid uvula	+	+	+	+	+	+ Bifid uvula	+	+ Groove posterior soft palate	+	11/11
Short stature (HP:0004322)	+	+	+	+	+	–	nr	–	+	–	na	6/9
Disproportionate short stature (HP:0003498)	+	+	–	–	–	–	nr	–	–	–	na	2/11
Thin/arched eyebrows (HP:0002553/ HP:0045074)	+	+	nr	+	+	nr	nr	+	nr	–	na	5/11

(Continues)

TABLE 1 (Continued)

	This study		Ehmke et al. (2014)[a]							Pferdehirt et al. (2015)	Schoner et al. (2017)	Summary
	I-1	I-2	I-1	I-2	I-3	I-4	I-5	I-6	I-7	I-1	Fetus	11
Hypertelorism (HP:0000316)	–	+	nr	+	+	+	nr	nr	nr	–	+	5/11
Proptosis (HP:0000520)	+	–	nr	–	nr	nr	nr	+	nr	+	+	4/11
Full cheeks (HP:0000293)	+	–	nr	+	+	+	nr	nr	nr	+	+	6/11
Low-set ears (HP:0000369)	+	+	+	–	nr	nr	nr	+	nr	–	+	5/11
Short neck (HP:0000470)	–	+	+	nr	nr	nr	nr	nr	nr	nr	+	3/11
Congenital heart defect (HP:0001627)	–	–	–	+	–	–	–	+	–	+	+	4/11
Pectus deformity (HP:0000766)	+	–	nr	nr	nr	nr	+	nr	nr	+	–	3/11
Joint hypermobility (HP:0001382)	+	+	nr	nr	nr	nr	nr	+	+	nr	na	4/11
Clinodactyly of fifth finger (HP:0004209)	+	+	nr	nr	nr	+	+	+	nr	–	nr	5/11
Short long bones (HP:0003026)	+	+	+	nr	nr	nr	nr	nr	nr	–	+	4/11
Genua valga (HP:0002857)	+	+	nr	nr	nr	+	nr	nr	nr	nr	na	3/11
Other features	Hip dysplasia		Short toes, adducted thumbs, feet edema			Obstruction of nasolacrimal duct		Bilateral M. Perthes	Brachymetacarpia, scoliosis	Pharyngomalacia, laryngomalacia	Short halluces and middle fingers	

Abbreviations: +, present; –, absent; (+), subtle/incomplete; na, not applicable; nr, not reported.

[a]I-3 and I-4 described in Manzke et al. (2008), I-5 described in Catel and Heintzen (1963), Manzke (1966), and Manzke et al. (2008)), I-6 described in Kant, Oudshoorn, Gi, Zonderland, and Van Haeringen (1998), I-7 described in Nizon, Alanay et al. (2012).

(GPAPP deficiency, MIM:614078) caused by pathogenic variants in *IMPAD1* (MIM:614010; Huber et al., 2009; Li et al., 2010; Vissers et al., 2011) becomes evident. Especially in GPAPP deficiency and DBQD1 disproportionate short stature is a typical feature (Faivre et al., 2004; Vissers et al., 2011). These conditions are caused by defects in proteoglycan metabolism, and it has been proposed that TGDS also plays a role in this pathway (Ehmke et al., 2014; Kitagawa, Uyama, & Sugahara, 2001; Moriarity et al., 2002; Nizon, Huber, et al., 2012; Vissers et al., 2011).

Overall, the phenotypic spectrum of *TGDS*-associated Catel-Manzke syndrome seems to be broader than previously assumed and clinical features can vary from one person to another, even though they harbor the same pathogenic variants. In summary, *TGDS*-associated Catel-Manzke syndrome should be considered in individuals with mild ulnar clinodactyly and radial deviation of the index fingers even without radiological evidence of an accessory bone and especially if the combination of micro-/retrognathia and (disproportionate) short stature is present.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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