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Development, behaviour and autism in individuals with *SMC1A* variants

Paul A. Mulder,[1] Sylvia Huisman,[2,3] Annemiek M. Landlust,[1] Jo Moss,[4,5] SMC1A Consortium,[*] Sigrid Piening,[1] Raoul C. Hennekam,[1,2] and Ingrid D.C.van Balkom[1]

[1]Autism Team Northern-Netherlands, Jonx Department of Youth Mental Health and Autism, Lentis Psychiatric Institute, Groningen, the Netherlands; [2]Department of Pediatrics, University of Amsterdam, Amsterdam, the Netherlands; [3]Prinsenstichting Institute, Purmerend, the Netherlands; [4]Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, UK; [5]Institute of Cognitive Neuroscience, University College London, London, UK

Introduction: Development and behaviour in Cornelia de Lange Syndrome (CdLS), including autism characteristics, have been described infrequently stratified to genetic cause and only a few studies have considered behavioural characteristics in relation to developmental level. Here, we describe the behavioural phenotype in individuals with CdLS with *SMC1A* variants. **Methods:** We performed an international, interdisciplinary study on 51 individuals with *SMC1A* variants. Results of questionnaire studies are compared to those in individuals with Down Syndrome and with Autism Spectrum Disorder. Results on cognition and self-injurious behaviour (SIB) are compared to those in individuals with CdLS caused by *NIPBL* variants. For Dutch participants with *SMC1A* variants we performed direct in-person assessments of cognition, autism, and added an interview and questionnaire on adaptive behaviour and sensory processing. **Results:** Individuals with *SMC1A* variants show a higher cognitive level and less SIB than individuals with *NIPBL* variants. Individuals with *SMC1A* variants without classic CdLS phenotype but with a Rett-like phenotype show more severe intellectual disability and more SIB compared to those with a CdLS phenotype. Autism is less present if outcomes in direct in-person assessments are evaluated taking developmental level into account compared to results based on a questionnaire. **Conclusions:** Behaviour in individuals with CdLS should be evaluated taking genetic cause into account. Detailed interdisciplinary approaches are of clinical importance to inform tailored care and may eventually improve quality of life of patients and families. **Keywords:** Behavioural phenotype; cornelia de lange syndrome; rett syndrome; autism; cognition; self-injurious behaviour.

Introduction

Cornelia de Lange Syndrome (CdLS) is an entity characterized by intellectual disability (ID), typical face, limb defects and behavioural problems (Kline et al., 2018; Mulder et al., 2016). CdLS can be caused by mutations in several genes, the most frequent ones being *NIPBL, SMC3* and *SMC1A* (Krantz et al., 2004; Deardorff et al., 2007; Nakanishi et al., 2012). Mutations in the gene *NIPBL* have been reported as causing the most typical CdLS phenotype, evident in arched eyebrows and long eyelashes, ID ranging from profound to normal/borderline, self-injurious behaviour (SIB) and autism characteristics (Bhuiyan et al., 2006). An atypical presentation of autism, repetitive and stereotypical behaviour, social withdrawal, anxiety and expressive-receptive language discrepancy have often been described in individuals with CdLS (Ajmone et al., 2014; Moss, Howlin, Magiati, & Oliver, 2012; Moss, Richards, Nelson, & Oliver, 2013; Oliver, Arron, Sloneem, & Hall, 2008).

SMC1A variants have been implicated initially in individuals with a mild variant of CdLS (Musio et al., 2006). Subsequent studies have indicated a broader *SMC1A* phenotype (Pie et al., 2016) including a Rett-like phenotype, but only a limited correlation was detected between genotype and somatic phenotype (Huisman et al., 2017). In genetic syndromes the somatic phenotype is usually described in detail, but behavioural and developmental features obtain less attention (Mulder et al., 2016). Few studies described somatic phenotypes in individuals with CdLS stratified by genetic cause (Nakanishi et al., 2012; Wulffaert et al., 2009), and even less take genetic cause into account when reporting on developmental and behavioural symptoms, and none take environmental factors into account.

In this study, we aim to delineate the behavioural phenotype in a cohort of individuals with *SMC1A* variants, by investigating developmental level, behaviour, autism and sensory processing. We compare outcomes with groups of individuals with Down Syndrome (DS) and with Autism Spectrum Disorder (ASD), compare cognition and behaviour depending of the site and nature of *SMC1A* variants, and to those with *NIPBL* variants. Finally, we perform fine-grained in-person assessments in all available individuals with *SMC1A* variants in the Netherlands.

Methods

We performed a cross-sectional study of an international cohort ($n = 51$) of individuals with *SMC1A* variants. We used a questionnaire pack for all participants in this study. For participants from the Netherlands ($n = 13$), available for

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*The members of the SMC1A consortium are listed in the appendix.

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further assessments, we added interviews and direct in-person assessments.

The acquisition of the study participants has been described in detail elsewhere (Huisman et al., 2017). In short, we invited all known individuals with *SMC1A* variants residing in the Netherlands, irrespective of their phenotype, to participate. Participants from other countries were invited through the CdLS World Federation.

The comparison groups had been recruited in earlier large cohort studies (Richards, Nelson, Moss, & Oliver, 2012) and existing data were used for the present study. Participants with ASD were recruited via the National Autistic Society (United Kingdom) and participants with DS were recruited via the Down syndrome Association (United Kingdom).

The behavioural questionnaire pack included the Wessex Scale (Kushlick, Blunden, & Cox, 1973), the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003), the Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver, 2008), Mood, Interest and Pleasure Questionnaire-Short (MIPQ-S; Arron, Oliver, Berg, Moss, & Burbidge, 2011), Challenging Behaviour Questionnaire (CBQ; Hyman, Oliver, & Hall, 2002) and Gastroesophageal Reflux Questionnaire (GRQ). The set of behavioural questionnaires is available in Danish, Dutch, English, French, German, Italian, Portuguese and Spanish (Baas et al., 2015).

In-depth behavioural data were collected from the Dutch cohort through direct in-person assessments, structured interviews and additional questionnaires (AML, SP, PAM). Assessments were conducted within the daily environment of the participant and in the presence of parent(s) or carer(s). Measures used are the Autism Diagnostic Observation Schedule -2 (ADOS-2; Lord et al., 2000), Bayley-III (Bayley, 2006) or Wechsler (Preschool and Primary or Adult) Intelligence Scale (WPPSI; Hendriksen & Hurks, 2009; WAIS; Wechsler, 2012), the Short Sensory Profile (SSP; Rietman, 2013) and the Vineland-2 structured interview (Sparrow, Cicchetti, & Balla, 2008). Video recordings of the ADOS assessments were assessed independently by a fourth clinician (IdV). Psychometric properties of each instrument are described in Appendix S1.

Participant groups were compared on age, sex and scores on the Wessex scale. Descriptive statistics were used to provide prevalence data in the three participant groups (*SMC1A*, DS and ASD) on the behavioural questionnaire pack. Scores on the CBQ, RBQ, GRQ, MIPQ and SCQ were compared between groups using the Kruskal–Wallis test. If significant differences between groups were found, Mann–Whitney *U* tests were conducted. For the in-depth behavioural data of the Dutch *SMC1A* cohort we used descriptive statistics.

We studied the genotype of *SMC1A* variants by differentiating missense versus other variants (missense variants result in proteins that have been changed, but still part of the protein is present; in other variants almost invariably no or only a very small part of the protein is formed which may have other consequences for protein functioning), as previously presented by Huisman et al. (2017). Mann–Whitney *U* tests were performed to identify phenotype-genotype correlations in individuals with *SMC1A* variants and to compare these with the *NIPBL* population described by Huisman et al. (2017).

Data collection on the *NIPBL* population is described in detail in Huisman et al. (2017). Data were collected from the Polish CdLS database (n = 43), of which most individuals have been previously reported (Kuzniacka et al., 2013; Yan et al., 2006), and from a previously published Dutch cohort (n = 24; Bhuiyan et al., 2006). Follow-up data that have become available since those publications have been added.

Data were analysed using IBM SPSS Statistics version 25 (Amsterdam, the Netherlands).

Ethical information

The present study has been supported by the national and international CdLS Support Groups. The Medical Ethics Committee of the Academic Medical Centre in Amsterdam (NL39553.018.12) approved the study. Informed consent was obtained for all participants prior to inclusion. The study was conducted in accordance with ethical standards (Declaration of Helsinki and later amendments).

Results

Parents of 51 individuals with an *SMC1A* variant from eight different countries were asked to fill out the questionnaires. We received completed questionnaires from 32 individuals (response rate 63%; Table 1).

The DS group was significantly older than the ASD and *SMC1A* groups ($p < .001$), whereas the ASD group consisted of significantly more males than the other two groups ($p < .001$). The *SMC1A* group was significantly more disabled and less mobile (both $p < .001$) and also used significantly less speech ($p < .001$) than both other groups. Vision and hearing problems were significantly (both $p < .001$) more present within the *SMC1A* and DS group compared to the ASD group.

Cognitive functioning ranged from profound ID to normal in the *SMC1A* group (Table 2). Post hoc analyses on the RBQ revealed significantly higher scores on compulsive behaviour and insistence on sameness for the ASD group in comparison to the *SMC1A* group ($p < .001$), scores on repetitive speech almost reached level of significance ($p = .019$). A significant difference was also reported for repetitive behaviour ($p < .001$) on the SCQ, with higher scores for the ASD group in comparison to the *SMC1A* group.

Observations during the direct in-person assessments made clear that all participants needed more processing time and often showed delays in shifting between tasks. Fast onset of patterns was often seen, presenting a quickly built-up predictable routine in (nonverbal) interaction between participant and researcher and a standard way of starting and completing a task. Stereotypic movements were also common. Initially participants were cautious at first contact but, in the presence of a parent or carer, this usually improved after 10–15 min. Repeated offering attractive stimuli, suitable to sensory interests of the participants, encouraged interaction between participant and researcher.

Table S1 contains detailed description of the performed assessments in the Dutch participants (n = 11).

Within the *SMC1A* group, individuals with a missense variant had significantly more hearing problems than individuals with other variants. No other significant differences were evident between individuals with a missense variant and other variants (see Tables S2 and S2a).

The *NIPBL* group showed significantly more impaired cognitive functioning ($p < .007$) than the *SMC1A* group. Especially severe and profound levels

Table 1 Participant characteristics of each group

	SMC1A			Comparison groups	
	All *N*[a] = 32	Missense variants *N*[a] = 22	Other variants *N*[a] = 10	Down syndrome *N*[a] = 139	Autism spectrum disorder *N*[a] = 247
Country of origin[b]					
Dutch cohort	11	8	3	–	–
International cohort					
UK	2	1	1	139	247
Other European countries	19	13	6	–	–
USA	–	–	–	–	–
Gender male (%)	12 (38)	10 (46)	2 (20)	61 (44)	214 (87)
Age (years)					
M (*SD*)range	12.6 (9.3)1.0–33.4	12.8 (9.8)1.0–33.4	12.2 (8.3)3.6–27.0	23.8 (12.2)4.7–47.8	12.0 (–6.0)3.1–45.8
Self help[c]					
Partly able/able[d]: *n* (%)	14 (44)	9 (41)	5 (50)	130 (94)	220 (89)
Mobility[c]					
Mobile[e]: *n* (%)	10 (31)	5 (23)	5 (50)	129 (93)	233 (94)
Vision[c]					
Normal: *n* (%)	15 (47)	9 (41)	6 (60)	86 (62)	235 (95)
Hearing[c]					
Normal: *n* (%)	21 (66)	11 (50)	10 (100)	90 (65)	238 (96)
Speech[c]					
Verbal: *n* (%)	19 (59)	12 (55)	7 (70)	131 (94)	227 (92)
Total severity score[f]					
Mean (range)	9.4 (6–13)	9.7 (6–13)	9 (8–10)	N/A	N/A

N/A, not applicable.
[a]*N* may vary across analysis due to missing data.
[b]UK, United Kingdom, Other European countries (Denmark, France, Germany Italy, Spain), USA, United States of America.
[c]Data is extracted from the Wessex Scale.
[d]Score of six or above on the total score of the self-help subscale. Categories merged due to small *N* in some samples.
[e]Score of six on the total score of the mobility subscale. Categories merged due to small *N* in some samples.
[f]Total severity score = Σ (prenatal growth + postnatal growth + head growth + limb malformation + face + intellectual/adaptive functioning; Bhuiyan et al., 2006), minimum score = 6, maximum score = 18. Only available for participants with *SMC1A* variants.

of ID were less prominent in the *SMC1A* group compared to the *NIPBL* group (5.0% and 25.0%–18.9% and 46.6%, respectively).

Two subgroups were identified in the Dutch cohort of *SMC1A* variants. One showed a phenotype similar to CdLS and one showed remarkable resemblance to Rett syndrome ($n = 5$; Huisman et al., 2017; Table S2). In the latter group all participants showed a severe/profound ID, stereotypic 'hand wringing', regression in development, and epilepsy. Birth weight and postnatal height in all these individuals was lower than in other individuals in the *SMC1A* cohort (Huisman et al., 2017).

When results on cognition from individuals with *SMC1A* variants with a Rett-like phenotype were excluded, significance of differences increased ($p < .001$). Profound ID was present in 4/5 participants with a Rett-like phenotype and severe ID in 1/5.

SIB was significantly more present in the *NIPBL* group (77.0%) compared to the *SMC1A* group (35.5%; $p < .001$; $Z = -3{,}883$). When data from participants with a Rett-like phenotype were excluded, differences in prevalence of SIB significantly increased, with less SIB present in the *SMC1A* group ($p < .001$; $Z = -4{,}696$).

Discussion

We aimed to delineate the phenotype of individuals with *SMC1A* variants in developmental context through investigation of development, behaviour, autism and sensory processing. Results show significant differences in severity of ID and prevalence of SIB between individuals with CdLS caused by *SMC1A* variants and those with CdLS caused by *NIPBL* variants, and increased significance if the physical phenotype was taken into account. Direct in-person assessments revealed clinically relevant observations on processing speed, sensory issues and social behaviour, and the influence of developmental level when considering behaviour.

Stratifying CdLS phenotypes by genetic cause shows significant differences in developmental levels and behavioural phenotypes. The *SMC1A* group demonstrates a higher level of cognitive functioning and less SIB compared to the *NIPBL* group. This may indicate that *NIPBL* and *SMC1A* have different functions in addition to their joint function as cohesion complex proteins (Huisman et al., 2017). The ASD group scored significantly higher on subdomains from the RBQ and the SCQ. Moss et al. (2012)

Table 2 Summary of behavioural characteristics and post hoc analyses

	SMC1A			Comparison groups		Kruskal–Wallis			Post hoc Mann–Whitney tests
	All *N*[a] = 32	Missense variants *N*[a] = 22	Other variants *N*[a] = 10	Down syndrome *N*[a] = 139	Autism spectrum disorder *N*[a] = 247	*df*	χ^2	*p* value	<.016[b]
CBQ[c]									
Self-injurious behaviour *N* (%)	10 (31.3)	8 (36.4)	2 (20.0)	13 (9.4)	103 (41.7)				
Severity score *Med (range)*	0 (0–12)	0 (0–12)	0 (0–5)	5 (0–10)	5 (2–13)				
RBQ[d]									
Stereotyped behaviour *N*; *Med* (range)	26; 8 (0–12)	19; 8 (0–12)	9; 6 (0–12)	136; 0 (0–12)	246; 7 (0–12)	2	84.29	<.001	ASD, SMC1A > DS
Compulsive behaviour *N*; *Med* (range)	26; 1.8 (0–20)	18; 1.8 (0–20)	8; 2.5 (0–15)	136; 1 (0–29)	245; 6 (0–32)	2	44.35	<.001	ASD > DS, SMC1A
Restricted preferences[e] *N*; *Med* (range)	9; 4 (0–10)	5; 0 (0–7)	4; 5.5 (4–10)	127; 2 (0–12)	218; 4 (0–12)	2	41.81	<.001	ASD > DS
Insistence on sameness *N*; *Med* (range)	26; 0 (0–8)	18; 0 (0–8)	8; 0 (0–4)	135; 1 (0–8)	242; 4 (0–8)	2	42.74	<.001	ASD > DS, SMC1A
Repetitive speech[e] *N*; *Med* (range)	9; 2 (0–10)	5; 1 (0–3)	4; 5 (0–10)	125; 1 (0–12)	217; 6 (0–12)	2	78.53	<.001	ASD > DS
GRQ[f]									
GERD behaviour *N*; *M* (*SD*)	28; 10.17 (8.46)	18; 12.22 (9.66)	10; 6.5 (3.86)	N/A	246; 9.79 (7.19)	1	0.016	.901	–
MIPQ[g]									
Mood *N*; *Med* (range)	29; 21 (7–24)	19; 21 (12–24)	10; 23 (7–24)	139; 22 (14–24)	246; 19 (7–24)	2	87.52	<.001	ASD > SMC1A, DS
Interest & pleasure *N*; *Med* (range)	29; 14 (4–24)	19; 14 (4–24)	10; 13.5 (7–20)	139; 19 (8–24)	246; 14 (1–24)	2	84.95	<.001	DS > SMC1A, ASD
Total *N*; *Med* (range)	29; 35 (15–48)	19; 35 (16–48)	10; 35.5 (14–43)	139; 41 (24–48)	246; 33 (11–48)	2	104.7	<.001	DS > SMC1A, ASD
SCQ[h]									
>ASD cut-off *N* (%)	18 (56.3)	12 (37.5)	6 (18.8)	20 (14.4)	247 (100)				
>Autism cut-off *N* (%)	14 (43.8)	10 (31.3)	4 (12.5)	10 (7.2)	195 (78.9)				
Communication; *Med* (range)	9.75 (1.63–13)	9.75 (1.63–13)	6 (1.63–13)	3 (0–13)	9 (3–13)	2	141.94	<.001	SMC1A, ASD > DS
Social interaction; *Med* (range)	9 (0–14)	9 (1–14)	8 (0–14)	3 (0–14)	10 (2–15)	2	146.77	<.001	SMC1A, ASD > DS
Repetitive behaviour; *Med* (range)	3 (0–6)	4.83 (0–6)	2 (1–5)	2 (0–7)	6 (2–8)	2	198.97	<.001	ASD > SMC1A, DS
Cognitive functioning[i]									
Normal *N* (%)	2/20 (10)	1/12 (8)	1/8 (13)	N/A	N/A				
Mild disability *N* (%)	4/20 (20)	2/12 (17)	2/8 (25)	N/A	N/A				
Moderate disability *N* (%)	8/20 (40)	4/12 (33)	4/8 (50)	N/A	N/A				
Severe disability *N* (%)	5/20 (25)	5/12 (42)	0/8 (0)	N/A	N/A				
Profound disability *N* (%)	1/20 (5)	0/12 (0)	1/8 (13)	N/A	N/A				

N/A, not applicable; *Med*m, median scores.
[a]*N* may vary across analysis due to missing data.
[b]*p* value after Bonferroni correction.
[c]CBQ: minimum severity score = 2, maximum severity score = 14.
[d]RBQ: maximum score on each subscale: Stereotyped behaviour = 12; Compulsive behaviour = 32; Restricted preferences = 12; Insistence on sameness = 8; Repetitive speech = 12.
[e]Scores for verbal individuals only.
[f]GRQ (questions 1–12): minimum score = 0, maximum score = 48.
[g]MIPQ: maximum score on each subscale: Mood = 24; Interest & Pleasure = 24; Total = 48.
[h]SCQ: ASD cut-off >15, Autism cut-off >20.
[i]Physician reported data, no validated testing data available.

reported similar findings with less repetitive behaviour in the CdLS group in comparison to the ASD group, using direct in-person assessments. Atypical presentation of ASD in individuals with CdLS has been reported before, although not stratified by genotype (Moss et al., 2013). Further studies of ASD in CdLS stratified to genetic cause may allow further characterisation of phenotype-genotype correlations useful for informing individual approaches by parents and/or caregivers.

Considerable gastroesophageal reflux disease (GERD) problems have been reported in CdLS (Hall, Arron, Sloneem, & Oliver, 2008; Kline et al., 2007), but we did not detect significant differences in GERD symptoms between the *SMC1A* group and the ASD group. GERD may occur less frequently in CdLS caused by *SMC1A* variants compared to those with *NIPBL* variants, but this could not be evaluated as there were no data on GERD problems based on the GRQ for the *NIPBL* group. Huisman et al. (2017) subdivided individuals with *SMC1A* variants, based on physical characteristics and behavioural traits other than SIB, in those with a CdLS phenotype and those with a Rett-like phenotype. We analysed cognition and SIB in both groups: participants with Rett-like phenotypes had more severe ID and showed more SIB than participants with CdLS phenotypes.

Physical characteristics, developmental level, and behaviour may disturb interactions between the individual and environment, impair participation in (social) activities, limit development of adaptive behaviour and increase challenging behaviour, all of which influence quality of life (Bhuiyan et al., 2006; de Winter, Jansen, & Evenhuis, 2011). Care for individuals with CdLS, based solely on physical and genetic findings, is not optimal and understanding behavioural characteristics and developmental level will undoubtedly improve care and support.

Previous publications have questioned the use of only questionnaires when assessing individual behaviour (Moss et al., 2012; Mulder et al., 2016). We performed direct in-person assessments and interviews in the Dutch participants which allowed considering outcomes on development and behaviour within the context of daily functioning. In CdLS individuals' prevalence rates of ASD, commonly assessed with questionnaires, range between 27% and 82% (Mulder et al., 2016). SCQ results in the present study showed that 8/9 Dutch participants scored above the clinical cut-off for ASD-spectrum and 7/9 scored above the Autism cut-off. However, in a direct in-person assessment of autism characteristics using the ADOS-2 three individuals scored 'No ASD' on the ADOS-2, one scored within 'high level of symptoms related to autism' range, two within 'moderate level of symptoms' and one within 'low level of symptoms'. Only two individuals were impaired by autism-related behaviour in their daily functioning, and two individuals showed adequate (social) behaviour when considering their developmental level.

Direct in-person assessment of cognition demonstrated that all verbally able participants showed difficulties in verbal comprehension and explaining concepts. This contrasts earlier findings (Ajmone et al., 2014), possibly due to differing methodology. Individuals with profound ID could fulfil a task if their processing speed was considered during assessments, for example through prolonged offering of visual task-stimuli. We noticed that almost all participants quickly built up routines in their actions, which might be brought on by anxiety (Richards, Moss, O'Farrell, Kaur, & Oliver, 2009).

These outcomes show the importance of careful and rigorous evaluation of ASD symptoms including direct in-person assessments. Direct in-person assessments also offer the opportunity to adapt assessments to the developmental level of an individual, allowing for more appropriate and relevant evaluation. Drawing conclusions on development and behaviour without considering developmental context carries the risk of misdiagnoses and subsequent inappropriate management.

This study is the first to describe preliminary results on sensory processing (SP) in individuals with *SMC1A* variants. SP is the management of sensory information to enable adequate adaptive responses to the environment and engagement in meaningful daily life activities (Baker, Lane, Angley, & Young, 2008). SP-issues are present in individuals across all levels of ID (Engel-Yeger, Hardal-Nasser, & Gal, 2011), but SP has received little research attention in individuals with CdLS. We report marked difficulties in SP in all studied Dutch participants based on the SSP-NL. Difficulties in the domains *weak/low energy* (tires easily, especially when standing or holding particular body position), *auditory stimuli* (is distracted or has trouble functioning if there is a lot of noise around) and *tactile stimuli* (expresses distress during grooming) were most prevalent. We used the information on SP to adapt our approach during the direct in-person assessments, for example by using attractive tactile, auditory or visual stimuli or by limiting distracting stimuli from the environment such as bright lights or presence of parent(s). This allowed drawing attention towards the requested item, which would have been impossible when following standardized procedures of the assessment, and yielded important information on opportunities and limitations in development and behaviour. Hochhauser and Engel-Yeger (2010) report that the more SP is disturbed, the lower the diversity of and participation in social activities. Effective intervention strategies support prevention of over- or under-stimulation, which may improve social inclusion (Schaaf, Toth-Cohen, Johnson, Outten, & Benevides, 2011). Studies on SP in individuals with ASD and/or ID showed a negative correlation with repetitive and stereotypical behaviour (Hazen, Stornelli, O'Rourke, Koesterer, & McDougle, 2014), SIB (Duerden et al., 2012), adaptive behaviour, and challenging behaviour (Tomchek, Little, & Dunn, 2015). Problems in

regulating sensory input correlated with difficulties in daily functioning. Further research on SP in CdLS, stratified by genetic cause, is useful to adequately adapt (learning) environment to meet sensory needs.

This is the first behavioural study in a relatively large cohort of individuals with *SMC1A* variants, and the first to stratify results for genetic causes. Evaluation of behaviour in relation to developmental level in the Dutch participants facilitated a nuanced description of autism and sensory processing.

We realize the present study has several limitations. Acquisition bias may have caused an overrepresentation of the CdLS phenotype (Huisman et al., 2017). Also, current available instruments for assessing development and behaviour are not usually appropriate for individuals with severe or profound ID (Moss et al., 2013). Direct in-person assessment of participating individuals enabled an accurate portrait of developmental level and behaviour. Adjusting standard procedures in some individuals, for example by allowing more time for a task, yielded abilities and behaviour that would have been missed if standard procedures had been followed. Furthermore, some data from the questionnaire pack should be interpreted with care. Results on vision, hearing and GERD problems based on the Wessex and GRQ are slightly different compared to the physician reported results described by Huisman et al. (2017). Wessex scores also show more verbally able patients than based on scores on the RBQ. This may have been caused by differences in defining what 'verbal' means and may have led to an interpretation bias of results. Data on cognition from the international *SMC1A* cohort should be interpreted with care, because we do not know if standardized measurements were used to determine the level of development mentioned in the questionnaire.

Conclusion

Cornelia de Lange Syndrome individuals with *SMC1A* variants show higher level of cognitive functioning and less SIB compared to those with *NIPBL* variants and a diagnosis of ASD warranted in only a few participants when behaviour was considered taking developmental level into account. We therefore emphasize that behavioural characteristics should be interpreted within the individual's developmental context in order to reduce misdiagnosis. We strongly advocate direct in-person assessments by behavioural scientists with experience in (severe) ID, and stratifying study samples by genetic cause. Fine-grained assessments and detailed, interdisciplinary approaches yield important information for tailored care, which may eventually contribute to improvement of quality of life.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Developmental and behavioural characteristics in Dutch individuals with SMC1A variants.

Table S2. Comparison of missense versus other SMC1A variants on gender, age and Wessex scores.

Table S2a. Comparison of missense versus other SMC1A variants on behavioural characteristics.

Appendix S1. Psychometric properties of used instruments.

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Correspondence

Paul A. Mulder, Autism Team Northern-Netherlands, Jonx Department of Youth Mental Health and Autism, Lentis Psychiatric Institute, Laan Corpus den Hoorn 102-2, 9728 JR Groningen, the Netherlands; Email: pa.mulder@lentis.nl

Key points

- Individuals with *SMC1A* variants (one of the genes known to cause CdLS) show a diverse developmental and behavioural phenotype.
- Self-injurious behaviour is less present and cognition less impaired in individuals with *SMC1A* variants compared to individuals with *NIPBL* variants.
- Autism Spectrum Disorder is clinically less present in *SMC1A* if evaluated taking developmental context into account.
- Development and behaviour are studied stratified by genetic cause to enable individualized description of the phenotype.
- Considering behaviour in developmental context, stratified to genetic cause, leads to increased clinical important specific information on development and behaviour.
- Detailed interdisciplinary methodology informs for tailored care, and may eventually improve quality of life.

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Appendix. International SMC1A Consortium

Ingrid Bader[1], Ingrid D.C. van Balkom[2], Anne-Marie Bisgaard[3a], Alice Brooks[4], Anna Cereda[5], Constanza Cinca[6], Dinah Clark[7], Valerie Cormier-Daire[8], Matthew A. Deardorff[7,9], Karin Diderich[7], Mariet Elting[10], Anthonie van Essen[†], David FitzPatrick[11], Cristina Gervasini[12], Gabriele Gillessen-Kaesbach[13], Katta M. Girisha[14], Raoul C. Hennekam[2,15], Yvonne Hilhorst-Hofstee[16], Saskia Hopman[17], Denise Horn[18], Sylvia Huisman[15,19], Mala Isrie[10], Sandra Jansen[20], Cathrine Jespersgaard[3b], Frank J. Kaiser[21], Maninder Kaur[7], Tjitske Kleefstra[20], Ian D. Krantz[7,9], Phillis Lakeman[22], Annemiek M. Landlust[2], Davor Lessel[23], Caroline Michot[8], Jo Moss[24,25], Paul A. Mulder[2], Sarah E. Noon[7], Chris Oliver[24], Ilaria Parenti[13,21], Juan Pie[26], Sigrid Piening[2], Beatriz Puisac[26], Feliciano J. Ramos[27], Egbert Redeker[22], Claudine Rieubland[28], Silvia Russo[29], Angelo Selicorni[30], Zeynep Tümer[3b], Rieneke Vorstenbosch[31], Irene M. de Vries[2], Tara L. Wenger[32], Jolanta Wierzba[33]

[1]Division of Clinical Genetics, Department of Pediatrics, Paracelsus Medical University Salzburg, Salzburg, Austria; [2]Autism Team Northern-Netherlands, Jonx Department of Youth Mental Health and Autism, Lentis Psychiatric Institute, Groningen, the Netherlands; [3a]Kennedy Center, Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital, Rigshospitalet, Glostrup, Denmark; [3b]Kennedy Center, Department of Clinical Genetics, Copenhagen University Hospital, Rigshospitalet, Glostrup, Denmark; [4]Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, the Netherlands; [5]Department of Pediatrics, ASST Papa Giovanni XXIII, Bergamo, Italy; [6]División Genetica, Hospital de Clínicas José de San Martín, Universidad de Buenos Aires, Buenos Aires, Argentina; [7]Division of Genetics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [8]Department of Medical Genetics, Reference Center for Skeletal Dysplasia, INSERM UMR 1163, Laboratory of Molecular and Physiopathological Bases of Osteochondrodysplasia, Paris Descartes-Sorbonne Paris Cité University, AP-HP, Institut Imagine, and Hôpital Universitaire Necker-Enfants Malades, Paris, France; [9]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [10]Department of Clinical Genetics, VU University Medical Center, Amsterdam, the Netherlands; [11]MRC Human Genetics Unit, IGMM, Western General Hospital, Edinburgh, United Kingdom; [12]Department of Health Sciences, Medical Genetics, University of Milan, Milan, Italy; [13]Institut für Humangenetik Lübeck, Universitätsklinikum Schleswig-Holstein, Lübeck, Germany; [14]Department of Medical Genetics, Kasturba Medical College, Manipal University, Manipal, India; [15]Department of Pediatrics Amsterdam UMC location AMC, University of Amsterdam, Amsterdam, the Netherlands; [16]Department of Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands; [17]Department of Genetics, University Medical Center Utrecht, Utrecht, the Netherlands; [18]Institute for Medical Genetics and Human Genetics, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; [19]Prinsenstichting Institute, Purmerend, the Netherlands; [20]Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands; [21]Section for Functional Genetics, Institute of Human Genetics, University of Lübeck, Lübeck, Germany; [22]Department of Clinical Genetics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [23]Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [24]Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, United Kingdom; [25]Institute of Cognitive Neuroscience, University College London, London, United Kingdom; [26]Unidad de Genética Clínica y Genómica Funcional, Facultad de Medicina, Universidad de Zaragoza, IIS Aragón, Zaragoza, Spain; [27]Unidad de Genética Clínica, Servicio de Pediatría, Hospital Clínico Universitario 'Lozano Blesa' CIBERER-GCV02 and Departamento de Pediatría, Facultad de Medicina, Universidad de Zaragoza, IIS Aragón Zaragoza, Spain; [28]Division of Human Genetics, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [29]Molecular Biology Laboratory, Istituto Auxologico Italiano, Milan, Italy; [30]UOC Pediatria, ASST Lariana, Como, Italy; [31]Severinus Institute, Veldhoven,

the Netherlands; [32]Division of Craniofacial Medicine, Seattle Children's Hospital, Seattle, Washington; [33]Departments of Pediatrics, Hematology, Oncology and Department of General Nursery, Medical University of Gdansk, Gdansk, Poland; †(Deceased) Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

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