Phenotypes and Genotypes in Individuals with *SMC1A* Mutations

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ABSTRACT

Will follow

Background

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KEY WORDS

SMC1A; NIPBL; Brachmann-De Lange syndrome; Rett syndrome; behavior; self-injurious behavior; severity score; syndrome delineation

INTRODUCTION

"Doctor, really wonderful that you have found that our child has a *SMC1A* mutation! But please, what does that mean for him, and what can we expect?" In an era dominated by diagnostic tests using micro-arrays and exome sequencing that demonstrate gene variants, this is in fact the main question that patients and their families like to have an answer on. This manuscript tries to provide some first answers to this question for one of these genes.

SMC1A is a gene known to cause Cornelia de Lange syndrome (CdLS). CdLS is a multisystemic disorder characterized by short stature, unusual face, congenital anomalies of especially distal upper limbs, and intellectual and developmental disabilities. Behavioral characteristics include autism spectrum disorders, social anxiety, and a predisposition to engage with challenging behavior, especially self-injurious behavior (SIB) (Huisman et al., under revision; Mulder et al., 2016). CdLS can be caused by a series of genes of which *NIPBL* (~70-75%) and *SMC1A* (~5%) are the two most frequent ones (Krantz et al., 2004, Tonkin et al., 2004, Bhuiyan et al., 2006, Musio et al., 2006, Deardorff et al., 2007, Huisman et al., 2013).

The CdLS phenotype caused by *SMC1A* mutations may differ from the phenotype in individuals with *NIPBL* mutations. SMC1A individuals have initially been presented with a mild CdLS phenotype: less marked facial CdLS features, no reduction defects or other malformations of the distal limbs, less effects on somatic growth (Musio et al., 2006, Borck et al., 2007, Deardorff et al., 2007). Subsequent publications reported on a more variable CdLS phenotype (Liu et al., 2009a, Liu et al., 2009b, Limongelli et al., 2010, Mannini et al., 2010, Pie et al., 2010, Rohatgi et al., 2010, Chatfield et al., 2012, Hoppman-Chaney et al., 2012, Gervasini et al., 2013, Ansari et al., 2014, Parenti et al., 2014, Yuan et al., 2015, Basel-

Vanagaite et al., 2016, Pie et al., 2016). Through the use of panel screening aimed at detecting variations in genes known to cause intellectual disability, and the use of untargeted trio exome analysis, *SMC1A* variants have increasingly been found in individuals in whom clinically CdLS was not expected, and in some of these patients the main clinical manifestation was an epileptic encephalopathy (de Ligt et al., 2012, Hansen et al., 2013, Gilissen et al., 2014, Goldstein et al., 2015, Jang et al., 2015, Lebrun et al., 2015, Tzschach et al., 2015, Fieremans et al., 2016, Jansen et al., 2016).

This urged us to initiate an interdisciplinary study in a relatively large series of individuals with a confirmed *SMC1A* mutation. We aimed to gather data on their physical and behavioral phenotype, to obtain some insight on the relative frequency of SMC1A individuals with an without suspected CdLS, and to compare the data to a set of CdLS individuals in whom a *NIPBL* mutation has been found (Bhuiyan et al., 2006, Yan et al., 2006). Here we report on the physical results of these studies and general data on cognition and adaptive functioning. The detailed results of the behavioral studies will be published elsewhere (Mulder et al., in preparation).

METHODS

Study design We performed a cross-sectional study of an as large as possible international series of individuals with a confirmed *SMC1A* mutation, using personal evaluations in Dutch participants, and questionnaire results and clinical pictures in patients from other countries.
Dutch SMC1A cohort The molecular genetic laboratory of the Amsterdam Medical Center has been the central Dutch site to perform *SMC1A* mutation analysis by Sanger sequencing, and was the first to offer panel analysis dedicated to detect variants in any of the genes known to

cause CdLS. We gathered the names of all individuals with a *SMC1A* mutation and asked the physicians in charge whether they would contact the family for permission to use the available data, and to obtain permission to contact the family. Eleven families were contacted of which ten families (11 patients) agreed to participate in the study.

Subsequently we contacted all Dutch molecular laboratories that perform exome sequencing asking whether they had detected an SMC1A mutation using panel screening for intellectual disability of untargeted trio analysis. If permitted we contacted the family asking them to participate in the study. One family was contacted and agreed to participate, a second patient had died in the meantime and only data and clinical pictures were obtained.

After written consent two authors (S.H.; R.C.H.) performed clinical evaluations (medical history, physical and morphological examination, clinical pictures) in nine patients (two had passed away), and another author (P.M.) performed direct behavioral assessments (ADOS & Bayley-III/WAIS-IV), SSP-NL and VABS-2) in seven of the remaining individuals (one more had died in the meantime). In addition we asked parents to fill out a set of behavioral questionnaires, which included the Repetitive Behavior Questionnaire (RBQ), Challenging Behavior Questionnaire (CBQ), Gastro-esophageal Reflux Questionnaire (GRQ).
International SMC1A cohort To collect data from a large group of SMC1A individuals we invited the members of the Scientific Advisory Committee of the CdLS World Federation from Denmark, France, Germany, Italy, Poland, Portugal, Spain, Sweden, U.K., and U.S.A. to participate. If positively answered we requested the colleagues to contact their molecular genetic laboratories to check for additional *SMC1A* positive individuals.

We forwarded to the physicians a comprehensive, dedicated questionnaire on somatic characteristics (morphology, malformations, neurodevelopment, physical health; see Supplemental materials) and asked to forward a letter with information and a set of behavioral questionnaires to the families. The set of behavioral questionnaires has been translated in a

separate project in various languages and is available in Danish, Dutch, English, French, German, Italian, Portuguese, and Spanish.

NIPBL comparison group We collected data from the Polish CdLS database containing only individuals with a confirmed *NIPBL* mutation which in part has been published (n=43) (Yan et al., 2006, Kuzniacka et al., 2013) and from a previous published Dutch cohort with *NIPBL* mutations (n=24) (Bhuiyan et al., 2006). To both sets data have been added that have become available since publication.

Severity score A severity score can be predictive of clinical course and maturation relative to other individuals affected by the same or related entity. Since Gillis and co-workers described the first severity classification system based on the CdLS phenotypic parameters limb reduction, cognitive abilities and growth, the severity scoring system has been modified and refined (Gillis et al., 2004, Bhuiyan et al., 2006, Kline et al., 2008). We used the classification system as suggested by Bhuiyan and co-workers, as it includes in a standardized manner all major CdLS parameters (facial morphology, limb anomalies, growth parameters (prenatal; postnatal; skull) and cognitive/adaptive level of abilities) in a non-interdependent manner.

Statistics Data were stored in Excel. Behavioral data were converted from the questionnaires into a coded SPSS file. All data were analyzed using IBM SPSS Statistics version 23.

Ethics The present study has been sustained and promoted by the national and international CdLS Support Groups, and approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam (NL39553.018.12).

RESULTS

We collected data of 48 individuals with a *SMC1A* mutation (34 missense, 14 other types of mutations). Participants came from the Netherlands (11 (23%)), USA (9 (19%)), the UK (8 (17%)) and smaller numbers from Denmark, France, Germany, Italy, Spain and Sweden. Somatic questionnaires were available of all participants, behavioral questionnaires from 32 participants, eight from the Netherlands and 24 from the other countries (response rate 65%). Median age was 13.5 years (range: 0-46 years), gender ratio was 15M to 33F (in the non-missense group 3M to 11F). Median age of clinical diagnoses was 4.8 years (range: 0-46 years), median age of last examination was 11 years (range: 0-40 years). Median age in the NIPBL group was 14 years (range: 0-46 years), gender ratio was 34M to 33F. The main results of the present study are presented in Tables I-IV. The data in the SMC1A group are compared to the 67 patients with a *NIPBL* mutation when possible. Some illustrations are depicted in Figure 1. In the text we only mention those data that are not yet mentioned in the tables.

Physical phenotype The congenital cardiac malformations consisted of three SMC1A individuals with pulmonic stenosis, three with atrial septal defects, two with persistent ductus arteriosus, and one with ventricular septal defect, dextrocardia, patent foramen ovale, coarctation, and pulmonary valve dysplasia each. For the genitourinary system cryptorchidism was scored as a minor anomaly and present in four of the 15 SMC1A boys (31/34 boys with *NIPBL* mutations had cryptorchidism). Early pubic hair development was reported in four girls with a *SMC1A* mutation.

Milestones In describing the milestones we left out SMC1A children below 5 years of age who were still too young to score with certainty whether they would or would not acquire the

milestone before age 5 years. If a child ≥5yr had not reached a milestone we scored this additionally.

Behavior The SMC1A cohort generally appears to have a less severe impaired cognition in comparison to the NIPBL cohort, but the reliability of the data in the NIPBL group is limited and therefore conclusions should only be drawn with caution.

Reasons for molecular analysis In the Dutch cohort three patients were clinically suspected to have CdLS before molecular testing. Of the other eight patients CdLS was mentioned but other diagnoses were thought to be more likely in five of them, and also in the other three CdLS was not suspected clinically. All patients originating from other countries were clinically suspected to have CdLS prior to molecular testing. The testing methods differed between patients depending on local policies and could be Sanger sequencing, panel analysis aimed at variants in one of the five genes known to cause CdLS, panel analysis aimed at variants in genes known to cause intellectual disability, or untargeted trio analysis.

DISCUSSION

We present here an overview of a relatively large series of individuals with a *SMC1A* mutation. The main clinical phenotype known to go along with *SMC1A* mutations is that f CdLS. We have therefore compared the phenotype in the present group of SMC1A patients with those who have a *NIPBL* mutation, with respect to the major characteristics of CdLS and taking the type of *SMC1A* mutation into account.

Growth is in general less disturbed in the SMC1A group compared to the NIPBL group. Prenatal growth is below 2 SD in 1/3rd of the SMC1A group, irrespective the nature of the *SMC1A* mutation. In the NIPBL group this was present in at least 2/3rd of the group.

Postnatal growth is decreased in 2/3rd of the SMC1A group for height and skull circumference, which is somewhat less marked compared to the NIPBL group. But weight is much more disturbed in the NIPBL group: possibly this is related with the much more frequent, more severe and more protracted feeding problems in this group.

Facially all signs that characterize CdLS in general can be present in individuals with a *SMC1A* mutation. All are occurring in a lower frequency compared to the NIPBL group though, but there are some exceptions: individuals with a missense mutation in *SMC1A* have the same frequency in periocular features as in the NIPBL group, and also the thinness of the upper vermillion is comparable between the two groups. There are further differences within the SMC1A group, the lower jaw and ears being more frequently resembling CdLS in general, but the number of individuals with a non-missense *SMC1A* mutation is small and results should be evaluated with care.

Limb reduction defects that can be very typical for CdLS are absent in the SMC1A group. Small hands, a proximally placed thumb, and clinodactyly of the fifth finger occur however and only somewhat less frequent than in the NIPBL group. The same holds for the skin findings cutis marmorata and hirsutism. Malformations of other organs show only small differences between the SMC1A and NIPBL group, and also within the various types of *SMC1A* mutations. Feeding problems are more common in the NIPBL group, gastro-esophageal reflux is as common in frequency as in the NIPBL group, and also constipation does not differ markedly. Seizures however are more frequent in the SMC1A group, and this is more marked in the group with non-missense SMC1A mutations.

A comparison of cognition and behavior is hampered by the lack of data in a considerable number of individuals in the SMC1A group. Based on this limited numbers it seems likely the overall level of cognitive and adaptive functioning is higher in the SMC1A group compared to the NIPBL group. This is so both in the Dutch group who have been

specifically evaluated in person by a social scientist to determine this, as in the data obtained from questionnaires from individuals from other countries, increasing likelihood that the figure is right. Self-injurious behavior did occur in the SMC1A group (only in individuals with a missense mutation) but not frequent and was not reported to be marked, while in the NIPBL group it was very common and also marked in frequency and intensity.

The general conclusion may be that overall individuals with an *SMC1A* mutation can show the phenotype that fits in with CdLS but as a group the frequency of the various signs and symptoms is lower than in the group with a *NIPBL* mutation. Major exceptions are the development of limb reduction defects which does not occur in the SMC1A group, and the increased frequency of seizures in the SMC1A group. Another major difference is the self-injurious behavior which is much more frequent and also severe in the NIPBL group (Mulder et al., in preparation).

The Dutch SMC1A group represents likely all known SMC1A group in the country at present, and includes both patients clinically diagnosed with CdLS and those in whom exome sequencing unexpectedly demonstrated a mutation. We recognize two groups in the Dutch cohort: individuals with a mild CdLS phenotype, and a group with an epileptic encephalopathy. The latter group has been reported before (de Ligt et al., 2012, Hansen et al., 2013, Gilissen et al., 2014, Goldstein et al., 2015, Jang et al., 2015, Lebrun et al., 2015, Tzschach et al., 2015, Fieremans et al., 2016, Jansen et al., 2016). In the Dutch cohort 6 of the 11 individuals present with such epileptic encephalopathy, although in the only male the epilepsy had resolved almost completely at age 12 years. All have severe or profound intellectual disabilities. In evaluating the female patients we were struck by the resemblance with advanced Rett syndrome (Table V). Further characteristics were a more impaired weight at birth and postnatal height compared to the others in the SMC1A group. Their faces were assessed as possible CdLS, except in the youngest girl which was assessed as mild CdLS.

Also hirsutism occurred less and cutis marmorata more than the others in the SMC1A group. We considered a cluster analysis to determine in detail which characteristics fit this phenotype, but numbers were considered too small to allow for meaningful results. In literature two patients has been described with developmental regression (Goldstein et al., 2015, Jansen et al., 2016), making the resemblance to Rett syndrome even more marked. In the Dutch group in two of the five girls regression is reported, but in two other girls the age of onset of epilepsy was 3-5 months, which may have masked any regression masked.

We conclude that within the group of individuals with *SMC1A* mutations a subgroup demonstrates a phenotype that does not so much resemble CdLS but is characterized by epileptic encephalopathy and severe-profound intellectual disabilities. Due to small numbers the exact phenotype has not emerged yet but likely more individuals will be recognized as exome sequencing using panels dedicated to detect variants in genes involved in intellectual disability is increasingly used worldwide. Analysis in larger series may yield better insight whether the phenotypes are truly separate or rather ends of a continuum. Of the 11 known SMC1A patients in the Netherlands five had an epileptic encephalopathy and a Rett-like phenotype. This may indicate this phenotype is much more common than anticipated. The mutations in the five patients are one missense and four other type of mutations, and these are spread over the whole gene (Fig. 2). Re a genotype-phenotype correlation …. Will follow

SMC1A is known as a gene causing a cohesinopathy (Musio et al., 2006). The entities tagged as cohesinopathies have been considered overlapping entities (Liu and Krantz, 2008). Indeed they share several physical and behavioral features, such as limited growth, several of the facial dysmorphisms, limb malformations, and intellectual disability. The cohesin complex and its regulators mediate sister-chromatid cohesion in dividing cells and are important for controlling gene expression (Remeseiro et al., 2013). Sharing major features supports the hypothesis that a disturbed cohesin function contributes to these characteristics

(Yuan et al., 2015). There are differences in the phenotypes caused by *SMC1A* mutations and *NIPBL* mutations. Such differences form an argument that the phenotype is caused not only as a result of the disturbed cohesion functioning but also by other functions (moonlighting) of the cohesion genes (Jeffery, 2014). A major difference in phenotype between the SMC1A and NIPBL group is the much higher and more severe self-injurious behavior in the latter. The absence of this behavioral trait in other cohesinopathies, including CdLS patients with mutations in other genes than *SMC1A*, and also in Roberts syndrome (Vega et al., 2005), is in favor of a moonlighting hypothesis. Mouse models knock-out for *Nipbl* have shown that *Nipbl* does have functions different from the cohesion function indeed (Kawauchi et al., 2009). Patients with cohesinopathies do share several physical signs and symptoms, and this argues against the self-injurious behavior being secondary these. Specifically gastro-esophageal reflux known to be associated with SIB (Luzzani et al., 2003) occurs in both the SMC1A and NIPBL group. Therefore further studies into the cohesinopathies and genes causing these, should not only be aimed at the cohesion and related functions, but also take into account potential other functions of the genes.

SMC1A incompletely escapes X-inactivation (Gervasini et al., 2013). Since there is no altered level of SMC1A transcripts and mutant proteins maintain a residual function (Liu et al., 2009a), and a dominant negative effect is considered the pathogenic mechanism in females with a *SMC1A* mutation, the level of allelic preferential expression might be one of the factors contributing to the wide phenotypic variability observed in these patients (Parenti et al., 2014). In the present study there is a remarkable distorted ratio of males and females with a *SMC1A* mutation. This is especially present in the 14 patients who have mutations other than missense mutations, of whom only three are males. These patients have an in frame deletion. In literature there are two other familial males (check Table III; may be reported twice in literature; Angelo, can you check please?) with one of these in frame deletions

(Musio et al., 2006). This seems to indicate that other types of mutations are not tolerated in males, leading to (likely very early) miscarriages, and explaining the distorted gender ratio.

The present study has several limitations. First, the CdLS phenotype in the SMC1A group is very likely overestimated in the cohort of patients from countries other than the Netherlands, due to acquisition bias, as patients suspected for having CdLS were referred to CdLS specialists, which we specifically invited to participate in the study. We have probed whether there were also SMC1A individuals known to them without CdLS phenotype but none was reported. We contacted the UK 100,000 genome project in order to obtain an estimate of the frequency of *SMC1A* mutations in a large group of individuals, but at the present such detailed question cannot yet be answered (Richard Scott, personal communication, 2016). Therefore the here presented phenotype is likely mainly representative of the CdLS phenotype and less of the epileptic encephalopathy "Rett-like" phenotype. The ratio between these two subgroups in the Netherlands seems to indicate that the latter group is even more frequent than the former, but numbers are small and therefore have a limited reliability.

Furthermore, cross sectional data collection using binary categories to describe features hampers to report gradations and changes over time. The large range of age at last evaluation may also have influenced the data reported here. Moreover, as the somatic questionnaire was extensive, understandably we had to deal with missing data in several patients. These experiences underline the importance of using standardized, longitudinal databases (Baas et al., 2015). The Dutch cohort was evaluated by the same investigators but the patients from other countries were not directly assessed by the same investigators. This may have influenced phenotype evaluations, especially with respect to morphology. As differences between the personally examined patients and patients evaluated by a group of others were small it seems unlikely this has played a major role however. The same holds,

even more strongly so, for cognitive functioning. We strongly advocate that primary data on cognitive and adaptive functioning and specific information on behavior, gathered by a social scientist, form an integrated part of the medical evaluation.

We conclude that *SMC1A* variants can cause a mild CdLS phenotype, but also a Rett-like phenotype. In the near future the increased use of exome and genome sequencing will yield *SMC1A* mutations in more individuals who were clinically not suspected to have CdLS. This should facilitate cluster analyses to identify that either allow separating the phenotypes or merging these into a spectrum. That should allow caregivers to answer the primary question of parents what it means if their child is found to have a *SMC1A* mutation.

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LEGENDS

Table I. General Overview of the Phenotype in Individuals with *SMC1A* Mutations Including Subdivision by Mutation Type, Compared to Those with *NIPBL* Mutations Reported in a Dutch and Polish Cohort

Table II. Natural History of Physical, Cognitive and Behavioral Development in Individuals with *SMC1A* Mutations Including Subdivision by Mutation Type, Compared to Those with *NIPBL* Mutations Reported in a Dutch and Polish Cohort.

Table III. Severity Score in Individuals with *SMC1A* Mutations Subdivided by Mutation Type Compared to Those with *NIPBL* Mutations Reported in a Dutch and Polish Cohort.

Table IV. Genotype in Individuals with *SMC1A* Mutation both from Literature and Present Series.

Table V. Rett-like characteristics in Individuals with *SMC1A* Mutations in Present Series and from Literature.

Figure 1. … Will follow; will be a series of pictures of SMC1A mutations, both faces, hands and feet

Figure 2. ….. Will follow; will be a cartoon depicting the SMC1A gene, indicating the nature of the mutations over the gene in the various functional regions, the mutations causing Rett like mutation, and the gender of the individual with each mutation

Supplementary materials

Report form for the physical data

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