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Autistic traits and cognitive abilities associated with two molecular causes of Silver-Russell syndrome

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Abstract

Silver-Russell syndrome is a rare genetic imprinting disorder. Two molecular causes of Silver-Russell syndrome have been identified: loss of methylation on chromosome 11p15 (11p15 LOM) and maternal uniparental disomy for chromosome 7 (matUPD7). Current understanding of the cognitive and behavioural phenotypes associated with these two molecular subtypes is limited. This study aimed to address this gap in the literature. The Social Responsiveness Scale (SRS-2), was used to assess autistic traits in individuals with 11p15 LOM (n = 47) and matUPD7 (n = 32). A subset of participants with 11p15 LOM (n = 18) and matUPD7 (n = 15) completed in-person assessments: the Autism Diagnostic Observation Schedule (ADOS-2) and the British Ability Scales (BAS3). Overall, 37.50% of the matUPD7 group and 10.64% of the 11p15 LOM group scored above the SRS-2 severe clinical cut-off. Based on the ADOS-2, 33.33% of the matUPD7 participants and 11.11% of the 11p15 LOM participants scored above cut-off for autism spectrum/autism. Intellectual ability was significantly lower in the matUPD7 group (mean = 79.86), compared to the 11p15 LOM group (mean = 98.56). However, there was no evidence of an uneven cognitive profile associated with either group or of an association between autistic traits and intellectual ability. Although both 11p15 LOM and matUPD7 have the same clinical diagnosis of Silver-Russell syndrome, there are some differences in the cognitive and behavioural phenotypes between these two molecular subtypes. This has implications for considering access to services, intervention and support within these populations, particularly in relation to learning and behaviour.

Keywords

Silver-Russell syndrome; Autism Spectrum Disorder; Intellectual ability

General Scientific Summary

This study provides novel insights into the cognitive and behavioural features associated with two molecular causes of Silver-Russell syndrome and highlights the need for individuals with this syndrome to have access to services, intervention and support for learning and behaviour.

Autistic traits and cognitive abilities associated with two molecular causes of Silver-Russell syndrome

Silver-Russell syndrome is a rare genetic imprinting disorder associated with restricted growth, initially described independently by Silver, Kiyasu, George, and Deamer (1953) and Russell (1954). The exact incidence is unknown but estimates range from 1 in 30,000 to 1 in 100,000 (Wakeling et al., 2017). The clinical features of the syndrome, according to the Netchine-Harbison clinical scoring system, are: small for gestational age (SGA), postnatal growth failure, relative macrocephaly at birth, protruding forehead, body asymmetry, and feeding difficulties and/or low BMI (Azzi et al., 2015). A clinical diagnosis of Silver-Russell syndrome is given if an individual has at least four of these clinical features. A molecular cause has been identified in approximately 60% of individuals with a clinical diagnosis of Silver-Russell syndrome. Specifically, 30 – 60% have loss of methylation on chromosome 11p15 (11p15 LOM) and 5 – 10% have maternal uniparental disomy for chromosome 7 (matUPD7) (Gicquel et al., 2005; Netchine et al., 2007; Preece et al., 1997). As Silver-Russell syndrome has two distinct molecular causes, the syndrome provides a unique opportunity to explore within-syndrome genotype-phenotype relationships. This is important as, although both of these molecular subtypes are diagnosed on the basis of the same clinical features, current understanding of the extent to which shared phenotypic similarities exist in relation to cognition and behaviour is limited.

Before the identification of the molecular causes of Silver-Russell syndrome, Lai, Skuse, Stanhope, and Hindmarsh (1994) assessed cognitive abilities in a sample of children (N = 25) with a clinical diagnosis of Silver-Russell syndrome, using the Weschler Intelligence Scale for Children, third edition (WISC-III). The findings identified a range of intellectual ability within the sample, ranging from mild/moderate intellectual disability to average intellectual ability, with a mean full scale IQ of 85.9. Intellectual ability was also

reported in a sample of children (N = 36) with Silver-Russell syndrome but again, molecular causes had not been identified in the majority of participants so it is likely that this sample included individuals with different molecular abnormalities (Noeker & Wollmann, 2004). In this study, IQ was assessed using the German edition of the Kaufman Assessment Battery for Children (K-ABC). A mean IQ of 96 was reported, with the majority of participants having IQ scores in the average range. The sample included two participants with matUPD7 and these participants had IQ scores of 81 and 84, indicating that both had borderline intellectual ability. Overall, these studies provide initial evidence to suggest that some individuals with Silver-Russell syndrome have below average intellectual ability but the findings are primarily based on individuals with a clinical diagnosis of Silver-Russell syndrome, so genotype-phenotype relationships cannot be inferred.

More recently, it has been suggested that ASD and intellectual disability are prevalent within the Silver-Russell syndrome population and particularly in individuals with matUPD7 (Azzi et al., 2015; Wakeling et al., 2010). However, although both of these studies included individuals with confirmed molecular diagnoses, the focus of these studies was to characterise the associated clinical phenotypes. Consequently, standardised scores were not reported so it is not clear how developmental delay, “diagnosed cognitive disabilities” or ASD were defined or assessed. In a sample of 64 individuals, Wakeling et al., (2010) reported that 20% of the 11p15 LOM group (N = 44) and 65% of the matUPD7 group (N = 20) had developmental delay. Furthermore, Azzi et al., (2015) reported a higher prevalence of “diagnosed cognitive disabilities” and autism/pervasive developmental disorder (PDD) in a sample of individuals with matUPD7, compared to individuals with 11p15 LOM. However, this information was reported within the supplementary material and it is not clear how autistic traits and “cognitive disabilities” were assessed.

Congenital syndromes with an identifiable genetic cause provide an important model for investigating genotype-phenotype relationships, particularly in relation to the often associated cognitive and behavioural impairments. For example, increased prevalence of autistic behaviours has been reported in a number of genetic syndromes, such as Cornelia de Lange syndrome ((Moss, Howlin, Magiati, & Oliver, 2012), Fragile X syndrome (Hatton et al., 2006) and Sotos syndrome (Lane, Milne, & Freeth, 2017). Furthermore, it has been suggested that approximately 10 – 20 % of individuals with ASD have an identifiable genetic syndrome (Abrahams & Geschwind, 2008). A range of measures can be used to assess the prevalence and profile of ASD behaviours, including parental-report and behavioural observation. Use of autism-specific standardised assessments enables autistic traits to be characterised in detail, rather than relying upon the prevalence of clinical diagnoses alone. For example, the Autism Diagnostic Observation Schedule, second edition (ADOS-2) and Social Communication Questionnaire (SCQ) have been used to characterise the prevalence and phenomenology of ASD in Cornelia de Lange syndrome and Cri du Chat syndrome (Moss et al., 2008). This approach is useful for identifying established support and interventions designed for ASD which may be beneficial for syndrome populations in which specific behaviours, such as social cognition or repetitive behaviours, may be problematic.

In some genetic syndrome populations, it has been suggested that the associated degree of intellectual disability increases the presence of autistic behaviours due to difficulty with cognitive compensation (Skuse, 2007). For example, greater severity of ASD behaviours has been associated with lower intellectual ability in genetic syndromes, such as Fragile X syndrome (Loesch et al., 2007) and Tuberous Sclerosis Complex (Granader et al., 2010; Jeste, Sahin, Bolton, Ploubidis, & Humphrey, 2008). Conversely, it has been suggested that higher IQ is not protective of ASD in Prader-Willi syndrome (Descheemaeker, Govers, Vermeulen, & Fryns, 2006), indicating variability in this relationship between syndromes.

Identifying congenital syndromes with a high incidence of ASD, as well as an identifiable molecular or genetic cause, and assessing relationships between autistic traits and intellectual ability will lead to improved understanding of the causal pathways of ASD, particularly in syndromes in which intellectual disability is less prevalent.

To date, cognitive abilities and autistic traits have not been systematically investigated in a sample of individuals with confirmed molecular diagnoses of Silver-Russell syndrome using standardised assessments. Thus, it is important to characterise the phenotypes associated with these molecular subtypes as this will have important implications for the diagnosis and management of Silver-Russell syndrome. Indeed, the frequency of developmental delay and behavioural issues was noted as an important direction for future research in the recently published Silver-Russell syndrome consensus statement (Wakeling et al., 2017). Thus, the primary aim of this study was to identify and compare the prevalence of autistic traits associated with two molecular causes of Silver-Russell syndrome (11p15 LOM and matUPD7). Secondary aims of this study were to assess cognitive abilities within these populations in order to establish and compare the intellectual ability of individuals with 11p15 LOM and individuals with matUPD7, and to assess relationships between autistic traits and cognitive abilities within these populations.

Method

Participants

The sample comprised 32 individuals with a molecular diagnosis of matUPD7 and 47 individuals with a molecular diagnosis of 11p15 LOM (see Table 1 for participant characteristics). Families self-reported the exact diagnosis received and participants were only included if they had received both a clinical and molecular diagnosis of Silver-Russell syndrome, specified as either 11p15 LOM or matUPD7. Participants were recruited via the

Child Growth Foundation (CGF; a UK charity that supports families of individuals affected by growth conditions) and the MAGIC Foundation (a US charity that supports families of individuals affected by growth conditions).

[Insert Table 1 about here]

Measures

Social Responsiveness Scale, second edition (SRS-2) (Constantino & Gruber, 2012). The SRS-2 is a 65-item standardised questionnaire, consistent with the DSM-5 criteria for ASD, designed to assess social communication impairment (SCI) and restricted interests and repetitive behaviours (RRB). Each item is coded on a Likert scale (0 = not true to 3 = almost always true). A total score provides an indication of severity of autistic behaviours, with a higher score indicating greater severity. Total scores can be categorised as non-clinical, mild, moderate or severe. Subscale scores indicate severity of difficulty with SCI and RRB. The SRS-2 has age-appropriate versions for both children and adults and has norms for children aged 2 years 6 months to adults.

Autism Diagnostic Observation Schedule, second edition (ADOS-2) (Lord et al., 2012). The ADOS-2 is a semi-structured, standardised, observational assessment designed to assess behaviours associated with ASD using a range of activities and social presses. The ADOS-2 has four modules which are developmentally appropriate for individuals of differing chronological age and language ability. All participants completed modules 2, 3 or 4 and the most appropriate module was chosen for each participant based on their age, developmental level and language ability. The ADOS-2 can be used with toddlers as young as 12 months through to adults. Within each module, behaviours of interest are assessed on the basis of

individual items. Item scores range from 0 (no evident abnormality) to 3 (marked abnormality) and scores on algorithm items are combined to provide a total ADOS-2 score. This total score can be converted to a calibrated severity score (maximum = 10), with higher scores indicating greater severity of autistic behaviours. For each module, cut-offs are provided in order to classify an individual as scoring in the non-spectrum, autism spectrum or autism range. Algorithm item scores can also be used to calculate domain-level scores for social affect and restricted and repetitive behaviours. The revised algorithm was used for module 4 (Hus & Lord, 2014).

The British Ability Scales, third edition (BAS3) (Elliott & Smith, 2011). The BAS3 is a standardised battery of cognitive tasks, designed to assess a range of cognitive abilities. There are two batteries: an early years (EY) battery, which has norms for children aged 3 – 7 years 11 months and a school age (SA) battery, which has norms for children aged 5 – 17 years 11 months. The BAS3 is appropriate for use with individuals of a wide age range, as well as individuals of varying intellectual ability. Each battery comprises six core scales which are used to determine a General Conceptual Ability (GCA) score. This is equivalent to an IQ score and provides a measure of overall intellectual ability. GCA scores are calculated as standard scores (M = 100, SD = 15) on the basis of the distribution of T-scores (M = 50, SD = 10) for the six core scales. Cluster scores can also be derived from the core scales, with two core scales corresponding to each cluster: verbal (V) ability, non-verbal reasoning (NVR) ability and spatial (S) ability.

Procedure

The parent/caregiver of each participant completed the SRS-2 (N = 79). In-person assessments (ADOS-2 and BAS3) were administered to a subset of participants in the UK (n = 33). These participants responded to advertisements for participation in this study and for logistical reasons, in-person assessments were only carried out in the UK. The majority of

these participants were visited at their home (n = 23) and a small number of participants completed the study at their school (n = 6), at the annual CGF convention in 2018 (n = 3) or at an alternative location (n = 1).

Ethical considerations

Participants aged 18 years and over provided written informed consent and for children under the age of 18 years, the parent/caregiver of the participant was required to give written informed consent. All participants provided verbal assent. The study received ethical approval from the ethics committee in the Department of Psychology, University of Sheffield.

Results

There was a significant difference in chronological age in years between the 11p15 LOM (M = 8.17, SD = 4.24) and matUPD7 (M = 11.63, SD = 7.12) groups, $t(77) = 2.70$, $p = .008$, $d = 0.62$, indicating that the 11p15 LOM group were significantly younger than the matUPD7 group. However, all of the measures used are standardised and normed for age and there were no significant associations between age and the other variables included in the subsequent analyses for either group, indicating that age differences were unlikely to affect the nature of the results. There were no sex differences observed in either group in relation to SRS-2 total T-scores, SRS-2 subscale scores, ADOS-2 calibrated severity scores or GCA scores.

Parent-reported autistic traits (SRS-2)

According to the SRS-2, clinical cut-off for ASD was considered as a total T-score ≥ 60 (Constantino & Gruber, 2012). In the 11p15 LOM group, 44.68% of participants scored above clinical cut-off and in the matUPD7 group, 53.13% of participants scored above clinical cut-off. Prevalence of parent-reported autistic traits, as assessed by total T-scores,

was significantly higher for the matUPD7 (M = 64.97, SD = 16.50) group, compared to the 11p15 LOM group (M = 57.96, SD = 13.20), $t(77) = 2.09$, $p = .04$, $d = 0.48$. Total T-scores above clinical cut-off were categorised as mild (60 – 65), moderate (66 – 75) or severe (≥ 76). The proportion of participants scoring in each of the severity categories differed between the groups, $X^2(3, N = 79) = 9.76$, $p = .021$. As can be seen in Figure 1, a greater proportion of the matUPD7 participants scored in the severe range (37.50%), compared to the 11p15 LOM participants (10.64%).

[Insert Figure 1 about here]

Comparison of T-scores on the two DSM-5 subscales (social communication impairment (SCI) and restricted interests and repetitive behaviours (RRB)) for the 11p15 LOM and matUPD7 groups, via a mixed measures ANOVA, revealed a significant main effect of subscale; $F(1, 77) = 21.09$, $p < .001$, $\eta\rho^2 = .215$, a significant main effect of group; $F(1, 77) = 5.73$, $p = .019$, $\eta\rho^2 = .069$, and a significant subscale x group interaction; $F(1, 77) = 5.38$, $p = .023$, $\eta\rho^2 = .065$. This demonstrates that the severity of behaviours and the profile of subscale scores differed between the groups. Post-hoc comparisons revealed no significant difference between SCI T-scores for the 11p15 LOM (M = 57.30, SD = 13.21) and matUPD7 (M = 63.03, SD = 15.93) groups, $t(77) = 1.74$, $p = .086$, $d = 0.40$. However, there was a significant difference between RRB T-scores for the 11p15 LOM (M = 59.40, SD = 13.42) and matUPD7 (M = 69.44, SD = 18.09) groups, $t(77) = 2.83$, $p = .006$, $d = 0.65$, demonstrating that both groups were reported as experiencing similar difficulty with social communication impairment but restricted interests and repetitive behaviours were reported as

more problematic for individuals with matUPD7, compared to individuals with 11p15 LOM (see Figure 2).

[Insert Figure 2 about here]

In-person assessments

A subset of participants completed in-person assessments in the UK: 11p15 LOM (n = 18) and matUPD7 (n = 15). See Table 1 for participant characteristics.

Observed autistic traits

The ADOS-2 was used to complement and extend the findings from the SRS-2 by observing and assessing autistic behaviours using a gold-standard behavioural observation (Lord et al., 2012). ADOS-2 calibrated severity scores were significantly higher in the matUPD7 group (M = 3.33, SD = 2.47, range = 1 – 10), compared to the 11p15 LOM group (M = 1.89, SD = 1.64, range = 1 – 6), $U = 72.00$, $p = .016$. On the basis of total scores, in the matUPD7 group, 66.67% (n = 10) had scores in the non-spectrum range, 13.33% (n = 2) had scores in the spectrum range and 20% (n = 3) had scores in the autism range. In the 11p15 LOM group, 88.89% (n = 16) had scores in the non-spectrum range, 0% (n = 0) had scores in the spectrum range and 11.11% (n = 2) had scores in the autism range. All of the participants who scored above cut-off on the ADOS-2 also had SRS-2 scores above clinical cut-off. See Table 2 for the total number of participants who completed each module and ADOS-2 domain-level scores.

[Insert Table 2 about here]

Cognitive ability

Participants completed either the SA battery (n = 28) or the EY battery (n = 5), depending on their age. One matUPD7 participant did not complete all of the SA battery core scales so was not included in the subsequent BAS3 analyses. Overall intellectual ability was assessed on the basis of general conceptual ability (GCA) scores. The matUPD7 group (M = 79.86, SD = 8.72, range = 57 – 91) had significantly lower GCA scores than the 11p15 LOM group (M = 98.56, SD = 19.23, range = 62 – 140), $t(24.90) = -3.67$, $p = .001$, $d = 1.47$. In addition, Levene's test revealed a significant difference in variance between the groups, $F = 6.06$, $p = .02$, due to considerable variability in GCA scores in the 11p15 LOM group which was not observed in the matUPD7 group (see Figure 3).

[Insert Figure 3 about here]

Comparison of cluster scores (V, NVR and S abilities) for the 11p15 LOM and matUPD7 groups, via a mixed measures ANOVA, revealed no significant main effect of cluster; $F(2, 60) = 0.15$, $p = .859$, $\eta\rho^2 = .005$, no cluster x group interaction; $F(2, 60) = 0.05$, $p = .947$, $\eta\rho^2 = .002$ and a significant main effect of group, $F(1, 30) = 11.96$, $p = .002$, $\eta\rho^2 = .285$. Overall, these findings provide no evidence for an uneven cognitive profile associated with either group (see Figure 4).

[Insert Figure 4 about here]

Relationships between autistic traits and intellectual ability

In the combined sample of participants with matUPD7 and participants with 11p15 LOM who completed the in-person assessments, there was no significant relationship between SRS-2 total T-scores and GCA scores, $r = .006$, $N = 32$, $p = .972$ and no significant relationship between ADOS-2 calibrated severity scores and GCA scores, $r = -.145$, $N = 32$, $p = .429$. The relationship between autistic traits and intellectual ability was then considered separately for each group. For participants with matUPD7, there was no significant relationship between SRS-2 total T-scores and GCA scores, $r = .015$, $N = 14$, $p = .959$, and no significant relationship between ADOS-2 calibrated severity scores and GCA scores, $r = .254$, $N = 14$, $p = .381$. For participants with 11p15 LOM, there was also no significant relationship between SRS-2 total T-scores and GCA scores, $r = .385$, $N = 18$, $p = .114$, and no significant relationship between ADOS-2 calibrated severity scores and GCA scores, $r = -.063$, $N = 18$, $p = .803$. This indicates that, in both groups, severity of autistic traits was not associated with overall intellectual ability.

Discussion

This study aimed to identify and compare the prevalence of autistic traits and the degree of intellectual ability associated with two distinct molecular causes of Silver-Russell syndrome; 11p15 LOM and matUPD7. Findings from both the parental-report measure (SRS-2) and the behavioural observation (ADOS-2) identified that autistic traits were prevalent in both groups but were more common in the matUPD7 group. Specifically, 37.50% of the matUPD7 group and 10.64% of the 11p15 LOM group scored above the severe clinical cut-off on the SRS-2, whilst 33.33% of the matUPD7 group were classified as scoring in the ADOS-2 spectrum or autism spectrum range, compared to 11.11% of the 11p15 LOM group. Intellectual ability was significantly lower in the matUPD7 group, compared to the 11p15

LOM group. There was no evidence of an uneven cognitive profile associated with either group or of an association between autistic traits and intellectual ability.

This is the first study to report the prevalence of autistic traits in individuals with 11p15 LOM and individuals with matUPD7 using standardised measures. Although previous research had reported descriptively that autism/PDD were more prevalent in matUPD7, compared to 11p15, it was not clear how autism/PDD had been defined or assessed (Azzi et al., 2015). In the present study, findings from both the SRS-2 and the ADOS-2 clearly demonstrated that autistic traits were reported and observed in both molecular subtypes but were more prevalent in matUPD7. Furthermore, when autistic traits were present in matUPD7 individuals, the tendency was for them to be rated as severe, according to the SRS-2. In the matUPD7 group, SRS-2 total T-scores ranged from 37 – 93 and in the 11p15 LOM group, these scores ranged from 40 – 89. ADOS-2 calibrated severity scores ranged from 1 – 10 in the matUPD7 group and from 1 – 6 in the 11p15 LOM group, indicating variability in severity of autistic traits in both groups. In terms of clinical implications, clinicians should be aware of the variability of autistic traits observed within both molecular subtypes and to consider the suitability of a clinical assessment for autism on an individual basis.

In a recent systematic review and meta-analysis, prevalence estimates of ASD phenomenology in twelve genetic syndromes ranged from 11% in 22q11.2 deletion syndrome to 61% in females with Rett syndrome (Richards, Jones, Groves, Moss, & Oliver, 2015). Thus, the findings from the present study indicate that the prevalence of ASD in 11p15 LOM and matUPD7 is comparable with that of other rare genetic syndromes, such as 22q11.2 deletion syndrome and Angelman syndrome, in which a similar prevalence of ASD has been reported (Richards et al., 2015). Importantly, in the present study, all of the participants who scored above clinical cut-off on the ADOS-2, also scored above clinical cut-off on the SRS-2, demonstrating good reliability between these measures. However, it is important to note that

some participants scored above clinical cut-off on the SRS-2 but clinically significant autistic behaviours were not observed during the ADOS-2, indicating reduced sensitivity of the SRS-2 in this population.

Previous research has used autism-specific standardised assessments to characterise the prevalence and phenomenology of ASD in other genetic syndromes (Garg et al., 2015; Moss et al., 2008). In the present study, comparison of scores on the two DSM-5 subscales revealed that the matUPD7 group were reported as having greater difficulty with RRB than the 11p15 LOM group but there was no difference in SCI scores between the groups. The finding of greater difficulty with RRB in the matUPD7 group is a novel finding which provides insight into the profile of autistic traits within this population and demonstrates the need for support with RRB in individuals with matUPD7.

In relation to intellectual ability, the findings indicated that intellectual functioning is not impaired in 11p15 LOM, as evidenced by a mean GCA of 98.56. Within this group, GCA scores ranged from 62 – 140, suggesting that the distribution of scores is commensurate with the general population. Previous research has identified a possible relationship between the degree of 11p15 hypomethylation and the severity of the clinical phenotype (Bruce, Hannula-Jouppi, Peltonen, Kere, & Lipsanen-Nyman, 2009). Although the relationship between the degree of 11p15 hypomethylation and intellectual ability has not yet been assessed, the severity of hypomethylation could account for the variability observed in GCA scores within the 11p15 LOM group in the present study. This will be an important direction for future research. Conversely, the mean GCA of the matUPD7 group was 79.86, with GCA scores ranging from 57 – 91. The majority of participants within this group had borderline intellectual functioning, demonstrating that intellectual ability in the matUPD7 group was lower than would be expected within the general population. This is consistent with previous research in which two individuals with matUPD7 have been reported as having borderline

intellectual ability (Noeker & Wollmann, 2004). Importantly, there was limited variability in GCA scores within this group, suggesting that individuals with matUPD7 tend to have borderline intellectual ability.

This is the first study to report quantitative scores in relation to cognitive abilities in a cohort of individuals with both molecular subtypes of Silver-Russell syndrome. Previous research has identified uneven profiles associated with other genetic syndromes, such as Williams syndrome (Mervis et al., 2000), Fragile X syndrome (Van Der Molen et al., 2010) and Sotos syndrome (Lane, Milne, & Freeth, 2019). However, in the present study, there was no evidence to indicate that either 11p15 LOM or matUPD7 are associated with an uneven cognitive profile, as evidenced by no difference between cluster scores within each group. Thus, the findings indicate that, due to the individual variability observed in cognitive strengths and difficulties within the 11p15 LOM and matUPD7 groups, appropriate educational strategies should be considered on an individual basis.

It has been proposed that intellectual disability increases the presence of autistic behaviours for individuals with genetic syndromes (Skuse, 2007) and associations between intellectual ability and autistic behaviours have been identified in some genetic syndromes (Granader et al., 2010; Jeste et al., 2008; Loesch et al., 2007). In the present study, in both the 11p15 LOM and matUPD7 groups, there was no evidence of an association between SRS-2 total T-scores and GCA scores or ADOS-2 total scores and GCA scores for either group. This indicates that, within the Silver-Russell syndrome population, prevalence of autistic traits, based on both parent-report and behavioural observation, is not associated with overall intellectual ability. In terms of clinical implications, this demonstrates that individuals with Silver-Russell syndrome should receive screening for ASD, regardless of their overall intellectual ability. However, it is important to note that cognitive abilities were only assessed

in a subset of participants so it will be important for future research to explore this association in a larger sample of individuals with Silver-Russell syndrome.

As noted in the recent Silver-Russell syndrome consensus statement, the frequency of associated clinical features, such as developmental delay and behavioural issues was suggested as an important direction for future research (Wakeling et al., 2017). The findings from the present study have started to address this gap in the literature and have significantly advanced understanding of the cognitive and behavioural phenotypes associated with 11p15 LOM and matUPD7. As the present study focused on behaviour in relation to ASD, it will be important for future research to assess other behaviours, such as anxiety, depression and attentional difficulties, in order to determine whether these are prevalent within the Silver-Russell syndrome population. This will improve understanding of the behavioural phenotypes associated with the Silver-Russell syndrome molecular subtypes.

Limitations

Participants in this study were recruited via patient support groups and therefore a limitation of this study is patient ascertainment bias. However, considerable variability was observed within the sample, both in relation to severity of autistic traits and intellectual disability, indicating that the sample was not restricted to those with greater difficulties. Furthermore, although autistic traits were assessed via parental report in an international sample, for logistical reasons, it was not possible to assess cognitive abilities in individuals with Silver-Russell syndrome outside of the UK. As access to genetic testing varies between countries, it will be important for future research to establish whether the findings from this study are representative of the Silver-Russell syndrome population in different countries, for example, in terms of intellectual ability or behavioural issues. Due to the nature of conducting research with rare populations, the statistical power of this study was limited. However, it is important to note that, considering the prevalence of Silver-Russell syndrome, this study

included a good sample size. In order to further understanding of the syndrome and the variability observed both within and between the molecular subtypes, it will be important for future research to consider relationships between different aspects of the phenotype in a larger sample.

Conclusion

In summary, this study provides the first characterisation of autistic traits and cognitive abilities associated with two molecular subtypes of Silver-Russell syndrome. Despite the same clinical diagnosis, it is clear that there are some differences in the cognitive and behavioural phenotypes associated with 11p15 LOM and matUPD7. Specifically, matUPD7 is associated with increased prevalence of autistic traits and lower intellectual ability, compared to 11p15 LOM, although there was considerable variability within both groups. Overall, this has important clinical implications in terms of screening for ASD within the Silver-Russell syndrome population and for identifying individuals, particularly those with matUPD7, who may benefit from access to services, intervention and support in relation to learning and behaviour.

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Table 1. Participant characteristics of the full sample and the subset who completed the in-person assessments

	Total sample		In-person assessment sub-sample	
Characteristics	matUPD7 (n = 32)	11p15 LOM (n = 47)	matUPD7 (n = 15)	11p15 LOM (n = 18)
Age (in years)				
Mean	11.63	8.17	14.27	8.63
SD	7.12	4.24	6.37	3.44
Range	2.58 – 28.17	2.50 – 20.00	8.08 – 28.17	4.42 – 15.75
Sex (n)				
Males	13	29	6	10
Females	19	18	9	8

Table 2. Mean ADOS-2 domain scores for the matUPD7 and 11p15 LOM groups by ADOS-2 module

	matUPD7 (n = 15)	11p15 LOM (n = 18)
Module 4	n = 5	n = 1
Social affect		
M (SD)	3.20 (2.77)	0.00
Restricted and repetitive behaviour		
M (SD)	2.00 (1.22)	0.00
Module 3	n = 10	n = 12
Social affect		
M (SD)	5.80 (5.20)	2.42 (3.34)
Restricted and repetitive behaviour		
M (SD)	2.00 (2.05)	1.00 (0.85)
Module 2	n = 0	n = 5
Social affect		
M (SD)	0.00	1.00 (1.00)
Restricted and repetitive behaviour		
M (SD)	0.00	1.40 (1.52)
Calibrated severity scores	n = 15	n = 18
M (SD)	3.33 (2.47)	1.89 (1.64)

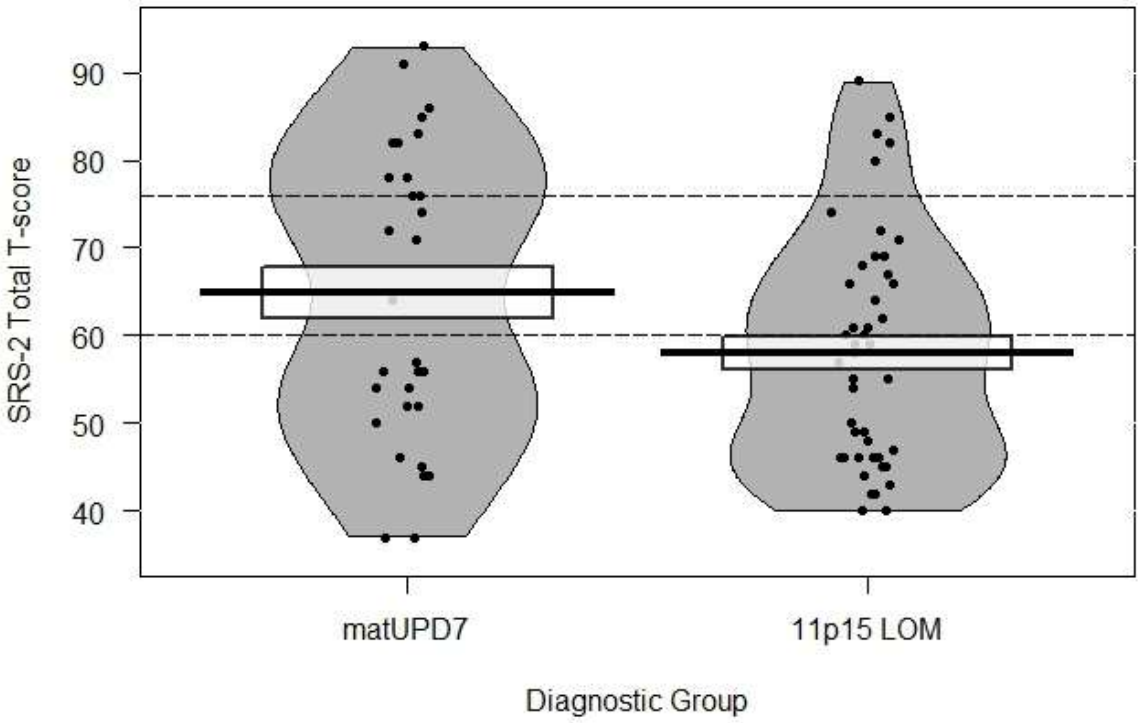

Figure 1. Pirate plot (Phillips, 2017) of SRS-2 total T-scores for the matUPD7 and 11p15 LOM groups. Points represent the raw data, the bold horizontal lines depict the mean and the rectangles represent standard error of the mean. The lower dashed horizontal line depicts a T-score of 60 which represents clinical cut-off. The upper dashed horizontal line depicts a T-score of 76 and scores on or above this line are categorised as severe.

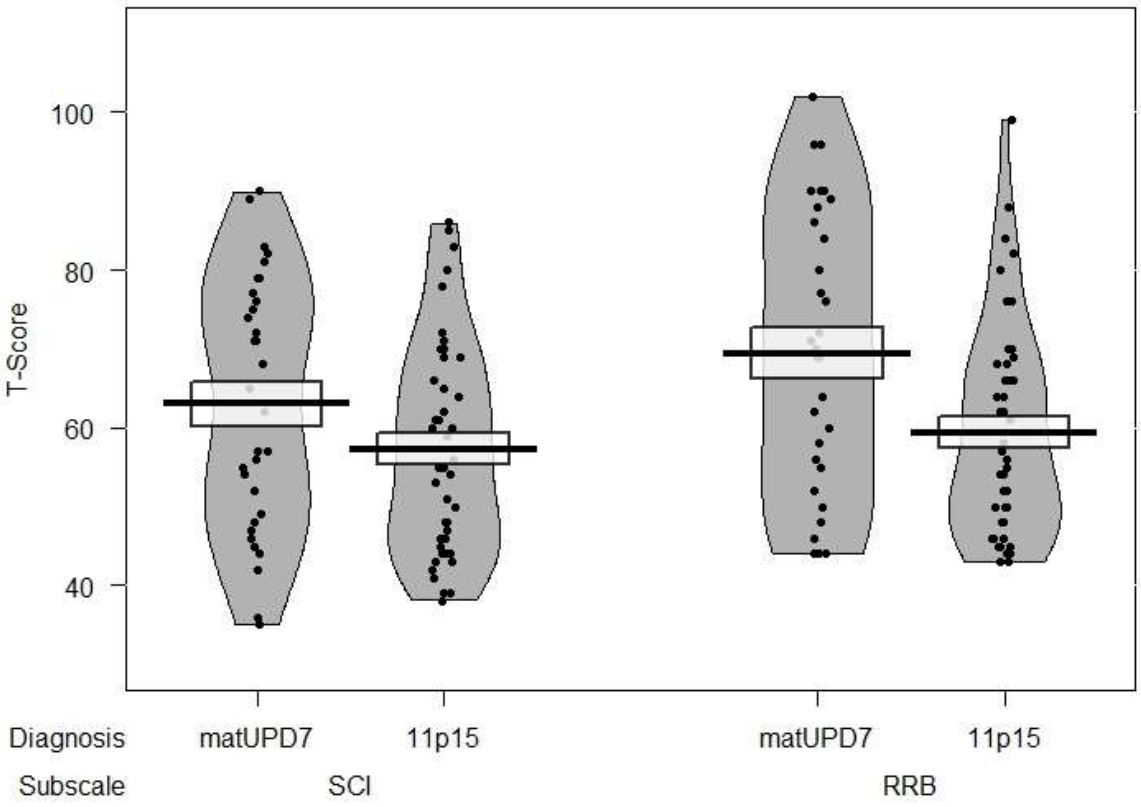

Figure 2. Pirate plot (Phillips, 2017) of T-scores for the social communication impairment (SCI) and restricted interests and repetitive behaviours (RRB) SRS-2 subscales for the matUPD7 and 11p15 LOM groups. Points represent the raw data, the bold horizontal lines depict the mean and the rectangles represent standard error of the mean.

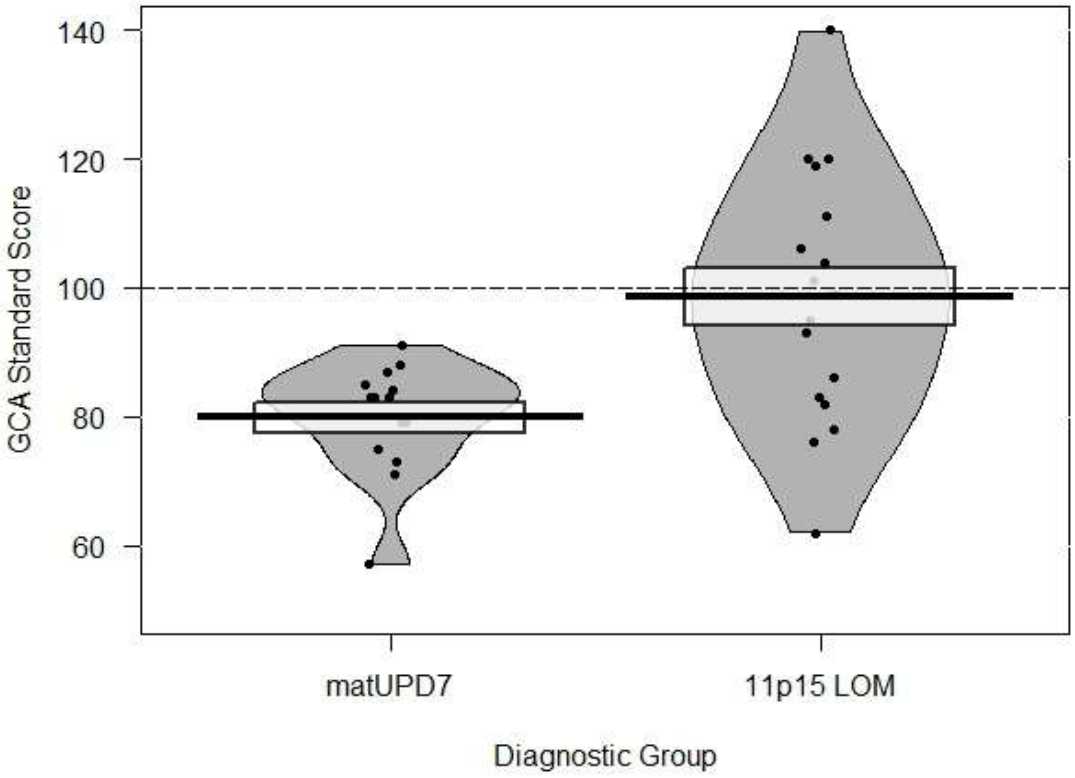

Figure 3. Pirate plot (Phillips, 2017) of general conceptual ability (GCA) scores for the matUPD7 and 11p15 LOM groups. Points represent the raw data, the bold horizontal lines depict the mean and the rectangles represent standard error of the mean. The dashed horizontal line depicts a GCA score of 100 which represents the general population average.

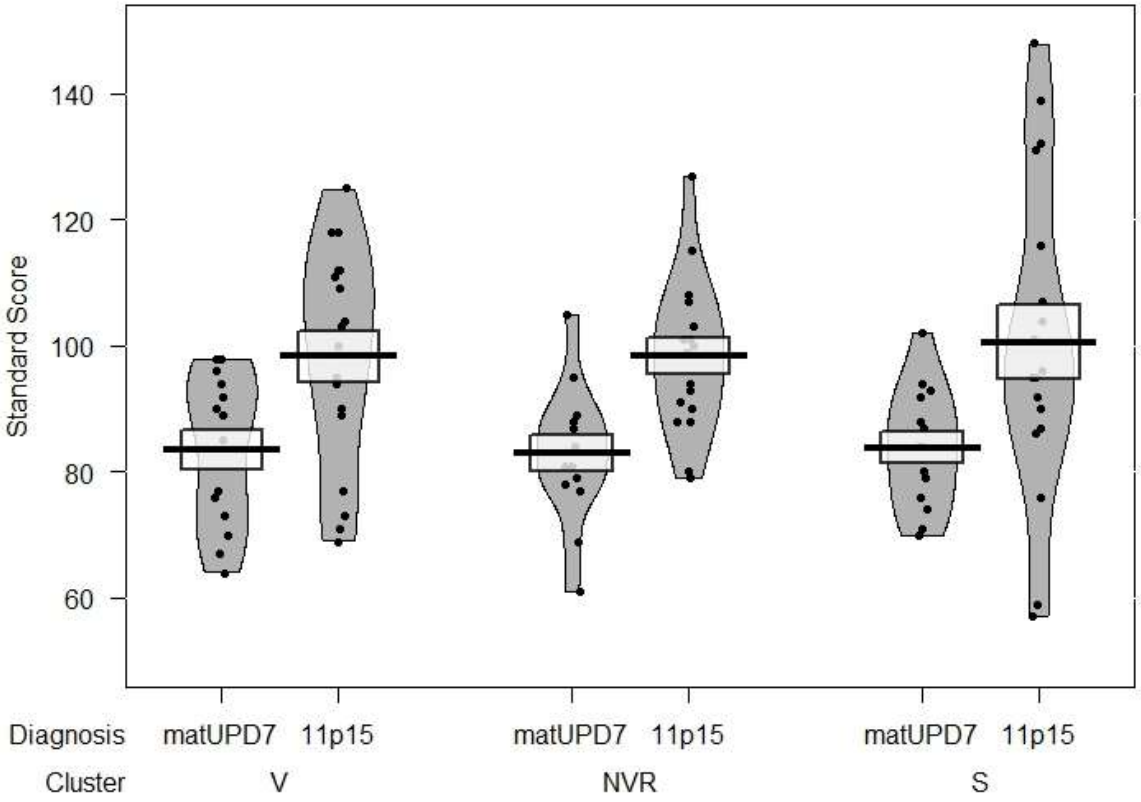

Figure 4. Pirate plot (Phillips, 2017) of standard scores for the verbal (V) ability, non-verbal reasoning (NVR) ability and spatial (S) ability clusters from the BAS3 for the matUPD7 and 11p15 LOM groups. Points represent the raw data, the bold horizontal lines depict the mean and the rectangles represent standard error of the mean.