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DOI:
[10.1111/jcpp.12979](https://doi.org/10.1111/jcpp.12979)

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Document Version
Peer reviewed version

Citation for published version (Harvard):
Mulder, PA, Huisman, S, Landlust, AM, Moss, J, SMC1A Consortium, Piening, S, Hennekam, RC, van Balkom, IDC & Oliver, C 2018, 'Development, behaviour and autism in individuals with SMC1A variants', *Journal of Child Psychology and Psychiatry and Allied Disciplines*. <https://doi.org/10.1111/jcpp.12979>

[Link to publication on Research at Birmingham portal](#)

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Development, Behaviour and Autism in Individuals with *SMC1A* variants

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| Journal: | <i>Journal of Child Psychology and Psychiatry</i> |
| Manuscript ID | JCPP-OA-2018-00210.R1 |
| Manuscript Type: | Original Article |
| Date Submitted by the Author: | 27-Jun-2018 |
| Complete List of Authors: | Mulder, Paul; Autism Team Northern-Netherlands, Jonx Department of Youth Mental Health and Autism, Lentis Psychiatric Institute Huisman, Sylvia; Department of Pediatrics, Amsterdam UMC location AMC, University of Amsterdam; Prinsenstichting Institute, Prinsenstichting Landlust, Annemiek; Autism Team Northern-Netherlands, Jonx Department of Youth Mental Health and Autism, Lentis Psychiatric Institute Moss, Joanna; Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham; Institute of Cognitive Neuroscience, University College London Piening, Sigrid; Autism Team Northern-Netherlands, Jonx Department of Youth Mental Health and Autism, Lentis Psychiatric Institute Hennekam, Raoul; Autism Team Northern-Netherlands, Jonx Department of Youth Mental Health and Autism, Lentis Psychiatric Institute; Department of Pediatrics, Amsterdam UMC location AMC, University of Amsterdam van Balkom, Ingrid; Autism Team Northern-Netherlands, Jonx Department of Youth Mental Health and Autism, Lentis Psychiatric Institute |
| Key Words: | Phenotype, Autism spectrum disorders, Intellectual disability, Self-injury, Genetics, behavioural |
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Development, behaviour and autism in individuals with *SMC1A* variants

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Abbreviated title: Behavioural phenotype in *SMC1A* variants

Conflict on interest statement: No conflicts declared.

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.

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Introduction

Cornelia de Lange Syndrome (CdLS) is an entity characterized by intellectual disability (ID), typical face, limb defects and behavioural problems (Mulder et al., 2016; Kline et al., 2018). 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 (Moss et al., 2012; Moss et al., 2013; Ajmone et al., 2014; Oliver et al., 2018).

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 (Wulffaert et al., 2009; Nakanishi et al., 2012), 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 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 et al., 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 and Cox, 1973), the Social Communication Questionnaire (SCQ; Rutter, Bailey and Lord, 2003), the Repetitive Behaviour Questionnaire (RBQ; Moss and Oliver, 2008), Mood, Interest and Pleasure Questionnaire-Short (MIPQ-S; Arron, Oliver, Berg, Moss & Burbidge, 2008), Challenging Behaviour Questionnaire (CBQ; Hyman, Oliver and 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

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(WPPSI; Hendriksen and Hurks, 2001; WAIS; Wechsler, 2012), the Short Sensory Profile (SSP; Rietman, 2013) and the Vineland-2 structured interview (Sparrow, Cicchetti and 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 vs. 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.

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).

Table 1

The DS group was significantly older than the ASD and *SMC1A* groups ($p < 0.001$), whereas the ASD group consisted of significantly more males than the other two groups ($p < 0.001$). The *SMC1A* group was significantly more disabled and less mobile (both $p < 0.001$) and also used significantly less speech ($p < 0.001$) than both other groups. Vision and hearing problems were significantly (both $p < 0.001$) 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 ($p < 0.001$), scores on repetitive speech almost reached level of significance ($p = 0.019$). A significant difference was also reported for repetitive behaviour ($p < 0.001$) on the SCQ, with higher scores for the ASD group in comparison to the *SMC1A* group.

Table 2

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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 (non-verbal) 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 minutes. 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 online for tables S2. and S2a.).

The *NIPBL* group showed significantly more impaired cognitive functioning ($p < 0.007$) than the *SMC1A* group. Especially severe and profound levels of ID were less prominent in the *SMC1A* group compared to the *NIPBL* group (5.0 % and 25.0 % to 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, online 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 ($p < 0.001$). 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%) ($p < 0.001$; $Z = -3,883$). 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 ($p < 0.001$; $Z = -4,696$).

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 and colleagues (2012) 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, Richards, Nelson and Oliver, 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 (Kline et al., 2007; Hall, Arron, Sloneem and Oliver, 2008), but we did not detect significant

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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 and colleagues (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 and 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, Howlin, Magiati and Oliver, 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 and 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 and Young, 2008). SP-issues are present in individuals across all levels of ID (Engel-Yeger, Hardal-Nasser and 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

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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 and 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 and McDougle, 2014), SIB (Duerden et al., 2012), adaptive behaviour, and challenging behaviour (Tomchek, Little and 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

CdLS 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:

Appendix S1. Psychometric properties of used instruments.

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

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

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

Acknowledgements

The authors are pleased to thank all participants and their families who have made this research possible. They also thank all those who have generously contributed their time, expertise and effort to translate the behavioural questionnaires into eight different languages. The authors have declared that they have no competing or potential conflicts of interest.

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Key points

- Individuals with *SMC1A* variants (one of the genes known to cause CdLS) show a diverse developmental and behavioural phenotype.
- SIB is less present and cognition less impaired in individuals with *SMC1A* variants compared to individuals with *NIPBL* variants.
- ASD is clinically less present in *SMC1A* if evaluated taking developmental context into account.
- Development and behavior 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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Tables

Table 1 Participant Characteristics of each Group

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

* N may vary across analysis due to missing data

** UK = United Kingdom, Other European countries (Denmark, France, Germany Italy, Spain), USA = United States of America

*** Age in years

^a Data is extracted from the Wessex Scale

^b Score of six or above on the total score of the self-help subscale. Categories merged due to small N in some samples

^c Score of six on the total score of the mobility subscale. Categories merged due to small N in some samples

^d 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.

N/A = not applicable

Table 2 Summary of Behavioural Characteristics and Post Hoc Analyses

| | SMC1A | | | Comparison Groups | | Kruskal-Wallis | | | Post hoc Mann-Whitney tests |
|---|-----------------------|---------------------------------|------------------------------|------------------------------|--|----------------|----------------|------------|--------------------------------|
| | All N* = 32 | Missense variants N* = 22 | Other variants N* = 10 | Down Syndrome N* = 139 | Autism Spectrum Disorder N* = 247 | df | X ² | P value | < .016 ^e |
| CBQ^a | | | | | | | | | |
| Self-injurious behaviour N (%) | 10 (31.3) 0 (0-12) | 8 (36.4) 0 (0-12) | 2 (20.0) 0 (0-5) | 13 (9.4) 5 (0-10) | 103 (41.7) 5 (2-13) | | | | |
| Severity score <i>Med**</i> (range) | | | | | | | | | |
| RBQ^b | | | | | | | | | |
| Stereotyped behaviour N; <i>Med</i> (range) | 26; 8 (0-12) | 19; 8 (0-12) | 9; 6 (0-12) | 136; 0 (0-12) | 246; 7 (0-12) | 2 | 84.29 | < | ASD, SMC1A > DS |
| Compulsive behaviour N; <i>Med</i> (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*** | 9; 4 (0-10) | 5; 0 (0-7) | 4; 5.5 (4-10) | 127; 2 (0-12) | 218; 4 (0-12) | 2 | 41.81 | < | ASD > DS |
| N; <i>Med</i> (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 |
| Insistence on sameness N; <i>Med</i> (range) | 9; 2 (0-10) | 5; 1 (0-3) | 4; 5 (0-10) | 125; 1 (0-12) | 217; 6 (0-12) | 2 | 78.53 | < | ASD > DS |
| Repetitive speech*** N; <i>Med</i> (range) | | | | | | | | < | |
| | | | | | | | | .001 | |

| | | | | | | | | | |
|---|--|--|--|--|---|-------------|----------------------------|-------------------------------------|---|
| GRQ^c GERD behaviour N; <i>Med</i> (SD) | 28; 10.17 (8.46) | 18; 12.22 (9.66) | 10; 6.5 (3.86) | N/A | 246; 9.79 (7.19) | 1 | .016 | .901 | - |
| MIPQ^d Mood N; <i>Med</i> (range) Interest & pleasure N; <i>Med</i> (range) Total N; <i>Med</i> (range) | 29; 21 (7-24) 29; 14 (4-24) 29; 35 (15-48) | 19; 21 (12-24) 19; 14 (4-24) 19; 35 (16-48) | 10; 23 (7-24) 10; 13.5 (7-20) 10; 35.5 (14-43) | 139; 22 (14-24) 139; 19 (8-24) 139; 41 (24-48) | 246; 19 (7-24) 246; 14 (1-24) 246; 33 (11-48) | 2 2 2 | 87.52 84.95 104.70 | < .001 < .001 < .001 | ASD > SMC1A, DS DS > SMC1A, ASD DS > SMC1A, ASD |
| SCQ^e > ASD cut-off N (%); > autism cut-off N (%); Communication; <i>Med</i> (range) Social interaction; <i>Med</i> (range) Repetitive behaviour; <i>Med</i> (range) | 18 (56.3) 14 (43.8) 9.75 (1.63-13) 9 (0-14) 3 (0-6) | 12 (37.5) 10 (31.3) 9.75 (1.63-13) 9 (1-14) 4.83 (0-6) | 6 (18.8) 4 (12.5) 6 (1.63-13) 8 (0-14) 2 (1-5) | 20 (14.4) 10 (7.2) 3 (0-13) 3 (0-14) 2 (0-7) | 247 (100) 195 (78.9) 9 (3-13) 10 (2-15) 6 (2-8) | 2 2 2 | 141.94 146.77 198.97 | < .001 < .001 < .001 | SMC1A, ASD > DS SMC1A, ASD > DS ASD > SMC1A, DS |
| Cognitive functioning^f Normal N (%) Mild disability N (%) Moderate disability N (%) Severe disability N (%) Profound disability N (%) | 2/20 (10) 4/20 (20) 8/20 (40) 5/20 (25) 1/20 (5) | 1/12 (8) 2/12 (17) 4/12 (33) 5/12 (42) 0/12 (0) | 1/8 (13) 2/8 (25) 4/8 (50) 0/8 (0) 1/8 (13) | N/A N/A N/A N/A N/A | N/A N/A N/A N/A N/A | | | | |

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

Appendix S1. Psychometric properties of used instruments.

Wessex Scale

Informant based questionnaire which measures the social and physical characteristics of children and adults with ID. It comprises five subscales: continence, mobility, self-help skills, speech and literacy. It also provides information on vision and hearing. Inter-rater reliability at subscale and item level is good (Kushlick, Blunden and Cox, 1973).

Social Communication Questionnaire

The SCQ (Rutter, Bayley and Lord, 2003) provides information on a child's body movements, use of language or gestures, and style of interacting. It is used as a screening instrument for epidemiological research and for describing ASD symptomatology. Clinical cut-off for ASD is attained when scoring >15, for Autism the score has to be >21. The questionnaire differentiates for ASD from other diagnoses with a sensitivity of .83 and a specificity of .75 (Charman et al., 2007).

Repetitive Behaviour Questionnaire

The RBQ measures five subscales with nineteen items: stereotyped behaviour, compulsive behaviour, insistence on sameness, restricted preferences and repetitive speech. Clinical cut-off at item level is attained when scores on an item is three or more. At subscale level, clinical cut-off is attained when on one or more items within the subscale is scored three or higher. Inter-rater reliability ranges from .46 to .80 at item level, retest reliability ranges from .61 to .93 at item level. Internal consistency was good at full-scale level ($\alpha > .80$) (Moss and Oliver, 2008).

Mood, Interest and Pleasure Questionnaire- Short

The MIPQ-S is derived from the MIPQ and consists of 12 items. The Mood subscale and Interest & Pleasure subscale each contain six items. The MIPQ-S shows a good internal consistency (Cronbach's

alpha coefficients: total = .88, Mood = .79, Interest and Pleasure = .87), inter-rater reliability (.85) and test–retest reliability (.97) (Arron, Oliver, Berg, Moss and Burbidge, 2011).

Challenging Behaviour Questionnaire

The CBQ is a brief questionnaire evaluating presence or absence of SIB, physical and verbal aggression, destruction of property and inappropriate vocalizations. Inter-rater reliability was found to be good with coefficients rating from .61 to .89 (Hyman, Oliver and Hall, 2002).

Gastroesophageal Reflux Questionnaire

The GRQ consists of 17 items about behaviours that is sometimes shown by individuals with learning disabilities that might be indicative for gastroesophageal reflux problems. Psychometric properties are not yet available. The GRQ has previously been developed for clinical use by prof. dr. C. Oliver and colleagues (University of Birmingham).

Autism Diagnostic Observation Schedule

The ADOS (Lord et al., 2000), a widely used, standardized instrument that assesses social interaction, communication, and imagination during a semi-structured interaction with an examiner. Psychometric characteristics of all modules show reliable and valid results (e.g. Bastiaansen et al., 2011).

Bayley-III

The *Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)* is an individually administered scale that assesses five key developmental domains in children between 1-42 months of age: cognition, language (receptive and expressive communication), motor (gross and fine), social-emotional and adaptive behaviour. In this study, we only performed the cognition tasks to evaluate

developmental level in severe or profound disabled individuals. The reliability coefficient of the cognition subscale is .91 (Bayley, 2006).

Wechsler Preschool and Primary Scale of Intelligence

The WPPSI-III is a standardized instrument to assess cognitive capacities in children aged from two years and six months to seven years and eleven months old. It measures capabilities on performal and verbal tasks. Overall reliability is good with coefficients ranging from .82 to .90. Test-retest reliability ranges from .73 to .80, inter-rater reliability ranges from .93 to .98 (Hendriksen and Hurks, 2011).

Wechsler Adult Intelligence Scale

The WAIS-IV contains subscales that provide index-scores on Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed. Psychometric properties on Index-scores are as following: split-half reliability on Index level ranges from .88 to .97, test-retest reliability ranges from .83 to .92 and inter-rater reliability ranges from .86 to .98 (Wechsler, 2012).

Vineland-2

The Vineland-2 measures level of adaptive functioning in three domains: communication, daily living skills and socialization. Scores can be computed into an adaptive composite score, which can be converted into a classification of adaptive level. Age equivalence can be determined for each subdomain score. Since there is no appropriate Dutch equivalent of the Vineland-2 available, we used the American version with corresponding standardization. Mean internal consistency reliability coefficients for domain and subdomains are in the good to excellent range according the criteria of Cicchetti, ranging .84 to .98 (Sparrow, Cicchetti and Balla, 2008). Test-retest reliability coefficients (intraclass correlation coefficient is used) for domain and subdomains range from .63 to .87 ('good' to 'excellent'). Inter-interviewer reliability coefficients (based on the intraclass correlation) for the domains range from .69 to .81 ('good' to 'excellent') (Sparrow et al., 2008).

Short Sensory Profile

Sensory processing was assessed using the Short Sensory Profile- Dutch Adaptation (SSP-NL; Rietman, 2013). This questionnaire gives an indication of possible difficulties in a person’s way of sensory processing (Dunn, 1999). Standardization of the SSP-NL is based on a sample of the Sensory Profile (SP-NL). Reliability is measured by estimating the reliability of the interitem-correlations (Guttman’s lambda-2). Reliability of interitem-correlations range from .63 to .86 (Rietman, 2013).

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

| Participant # | SMC1ANL002 | SMC1ANL004 | SMC1ANL005 | SMC1ANL006 | SMC1ANL008 |
|--------------------------|---|--|--|--|--|
| Mutation variant | frameshift | missense | missense | missense | frameshift |
| Test age (years; months) | 8;1 | 9;9 | 35;2 | 23;7 | 14;8 |
| Vision | poor | poor | normal | normal | normal |
| Hearing | normal | poor | (almost) deaf | normal | normal |
| Speech | no words | no words | normal | normal | no words |
| CBQ ^a | SIB: no | SIB: hits self with body and object. Destruction of property. | SIB: no | SIB: no | SIB: no |
| MIPQ ^b | Mood: 24 Interest & Pleasure: 13 Total: 37 | Mood: 23 Interest & Pleasure: 12 Total: 35 | Mood: 19 Interest & Pleasure: 14 Total: 33 | Mood: 40 Interest & Pleasure: 20 Total: 60 | Mood: 23 Interest & Pleasure: 14 Total: 37 |
| SCQ ^c | Total: 23 | Total: 31 | Total: 17 | Total: 22,27 | Total: 25 |
| RBQ ^d | Total: 12 | Total: 19 | not reported | Total: 5 | Total: 16 |
| GRQ ^e | Total: 3 | Total: 19 | Total: not reported | Total: 0 | Total: 6 |
| SSP-NL ^f | | | | | |
| Definitive Difference | Tactile sensitivity, underresponsive / seeking sensation, low energy / weak, visual / auditory sensitivity | Movement sensitivity, low energy / weak | Tactile sensitivity, movement sensitivity, low energy / weak. | Movement sensitivity, low energy / weak | Tactile sensitivity, low energy / weak. |
| Probable Difference | Auditory filtering | Tactile sensitivity, Auditory filtering | Taste / smell sensitivity, underresponsive / seeking sensation | Tactile sensitivity, Auditory filtering | |
| Vineland-2 ^g | Profound deficit | Profound deficit | Severe-moderate deficit | Moderate-mild deficit | Profound deficit |
| Cognition ^h | Developmental Age = 4 months [Bayley-III] | Developmental Age = 11 months [Bayley-III] | Developmental Age = 40-42 months [Bayley –III] | Perceptual Reasoning Index 77 (95%-ci 71-86) [WAIS-IV] | Developmental Age = 5 months [Bayley-III] |
| ADOS-2 ⁱ | Autism Spectrum - Low level of symptoms related to ASD | Autism - High level of symptoms related to ASD | No ASD Spectrum - Low level of symptoms related to ASD | No ASD Spectrum | Autism Spectrum - Moderate level of symptoms related to ASD |
| Other / Observations | Low muscle tone; intentional communicative sounds (dissatisfied or satisfied); tactile stimuli mostly pleasant (satisfied sound); quickly builds routines; need for long processing time; delayed shifting between tasks/stimuli. | Quick reaction on auditory and movement stimuli; reaches; gestures ‘mine’; dyadic contact possible; uses indicative pronoun ‘that’; stereotypic movements (e.g. clapping hands); unintentional communicative sounds of (dis)satisfaction; need for long processing time; delayed shifting between tasks/stimuli. | Excited mood; awaiting contact; quickly builds patterns; seeks predictability and confirmation; diverse mimics; descriptive gestures; adequate but delayed speech; need for long processing time; delayed shifting between tasks/stimuli; good Joint Attention skills. | Strains oneself (non-verbal signs: tension in shoulders and hands, red cheeks); adequate but delayed speech; need for long processing time; delayed shifting between tasks/stimuli; good Joint Attention skills. | Low muscle tone; awaiting contact; reacts on auditory and tactile stimuli, less on visual stimuli; quickly tired; some intentional communicative (dis)satisfied sounds; tactile stimuli trigger responses; asks for repetition; Need for longer processing time; delayed shifting between tasks/stimuli. |

| Participant # | SMC1ANL009 ^a | SMC1ANL015 | SMC1ANL014 | SMC1ANL001 ^{**} | SMC1ANL003 ^{**} | SMC1ANL007 ^{**} |
|---|--|---|---|---|--------------------------|---|
| Mutation variant | missense | missense | missense | missense | missense | nonsense |
| Test age (years; months) | 32;1 | 5;9 | 26;2 | 9;6 | 9;7 | 4;3 |
| Vision | normal | normal | normal | poor | not reported | poor |
| Hearing | normal | normal | normal | poor | not reported | normal |
| Speech | normal | normal | normal | odd words only | not reported | odd words only |
| CBQ ^a | N/A | SIB: no | N/A | SIB: no | SIB: not reported | SIB: no |
| MIPQ ^b | N/A | Mood: 24 Interest & Pleasure: 22 Total: 46 | N/A | Mood: 12 Interest & Pleasure: 4 Total: 16 | not reported | Mood: 7,22 Interest & Pleasure: 7,44 Total: 14,66 |
| SCQ ^c | N/A | Total: 6 | N/A | Total: 25 | Total: 31 | Total: 24 |
| RBQ ^d | N/A | Total: 2 | N/A | Total: 8 | not reported | missing |
| GRQ ^e | N/A | Total: 4 | N/A | Total: 9 | Total: not reported | Total: 10 |
| SSP-NL ^f Definitive Difference | N/A | Movement sensitivity, low energy / weak | | not reported | not reported | not reported |
| Vineland-2 ^g Cognition ^h | N/A | Moderate deficit | N/A | not reported Profound ^{***} | not reported | not reported Profound ^{***} |
| ADOS-2 ⁱ | Unknown Autism Questionnaire: Clinical score within group 'Women with ASD' at domain 'attention for details' | No ASD Spectrum | Autism Spectrum - Moderate level of symptoms related to ASD | not reported | not reported | not reported |
| Other / observations | Good Joint Attention skills; need for long processing time. SCL-90-R: High score on Depression and Sleep scales Self-reported: Problems with explaining concepts; visually oriented (remembers visual information better); no self- injurious behaviour. | Verbal receptive better than expressive skills; need for visual supportive communication; socially responsive; Can be flooded if new, unknown incentives; need for long processing time; delayed shifting between tasks/stimuli; builds quickly routines; good Joint Attention skills. Carer-reported: Physical aggression; destruction of properties; stereotypic movements if tension increases. | Awaiting contact, hardly any initiative. Very limited non-verbal communication. Reciprocity is minimal. Longer time needed to process information, delayed shifting between tasks. Quickly builds routines. Difficulty in recognizing and explaining social- emotional concepts. Self-reported: mild deficit in adaptive abilities; gets community support. | not reported | not reported | not reported |

^a Challenging Behaviour Questionnaire: SIB present yes/no

^b Mood, Interest & Pleasure Questionnaire: min - max scores on subscale Mood (0 - 24), subscale Interest & pleasure (0 - 24), total score (0 - 48)

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^c **Social Communication Questionnaire:** min - max scores (1 - 39), Clinical cut-off for ASD >15, for Autism >21 (ASD = Autism Spectrum Disorder)

^d **Repetitive Behaviour Questionnaire:** min - max scores (0 - 76)

^e **Gastroesophageal Reflux Questionnaire:** min - max scores (0-48)

^f **Short Sensory Profile-NL:** Definitive Difference = 2 SD from Mean, Probable Difference = 1SD from Mean

^g **Vineland-2:** total score based on: Communication, Daily Livings Skills and Socialization; Motor skills are excluded.

^h Used instruments to assess cognition were chosen based on clinical judgement and daily functioning.

ⁱ **Autism Diagnostic Observation Schedule-2:** module was chosen based on verbal and adaptive abilities.

* Different instruments were chosen for this participant. Level of functioning precluded assessment battery, this also counted for the SSP-NL and Vineland-2. In order to get relevant data on daily functioning, the Autism Questionnaire and Symptom Checklist-90-Revised were used.

** Unfortunately these patients were lost during follow-up or have died and therefore assessment with additional questionnaires, interviews and direct in-person assessments was impossible.

*** Physician reported data

N/A = Not applicable

For Peer Review

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

| | <i>SMC1A</i> | | | <i>Mann-Whitney Test</i> |
|---|----------------|------------------------------|---------------------------|--------------------------|
| | All N* = 32 | Missense variants N* = 22 | Other variants N* = 10 | $\alpha < .05$ |
| Gender Male (%) | 12 (38) | 10 (46) | 2 (20) | |
| Age*** | | | | |
| M (SD) | 12.6 (9.3) | 12.8 (9.8) | 12.2 (8.3) | .968 |
| range | 1.0 - 33.4 | 1.0 - 33.4 | 3.6 - 27.0 | |
| Self Help^a | | | | |
| Partly able/able ^b : n (%) | 14 (44) | 9 (41) | 5 (50) | 1.000 |
| Mobility^a | | | | |
| Mobile ^c : n (%) | 10 (31) | 5 (23) | 5 (50) | .248 |
| Vision^a | | | | |
| Normal: n (%) | 15 (47) | 9 (41) | 6 (60) | .618 |
| Hearing^a | | | | |
| Normal: n (%) | 21 (66) | 11 (50) | 10 (100) | .025 (Missense < Other) |
| Speech^a | | | | |
| Verbal: n (%) | 19 (59) | 12 (55) | 7 (70) | .717 |
| Total severity score^d | | | | |
| Mean (range) | 9.4 (6-13) | 9.7 (6-13) | 9 (8-10) | N/A |

* N may vary across analysis due to missing data

** UK = United Kingdom, Other European countries (Denmark, France, Italy, Spain, Germany), USA = United States of America

*** Age in years

^a Data is extracted from the Wessex Scale (Kushlick et al., 1973)

^b Score of six or above on the total score of the self-help subscale. Categories merged due to small N in some samples

^c Score of six on the total score of the mobility subscale. Categories merged due to small N in some samples

^d 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.

N/A = not applicable

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

| | <i>SMC1A</i> | | | Mann-Whitney Test |
|---|------------------|-------------------|------------------|-------------------|
| | All | Missense variants | Other variants | |
| | N* = 32 | N* = 22 | N* = 10 | α < .05 |
| CBQ | | | | |
| Self-injurious behaviour N (%) | 10 (31.3) | 8 (36.4) | 2 (20.0) | .242 |
| Severity score ^a <i>Med</i> ** (range) | 0 (0-12) | 0 (0-12) | 0 (0-5) | .232 |
| RBQ^b | | | | |
| Stereotyped behaviour N; <i>Med</i> (range) | 26; 8 (0-12) | 19; 8 (0-12) | 9; 6 (0-12) | .980 |
| Compulsive behaviour N; <i>Med</i> (range) | 26; 1.8 (0-20) | 18; 1.8 (0-20) | 8; 2.5 (0-15) | .661 |
| Restricted preferences ^{***} N; <i>Med</i> (range) | 9; 4 (0-10) | 5; 0 (0-7) | 4; 5.5 (4-10) | .167 |
| Insistence on sameness N; <i>Med</i> (range) | 26; 0 (0-8) | 18; 0 (0-8) | 8; 0 (0-4) | .665 |
| Repetitive speech ^{***} N; <i>Med</i> (range) | 9; 2 (0-10) | 5; 1 (0-3) | 4; 5 (0-10) | .133 |
| GRQ^c | | | | |
| GERD behaviour N; <i>M</i> (SD) | 28; 10.17 (8.46) | 18; 12.22 (9.66) | 10; 6.5 (3.86) | .195 |
| MIPQ^d | | | | |
| Mood N; <i>Med</i> (range) | 29; 21 (7-24) | 19; 21 (12-24) | 10; 23 (7-24) | .144 |
| Interest & pleasure N; <i>Med</i> (range) | 29; 14 (4-24) | 19; 14 (4-24) | 10; 13.5 (7-20) | .448 |
| Total N; <i>Med</i> (range) | 29; 35 (15-48) | 19; 35 (16-48) | 10; 35.5 (14-43) | .818 |
| SCQ^e | | | | |
| > ASD cut-off N (%); | 18 (56.3) | 12 (37.5) | 6 (18.8) | .663 |
| > Autism cut-off N (%); | 14 (43.8) | 10 (31.3) | 4 (12.5) | .392 |
| Communication; <i>Med</i> (range) | 9.75 (1.63-13) | 9.75 (1.63-13) | 6 (1.63-13) | .795 |
| Social interaction; <i>Med</i> (range) | 9 (0-14) | 9 (1-14) | 8 (0-14) | .856 |
| Repetitive behaviour; <i>Med</i> (range) | 3 (0-6) | 4.83 (0-6) | 2 (1-5) | .640 |
| Cognitive functioning^f | | | | |
| Normal N (%) | 2/20 (10) | 1/12 (8) | 1/8 (13) | N/A |
| Mild disability N (%) | 4/20 (20) | 2/12 (17) | 2/8 (25) | N/A |
| Moderate disability N (%) | 8/20 (40) | 4/12 (33) | 4/8 (50) | N/A |
| Severe disability N (%) | 5/20 (25) | 5/12 (42) | 0/8 (0) | N/A |
| Profound disability N (%) | 1/20 (5) | 0/12 (0) | 1/8 (13) | N/A |

^a N may vary across analysis due to missing data

^{**} *Med* = Median scores

^{***} Scores for verbal individuals only

^a Challenging Behaviour Questionnaire: minimum severity score = 2, maximum severity score = 14.

^b Repetitive Behaviour Questionnaire, maximum score on each subscale: Stereotyped behaviour = 12; Compulsive behaviour = 32; Restricted preferences = 12; Insistence on sameness = 8; Repetitive speech = 12

^c Gastroesophageal Reflux Questionnaire (questions 1-12): minimum score = 0, maximum score = 48.

^d Mood, Interest & Pleasure Questionnaire: maximum score on each subscale: Mood = 24; Interest & Pleasure = 24; Total = 48.

^e Social Communication Questionnaire: ASD cut-off >15, Autism cut-off >20.

^f Physician reported data, no validated testing data available

N/A = Not Applicable