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Short report: Behavioural characterisation of SOX11 syndrome

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ABSTRACT

Background: SOX11 syndrome is a rare condition caused by deletions or de novo point mutations of the SOX11 gene. SOX11 is a transcription factor gene that plays an important role in brain development.

Aims: The aim of this study was to quantitatively evaluate the behavioural profiles of individuals with SOX11 syndrome.

Methods and procedures: The Vineland Adaptive Behaviour Scales 3 (VABS-3) and the Social Responsiveness Scale 2 (SRS-2) were completed by parents of 21 children and young adults with SOX11 syndrome.

Outcomes and results: Most were found to have borderline (33 %) or mild (39 %) impairment in adaptive behaviour, with more difficulties in communication and daily living than socialisation in the cohort overall. Most (90 %) were found to exhibit clinically relevant levels of autistic traits, with 62 % scoring in the "severe" range, though social motivation was observed to be a relative strength in the cohort overall.

Conclusions and implications: This study presents the first standardised evaluation of adaptive behaviour and autistic traits of individuals with SOX11 syndrome. This will improve clinicians, educators and parents' understanding of SOX11 syndrome.

What this paper adds?

Based on parent-report questionnaire responses, this study conducted the first evaluation of the adaptive behaviour and autistic traits of children and young adults with SOX11 syndrome. The results showed that individuals with SOX11 syndrome generally have impairments in adaptive behaviour, particularly daily living skills and communication and significant autistic traits in relation to both social communication difficulties and restricted interests and repetitive behaviours.

1. Introduction

Neurodevelopmental disorders (NDD) are a diverse group of conditions that impact brain development and various aspects of daily living. Genomic studies have revolutionised understanding of the aetiology of NDD. It is now recognised that 30–50 % of people with a NDD will have a copy number variant (CNV) or pathogenic single nucleotide variant (SNV) (Srivastava et al., 2019). While many hundreds of novel causes of NDD have been defined at the genomic level, the clinical delineation of these remains superficial. This limits the ability of clinicians to counsel families and creates an 'information gap' leaving families isolated and anxious. Many studies

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have demonstrated the utility of routinely used clinical measures of neurodevelopmental and adaptive features in delineating the phenotype of rare genetic conditions (e.g. Lane et al., 2017; Lee et al., 2022; Richards et al., 2017), but further work is needed to understand the phenotypic profiles of currently poorly understood genetic conditions.

SOX11 syndrome is associated with pathogenic SNV or CNVs affecting the *SOX11* gene. The human *SOX11* gene is located on chromosome 2p25.2 and is classified as a member of the SOXC subfamily, along with *SOX4* and *SOX12*. Members of the SOXC are grouped due to their molecular similarity and partial functional redundancy. They play partially similar yet vital roles in regulating the development of the nervous system and other tissues during embryonic development (Tsang et al., 2020) and *SOX11* mutation has been shown to impair neurogenesis (Turan et al., 2019). Clinical case series have described the broad neurological phenotype of SOX11 syndrome, common co-occurring diagnoses are intellectual disability and autism, and common medical issues include renal malformations and hypogonadism (Al-Jawahiri et al., 2022; Hempel et al., 2015; Tsurusaki et al., 2014). Several other clinical features have also been reported including coarctation of the aorta (Okamoto et al., 2018), cleft palate (Khan et al., 2018), and glaucoma (Diel et al., 2021). A recent report on three new Chinese cases with *SOX11* mutation report a variable phenotype, mainly involving developmental delay, intellectual disability, short stature, microcephaly, facial deformaties and cryptorchidism (Ding et al., 2022). However, to date there has been no detailed behavioural phenotyping of individuals with SOX11 syndrome using standardised measures.

The primary aim of this study was to present the first evaluation of adaptive behaviour and autistic traits of individuals with *SOX11* SNVs and CNVs using standardised measures. Given the clinical case series reports to date, it was hypothesised that adaptive behaviour would frequently be impaired and that a significant proportion of individuals with SOX11 syndrome would score above clinical cut-off for autistic traits. A secondary aim of this study was to investigate whether difficulties in terms of adaptive behaviour and autistic traits tend to increase or decrease relative to changes typically expected with age.

2. Methods

2.1. Participants

Twenty-one parents of individuals with SOX11 syndrome completed standardised questionnaires. The mean age of the individuals with SOX11 syndrome was 10.04 years (*SD* 5.46); Age range: 3 years, 1 month - 21 years, 6 months. Ten individuals with SOX 11 syndrome were male and 11 were female. Eight were resident in the United Kingdom, eight were resident in the United Stated of America, three were resident in Europe, one was resident in Australia, one was resident in West Asia. Eighteen had a SNV, three had a CNV (small deletion). Participants were recruited via clinical contacts of consultant clinical geneticist XX and via a closed social media family support group for SOX11 syndrome with worldwide membership.

2.2. Measures

Two standardised parent/ caregiver-reported measures were administered. Licensing was received from the publishers to allow online administration of the questionnaires. Adaptive behaviour was evaluated using the Vineland Adaptive Behaviour Scales, Third Edition (VABS-3; Sparrow et al., 2016). The VABS-3 core 120-item scale was used which can be used to assess adaptive behaviour from birth to 90 years old. Parents/care-givers are asked to respond to items on a 3-point scale comprising 0 (never), 1 (sometimes), and 2 (usually or often). Scores (adjusted for age) were computed for the adaptive behaviour composite (ABC) and domain-level communication, daily living skills, and socialisation scales indicating levels of functioning compared to others in their age group. The VABS-3 was completed by 18 respondents. Autism-related social behaviours were evaluated via the Social Responsiveness Scale, Second Edition (SRS-2; Constantino & Gruber, 2012). The SRS-2 is a 65-item questionnaire with each item being coded on a Likert scale (0 = not true to 3 = almost always true), designed to assess behaviour associated with autism, with a higher score indicating greater difficulty. Domain level T-scores (adjusted for gender) were computed for social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behaviours (RRB), in addition to the composite Social Communication Index T-score (SCI; sum of social awareness, social cognition, social communication, social motivation), and a total T-score score (sum of all

Table 1
Summary of SRS-2 and VABS-3 standardised scores for SOX11.

	N	Mean (SD)	Range
SRS-2			
SRS-2 total score	21	76.57 (11.77)	54–99
Social communication index	21	74.76 (11.37)	54–99
Social awareness	21	72.29 (12.98)	51–96
Social cognition	21	75.48 (12.51)	47–100
Social communication	21	75.76 (10.27)	54–95
Social motivation	21	61.48 (13.41)	40–91
Restricted interests and repetitive behaviours	21	78.29 (11.79)	55–98
VABS-3			
Adaptive behaviour composite	18	63.33 (14.41)	20–89
Communication	18	60.39 (15.54)	20–96
Daily living skills	18	61.44 (17.99)	20–86
Socialisation	18	67.94 (16.27)	20–94

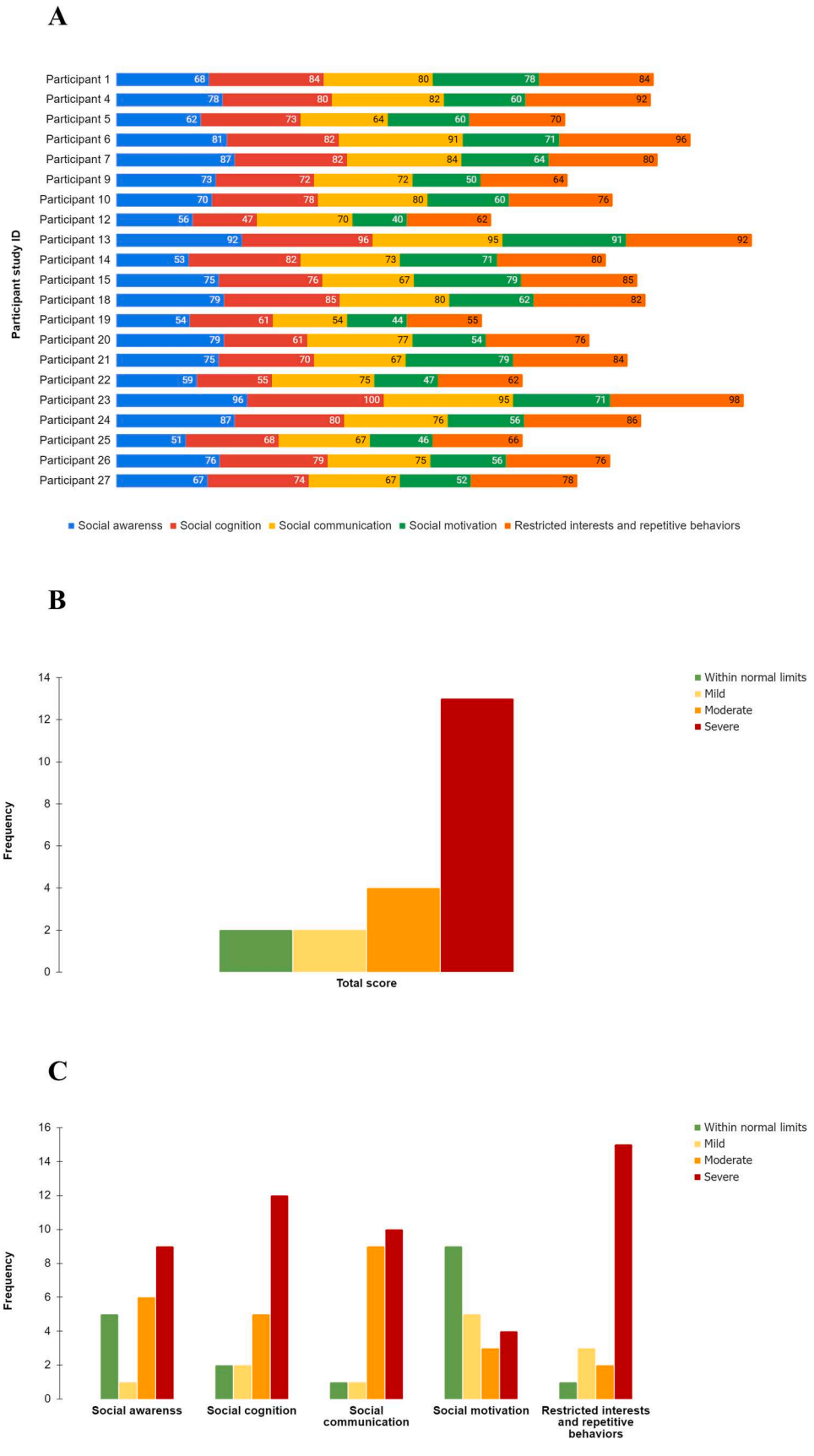

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Fig. 1. Adaptive behaviour of SOX11 syndrome. A) VABS-3 standardised domain-level scores for each participant. B) Frequency of individuals scoring within normal limits and within borderline, mild, moderate, severe, and profound impairment ranges for ABC, and C) domains. Note that the total number of participants assessed was 18.

subscales). The adult, school-age and pre-school-age forms were used as appropriate. The SRS-2 was completed by 21 respondents.

2.3. Ethical approval

Ethical approval was obtained from the University of Sheffield Medical School Research Ethics Board. Written informed consent was obtained from questionnaire respondents.

2.4. Competing interests statement

The authors have no competing interests to declare.

3. Results

3.1. Adaptive behaviour profile

Vineland Adaptive Behaviour Scales-3 (VABS-3) scores are presented in Table 1. Lower scores indicate having more impaired adaptive behaviour. Scores of 70–84 indicated borderline impairment, 55–69 mild impairment, 40–54 moderate impairment, 25–39 severe impairment, and ≤ 24 profound impairment (see Fig. 1A for domain-level scores of each participant). Overall, the majority of the participants' scores indicate borderline or mild impairment in adaptive functioning (Fig. 1B and C). A Friedman test showed significant differences between the domain scores of communication, daily living skills, and socialisation. A main effect of domain was found, $\chi^2(2) = 12.49$, $p = .002$; post hoc non-parametric analyses showed the scores were significantly lower in communication ($p = .001$, Hedges' $g = .11$) and daily living skills ($p = .015$, Hedges' $g = .08$) compared to socialisation. The significance threshold was at $p \leq .033$ in accordance with the Benjamini-Hochberg method.

3.2. Autistic behaviour profile

Social Responsiveness Scale-2 (SRS-2) scores are presented in Table 1. Higher scores represent greater severity of autism-related behavioural traits. Scores of ≤ 59 are within normal limits, 60–65 mild, 66–75 moderate, or ≥ 75 severe impairment (scores ≥ 60 are considered clinically relevant; see Fig. 2A for treatment subscale scores of each participant). The majority of participants fell in the severe impairment category in SRS-2 total scores and in all subscales apart from social motivation where participants showed a range of severity levels with the majority scoring within normal limits (Fig. 2B and C).

A Friedman test was conducted to determine whether the observed differences were statistically significant in terms of the participants' autism-related behavioural traits across the different SRS-2 treatment subscales. A main effect of domain was found, $\chi^2(4) = 33.90$, $p < .001$, post hoc non-parametric analyses showed the social motivation scores were significantly lower than social cognition ($p < .001$, Hedges' $g = .24$), communication ($p < .001$, Hedges' $g = .30$), and awareness ($p = .003$, Hedges' $g = .18$), whereas RRB was significantly higher than awareness ($p = .006$, Hedges' $g = .11$). A significance threshold of $p \leq .022$ was used, as determined via the Benjamini-Hochberg method.

3.3. The impact of age on adaptive and autistic behaviour traits in SOX11

Spearman's correlation analyses were conducted to examine whether age impacts adaptive ability (VABS-3 composite score) and social behaviour (SRS-2 total t-score) in SOX11. There was a significant negative correlation between age and VABS-3 composite scores; $r_s = -.56$, $p = .017$ indicating increased difficulties at older ages. There was also a significant positive correlation between age and SRS-2 total score; $r_s = .46$, $p = .037$ indicating increased social behaviour difficulties at older ages. Note that VABS-3 composite scores and SRS-2 total t-scores are standardised for age. These analyses enable investigation of whether difficulties are relatively more or less apparent at younger or older ages given the expected progression with age. To investigate further, spearman's correlation analyses were also conducted on total raw scores for the VABS-3, finding no significant correlation between age and VABS-3 total raw scores, $r_s = .35$, $p = .158$ indicating a plateau in adaptive behaviour development. There was also a significant positive correlation between age and SRS-2 total raw scores, $r_s = .52$, $p = .016$ indicating increased reports of absolute social behaviour difficulties with age. Overall, the results indicate that adaptive behaviour difficulties and social behaviour difficulties were more apparent in the older individuals in this cohort. (Note that lower scores in VABS-3 indicate higher severity, whereas higher scores in SRS-2 indicate higher severity).

4. Discussion

The current paper quantitatively examined adaptive ability and autistic traits in individuals with SOX11 syndrome. Overall, we

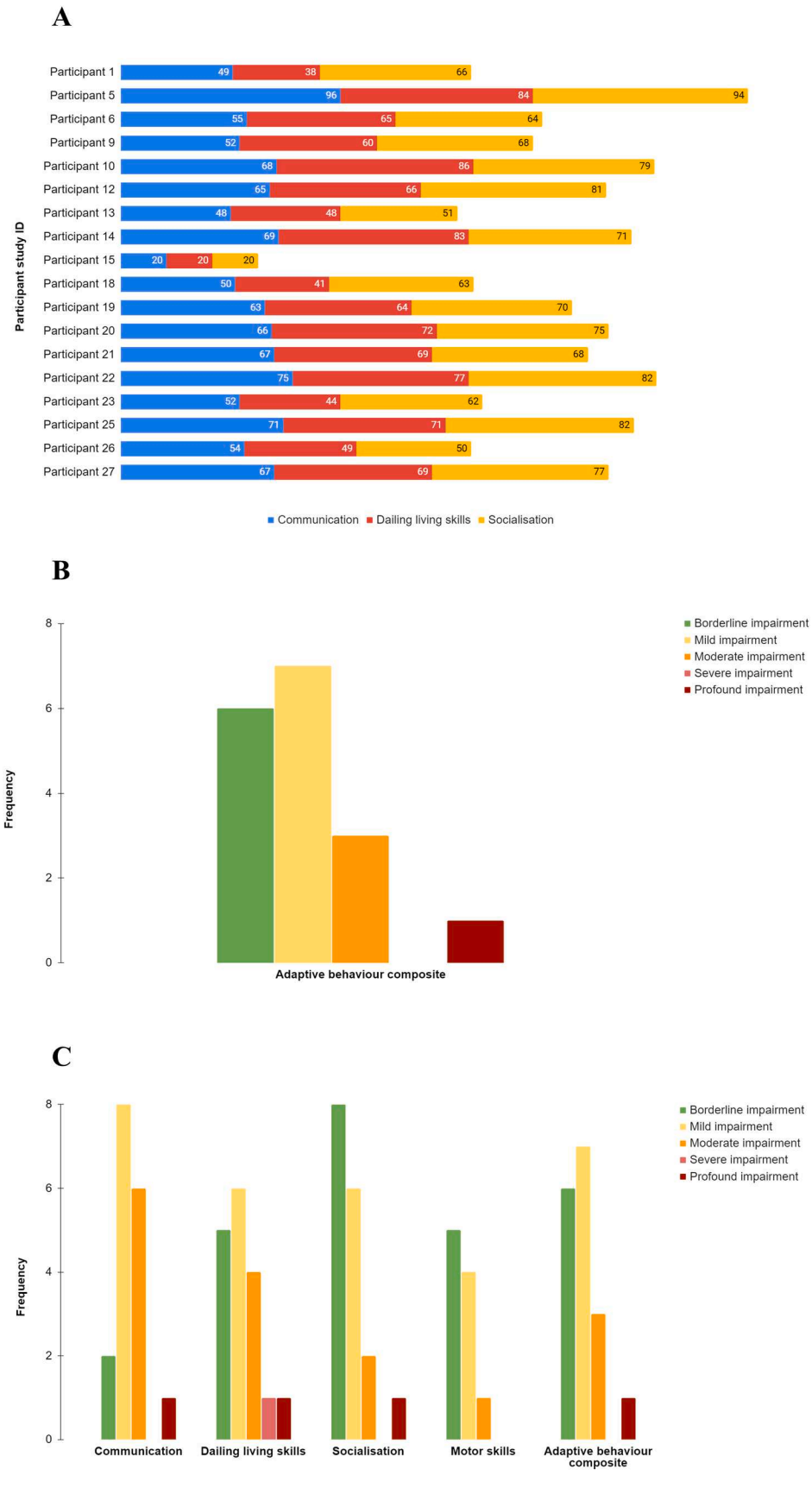

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Fig. 2. Autism-related social impairment in SOX11 syndrome. A) SRS-2 T-scores of treatment subscales for each participant. B) Frequency of individuals scoring within the normal, mild, moderate, and severe impairment ranges for SRS-2 total, and C) for treatment subscales. Note that the total number of participants assessed was 21.

found that SOX11 individuals generally experience mild impairment in adaptive behaviour and clinically relevant autistic traits.

In relation to adaptive behaviour, the majority of the SOX11 cohort showed borderline (33 %) or mild (39 %) impairment in adaptive behaviour. Mean SOX11 adaptive behaviour scores indicated mild impairment. SOX11 syndrome individuals showed the least impairment in socialisation (i.e., interpersonal relationships, play and leisure, ability to cope with social rules) compared to communication (i.e., taking in information, verbal expression, reading and writing) and daily living skills (i.e., everyday tasks such as self-care, helping around the home and functioning in the community) which were more impaired. Overall, the findings imply that individuals with SOX11 syndrome are likely to experience challenges in everyday life. This is in line with previous clinical reports of frequent developmental delay/intellectual disability diagnoses in SOX11 syndrome individuals (Al-Jawahiri et al., 2022; Hempel et al., 2015). Our finding that poor adaptive skills were more pronounced with increased age indicates that challenges in daily life may become more apparent as SOX11 syndrome individuals get older. However, a negative relationship between age and adaptive behaviour skills has been consistently observed in autistic cohorts (Pathak et al., 2019; Pugliese et al., 2015) and hence is not unexpected.

In the present cohort, according to the SRS-2, 90 % of SOX11 individuals had clinically relevant autism-related behaviours, with 62 % of those scoring within the severe symptom severity range. Mean SOX11 syndrome SRS-2 total scores indicated severe symptom severity. This indicates that SOX11 syndrome individuals are likely to experience difficulties that lead to substantial interference in everyday social interactions. Our findings indicate that social behaviour differences may also become more apparent with increased age. Such strong association between SOX11 syndrome and autistic behaviour has not been indicated in prior reports where inferences about autistic behaviour could only be made from reports of clinical diagnoses. For example, among 10 cases of individuals with SOX11 deletions or de novo point mutations reported by Hempel et al. (2015), just three were reported to have an autism diagnosis. In regard to specific social behaviours, the current study indicated social motivation (i.e., motivation to initiate and maintain a social contact) as a relative strength in SOX11 individuals relative to differences in social cognition, communication, awareness and RRB, with most differences observed in RRB. This could have clinical relevance as strengths in social motivation in SOX11 may be leveraged to support differences in other social domains. Importantly, the variation in individual social behaviour profiles observed, indicates the value of multi-modal assessment of autism traits in SOX11 syndrome and tailored intervention according to individual needs. For example, there was high variation in the level of difference in social awareness with 24 % of SOX11 individuals scoring within normal limits. A similar overall profile of relative strengths in social motivation and relative difference in RRB has been observed in other genetic conditions; William's syndrome (Lee et al., 2022), Down syndrome (Lee et al., 2022), and DYRK1A syndrome (Morison et al., 2022). Contrastingly, SYT1 individuals have been reported to have elevated scores in the SRS-2 SCI subscales (awareness, communication, cognition, and motivation) and relatively lower scores in RRB (Melland et al., 2022). Individuals with non-syndromic autism have been reported to have elevated scores in all SRS-2 subscales (SCI subscales and RRB; Lee et al., 2022). This suggests that SOX11 presents a similar social behaviour profile to certain genetic conditions, possibly linked to associated underlying neurobiology, and a distinct profile from other genetic conditions and non-syndromic autism.

In future, it would be informative to compare the phenotypes of groups of individuals with certain SOX11 variants, located in the high-mobility group (HMG) DNA binding domain, against other SOX11 variants, outside the HMG box region. Specific SOX11 variants may contribute differently to certain neurodevelopmental traits and severity. It would also be beneficial to investigate the differential impact of SOX11 variants against SOX11 deletions on the heterogeneity and severity of phenotypes. A detailed evaluation and understanding of the profile of phenotypes in SOX11 syndrome, including specifically focussing on narrower age ranges and using tools involving direct observation of behaviour, such as in-person autism assessments, will pave the way for providing evidence-based specialised support services and treatments for families affected by SOX11 syndrome.

In conclusion, this study provides new information about the SOX11 syndrome developmental phenotype. This information may help to support the understanding of SOX11 syndrome among clinicians and families at the time of diagnosis, to inform suitable intervention and reduce uncertainty in regard to future developmental outcomes.

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Data Availability

The authors do not have permission to share data.

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