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ORIGINAL ARTICLE

Neurocognitive, adaptive, and psychosocial functioning in individuals with Robinow syndrome

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Abstract

It has been estimated that 10–15% of people with Robinow syndrome (RS) show delayed development, but no studies have formally assessed developmental domains. The objective of this study is to provide the first description of cognitive, adaptive, and psychological functioning in RS. Thirteen participants (10 males) aged 4–51 years were seen for neuropsychological screening. Eight had autosomal-dominant RS (*DVL1*, *n* = 5; *WNT5A*, *n* = 3), four had autosomal-recessive RS (*NXN*, *n* = 2; *ROR2*, *n* = 2), and one had a mutation on an RS candidate gene (*GPC4*). Participants completed measures of intellectual, fine-motor, adaptive, executive, and psychological functioning. Findings indicated generally average intellectual functioning and low-average visuomotor skills. Adaptive functioning was average in autosomal-recessive RS (RRS) but low average in autosomal-dominant RS (DRS). Parent-report indicated executive dysfunction and attention problems in 4/8 children, 3/4 of whom had a *DVL1* variant; adult self-report did not indicate similar difficulties. Learning disabilities were also reported in 4/8 individuals with DRS, 3/4 of whom had a *DVL1* variant. Peer problems were reported for a majority of participants, many of whom also reported emotional concerns. Altogether, the findings indicate average neurocognitive functioning in RRS. In contrast, DRS, especially *DVL1* pathogenic alleles, may confer specific risk for neurodevelopmental disability.

KEYWORDS

adaptive, cognitive, psychological, Robinow syndrome, social

1 | INTRODUCTION

Robinow syndrome (RS) is a very rare skeletal disorder characterized by short stature, mesomelic limb shortening, brachydactyly, genital hypoplasia, and distinctive craniofacial features (Mazzeu & Brunner, 2020; Robinow, Silverman, & Smith, 1969). The exact prevalence is unknown, but fewer than 250 cases have been reported in the literature. RS is a genetically heterogeneous condition, although all known pathogenic variants reside in genes in the noncanonical Wnt signaling pathway. Two types of RS have been identified: autosomal-recessive RS (RRS) is caused by bi-allelic variants affecting *ROR2* (Afzal et al., 2000; van Bokhoven et al., 2000) or *NXN* (White et al., 2018), whereas autosomal-dominant RS (DRS) is caused by heterozygous variants affecting *DVL1* (White et al., 2015, Bunn et al., 2015), *DVL3* (White et al., 2016), *FZD2* (White et al., 2018), or *WNT5A* (Person et al., 2010). An additional gene, *GPC4*, is considered a Robinow candidate (White et al., 2018). Both RRS and DRS share a majority of clinical features, though DRS is typically considered to have a milder skeletal phenotype. Case studies have reported diverse neurological abnormalities including periventricular cortical dysplasia (Guillen-Navarro, Wallerstein, Reich, Zajac, & Ostrer, 1997), white matter atrophy with seizures (McPherson, Zaleski, & Giampietro, 2006), communicating hydrocephalus (Kantaputra, Gorlin, Ukarapol, Unachak, & Sudasna, 1999; Saal, Greenstein, Weinbaum, & Poole, 1988), and Moyamoya disease (Qaiser, Scott, & Smith, 2009), though it is not known if such anomalies are common in RS.

There is limited research on neurocognitive development in RS. In an early review of the literature, Butler and Wadlington (1987) reported "delayed development or mental retardation" in five of 27 patients with RS, though the criteria for these designations were not provided. Soliman, Rajab, Alsami, and Bedair (1998) evaluated 14 children and adolescents with RRS from six Omani families. They reported normal developmental milestones and average school performance in 12 of 14 participants, and "mild developmental delay affecting the fine motor skills and language" in two participants, which they characterized as "mental retardation." Mazzeu et al. (2007) reported on 37 patients with RRS and 51 patients with DRS, 38 of whom were personally evaluated, and 50 whose cases were taken from the literature. "Developmental delay/mental retardation" was reported in 20.5% of individuals with DRS and 7.4% of individuals with RRS. In all of these reports, the criteria used for developmental delay and mental retardation were not specified, and no data from standardized assessments were presented, making it difficult to interpret these findings.

Even less is known regarding the psychological functioning of individuals with RS. In general, there is evidence of increased social difficulties (teasing, isolation) in individuals with skeletal dysplasias (Thompson, Shakespeare, & Wright, 2008), craniofacial anomalies (Feragen & Stock, 2017), and short stature (Lee et al., 2009; Quitmann, Bullinger, Sommer, Rohenkohl, & Bernardino Da Silva, 2016), and these difficulties in turn may be associated with reduced quality of life and internalizing symptoms. However, no studies to our knowledge have specifically examined psychological and social functioning in RS. The purpose of the current study was to provide the first description of cognitive, adaptive, and psychological functioning in individuals with RS using standardized assessment measures.

2 | METHODS

2.1 | Participants

Participants were 13 individuals with RS verified using whole-exome sequencing or Sanger sequencing of the target gene. See Table 1 for demographic and genetic information. Informed consent was obtained from adult participants and caregivers of minor participants prior to testing, and whenever possible, child assent was also obtained. The study was approved by the institutional review board at Baylor College of Medicine (protocol no. H-43246). Each participant was tested individually in a private room at the hospital by one of the authors, who are licensed psychologists (D. D. S., M. E. A.) or a post-doctoral fellow in psychology (R. H. F.).

2.2 | Measures

Demographic information and clinical history was collected on a questionnaire completed by adult participants and caregivers of minor participants. Cognitive functioning was assessed with the *Wechsler Abbreviated Scale of Intelligence-Second Edition* (WASI-II; Wechsler, 2011), a brief measure of verbal, non-verbal, and general cognitive ability in individuals ages 6:0 to 90:11. Two subtests (Vocabulary and Matrix Reasoning) were administered in order to obtain an estimated Full Scale IQ for each participant, with the exception of one participant who was outside the age range of this measure. Raw scores for each subtest were converted to T scores with a mean of 50 and *SD* of 10, and were used to compute the estimated IQ standard score (SS) with a mean of 100 and *SD* of 15. Visuomotor functioning was assessed with the *Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition* (Beery VMI; Beery & Beery, 2004). The Beery VMI is an assessment of how well a child or adult can copy developmentally sequenced geometric shapes. It specifically assesses for deficits related to visual motor integration in individuals ages 2:0 to 99:11. Raw scores are converted to SSs with a mean of 100 and *SD* of 15. SSs between 90 and 110 are considered average.

Executive functioning was assessed using the *Behavior Rating Inventory of Executive Function* (BRIEF) questionnaire (Gioia, Isquith, Guy, & Kenworthy, 2000). There are several versions of the BRIEF including one for preschool-age populations (ages 2:0 to 5:11), one for children ages 5:0 to 18:0, and one for adults ages 18:0 to 90:0. Individuals completing the form report on the frequency of each behavior from "never" to "often." For the preschool version of the BRIEF, clinical scales combine to form three indexes (Inhibitory Self-Control Index [ISCI], Flexibility Index [FI], and Emergent Metacognition Index [EMI]),

TABLE 1 Patient characteristics

Age, years (*M*, range)	
Children (*n* = 8)	10.2 (4.9–14.7)
Adults (*n* = 5)	35.4 (20.9–51.3)
Sex (*n*, %)	
Female	3 (23%)
Male	10 (77%)
Race/ethnicity (*n*, %)	
Black	1 (8%)
White	8 (62%)
Biracial	1 (8%)
Hispanic	1 (8%)
Middle eastern	1 (8%)
Not specified	1 (8%)
Mutation (*n*, %)	
Dominant	8 (61.5%)
DVL1	5
WNT5A	3
Recessive	4 (30.8%)
ROR2	2
NXN	2
X-linked	1 (7.7%)
GPC4	1

and one summary composite (Global Executive Composite [GEC]). For the child and adult versions, clinical scales combine to form two indexes (Behavioral Regulation Index [BRI] and the Metacognition Index [MI]) and one summary composite (GEC). Raw scores are converted to T scores. T scores at or above 65 are considered clinically significant (Gioia et al., 2000).

Adaptive functioning was assessed using the *Adaptive Behavior Assessment System, Third Edition* (ABAS-3; Harrison & Oakland, 2015). The ABAS-3 assesses adaptive skills across the lifespan and yields a total score as well as scores for Conceptual, Social, and Practical adaptive skills. Caregivers of the minor participants completed either the form for children ages 5 and younger, or the form for children 5 to 21. Individuals completing the form report on the frequency of how independently the individual engages in the task or exhibits the behavior from "never" to "almost always." Raw scores for each adaptive skills area are converted to scaled scores with a mean of 10 and *SD* of 3. Scaled scores are then summed and converted to SSs for each adaptive domain (Conceptual, Social, and Practical). SSs between 90 and 110 are considered average (Harrison & Oakland, 2015).

We evaluated psychological and social functioning using the *Strengths and Difficulties Questionnaire* (SDQ; Goodman, Meltzer, & Bailey, 1998) self-report form for youth, and *Patient-Reported Outcomes Measurement Information System* (PROMIS) measures for both the children and the adults (Cella, Yount, Rothrock, et al., 2007). The SDQ is a screening instrument that asks questions related to emotional problems (symptoms of anxiety and depressed mood), conduct problems, hyperactivity/inattention, peer relationships, and prosocial behaviors. Participants ages 11–17 completed the self-report version of the SDQ by reporting on how true each statement is from "not true" to "certainly true" about themselves. Cut scores are then derived based on participant age and normative data. Caregivers of minor patients completed the PROMIS Pediatric Profile 25 v1.0, which assesses functioning in the following domains: Physical Function and Mobility, Anxiety, Depressive Symptoms, Fatigue, Peer Relationships, and Pain Interference. Adult participants completed the PROMIS-57 Profile V1.0, which assesses self-reported Physical Function, Anxiety, Depression, Fatigue, Sleep Disturbance, Satisfaction with Social Role, and Pain Interference. Raw scores are converted to T scores. Scores on the PROMIS scales between 60 and 69 indicate moderate concerns, and scores 70 and above indicate more severe concerns (Cella et al., 2010; Rothrock et al., 2010). Finally, symptoms of Attention Deficit/Hyperactivity Disorder (ADHD) were assessed in the children using parent report on the 18 ADHD symptom items from the NICHQ Vanderbilt Assessment Scale (Wolraich et al., 2003).

2.3 | Data analysis

Data were analyzed using SPSS 25 (IBM Corp., 2017). Descriptive statistics were generated for all variables. To examine differences by genetic variants, we grouped participants as having either DRS (*DVL1* or *WNT5A* mutations; $n = 8$) or RRS (*NXN* or *ROR2* mutations; $n = 4$) given the small sample size. The participant with a variant affecting gene candidate *GPC4* was not included in the statistical analyses comparing DRS versus RRS. Group differences were analyzed with Fisher's exact test for categorical variables, and independent samples t-tests for continuous variables. *t*-tests were used as none of the scores differed significantly from normal per the Shapiro–Wilk test, and the variances did not differ significantly between groups on any measure per Levene's test for equality of variance. Alpha was set at .05 for all analyses.

3 | RESULTS

As can be seen in Table 1, our sample was primarily male (77%) and White (62%), and the majority (61.5%) had DRS. Results are presented below by domain of functioning. Not all participants completed all measures, hence the slightly different sample sizes.

3.1 | Speech, motor, and physical functioning

A majority of participants reported a history of having received speech and language therapy (75.0%), occupational therapy (66.7%), and physical therapy (75.0%). Almost all of the children received these services (100, 100, and 86%, respectively), compared to smaller pluralities of the adults (40, 20, and 60%, respectively). Five of seven children (71.4%) had reported problems with speech/articulation, and six of seven children (85.7%) had reported problems with handwriting or note-taking in school (information was not provided for the eighth child).

Current physical functioning was assessed via parent and self-report on the PROMIS scales. Overall, findings were within the average range (Table 2). Eight of 10 participants who completed these scales had DRS, so subgroup comparisons could not be made. Two of 10 participants (one child, one adult) had significant current difficulties with physical function and mobility, 1/9 had significant problems with fatigue, and 1/9 had significant interference from pain. Despite common use of continuous positive airway pressure (CPAP) in this population, none of the adults reported sleep problems (scale not completed for the children).

Visuomotor integration skills were assessed using the Beery VMI (Table 3). Overall functioning across children and adults was in the low-average range (SS range 45–11), though the median score was average (SS = 93.5). Two participants had impaired functioning (SS < 70), three were in the low-average range, six were average, and one was above-average. The mean was lower for the RRS group (SS = 76.3 vs. 92.5), but this difference appears to have been driven by an outlier and was not statistically significant.

3.2 | Cognitive and adaptive functioning

Overall estimated intellectual functioning was in the average range (M = 97.4, SS range 79–117), with average vocabulary knowledge and

TABLE 2 Functional and psychosocial scales

PROMIS	T-score (*M*, *SD*)	# impaired
Physical functioning & mobility (*n* = 10)	46.7 (7.8)	2/10
Fatigue (*n* = 9)	47.2 (8.8)	1/9
Pain interference (*n* = 9)	54.1 (8.4)	1/9
Sleep disturbance (*n* = 5, adults only)	44.7 (10.8)	0/5
Applied cognition, general concerns (*n* = 10)	33.2 (10.8)	0/10
Anxiety (*n* = 10)	51.5 (8.6)	1/10
Depression (*n* = 10)	51.6 (6.8)	1/10
Strengths & Difficulties Questionnaire (*n* = 5)	Total score (*M*, *SD*)	# impaired
Total problems	17.2 (2.8)	2/5
Emotional	5.6 (1.9)	2/5
Conduct	1.6 (1.8)	0/5
Inattention/hyperactivity	5.4 (2.3)	1/5
Peer problems	4.6 (2.2)	4/5
Prosocial	8.6 (1.1)	0/5
Vanderbilt ADHD symptoms scale (*n* = 7)	# symptoms (*M*, *SD*)	# impaired
Inattention	4.1 (4.2)	3/7
Hyperactive/impulsive	2.3 (3.5)	2/7

Note: Impairment refers to *t*-scores ≥60 (PROMIS), high or very high scores on the Strengths & Difficulties Questionnaire, or six or more clinically significant symptoms on the Vanderbilt ADHD symptoms scales.
Abbreviation: PROMIS, Patient-Reported Outcomes Measurement Information System.

nonverbal reasoning (Table 3). Only one participant had a Full Scale IQ in the very low range (SS = 79), two were in the low average range (80–89), eight were in the average range (90–109), and one was above-average (≥110). None of the participants fell in the range of intellectual disability. There were no differences in IQ between the RRS and DRS groups.

Adaptive functioning, which was obtained for the children only, fell in the low-average range overall (ABAS-III Global Adaptive Composite, M = 88.1, range 74–112). Three of eight children had a Global Adaptive Composite score in the very low range, two were in the low-average range, two were average, and one was above average. Practical skills were lower overall than social skills and conceptual skills. Compared to the RRS group, the DRS group had significantly lower global adaptive skills, $t(5) = -3.3$, $p = .021$, conceptual skills, $t(5) = -4.5$, $p = .007$, and practical skills, $t(5) = -3.7$, $p = .015$.

3.3 | Attention and executive functioning

A history of attention problems was reported by caregivers of 4/7 children (57%) on the demographics and history questionnaire. On the Vanderbilt ADHD symptom scale, 3/7 children had six or more symptoms of inattention, while 2/7 had six or more symptoms of hyperactive/impulsive behavior (six or more symptoms representing a clinically significant concern within a domain). Attention problems were more common among children with a *DVL1* mutation (3/5) than other mutations (1/7), though this difference was not significant ($p = .222$, *Fisher's exact test*). All five adults denied any history of attention problems.

On the BRIEF (Table 3), clinically significant executive dysfunction was indicated by parent report in 4/8 children (50%), two of whom had deficits in both behavioral regulation and metacognition, and two of whom had deficits in metacognition alone. In contrast, none of the adults reported any executive dysfunction. Participants with DRS had higher scores (i.e., worse executive functioning) on the BRIEF scales compared to the RRS group, but none of these differences reached statistical significance (Table 3).

3.4 | Learning, school, and job functioning

Information on school and job functioning was obtained from the demographics and history questionnaire. Of the eight children, six were enrolled in public school, one was homeschooled, and one had not yet started school. Four of the seven school-aged children received special education services through the public school system, three for learning disability, and one for speech impairment. Three of seven children received school services for hearing impairment. Five of seven children had an Individualized Education Plan in place at school, and one received classroom accommodations through a Section 504 Plan (similar data were not collected for the adults). None of the participants had a reported history of grade retention.

Learning disabilities were reported in 3/7 children and 1/5 adults. One child had reported disabilities in reading, math, and writing, one had a math disability, and one had a writing disability; type of learning disability was not reported for the adult. One of the children without a learning disability nonetheless had reported problems in math. Learning disabilities were more common in individuals with DRS (4/8) than RRS (0/3), though this difference was not significant ($p = .212$, *Fisher's exact test*). Of note, 3/5individuals with *DVL1* mutations had a reported learning disability.

Among the adults, one completed high school, two completed some college, one had a 2-year degree, and one had a 4-year degree. In terms of employment, one participant was a lunchroom supervisor and domestic engineer, one an office assistant, and one worked in maintenance. Two participants did not report their current employment.

3.5 | Psychosocial functioning

On the PROMIS scales (Table 2), caregiver report indicated significant symptoms of depression in 1/5 children, and significant symptoms of anxiety in 1/5 children (a different child). Of note, the child with a history of depression also had significant problems with pain. Self-reported problems in these areas were higher among the five children older than 10 who completed the Strengths & Difficulties Questionnaire: 2/5

TABLE 3 Cognitive and adaptive scales

WASI-II	Total (*n* = 12)	DRS (*n* = 8)	RRS (*n* = 3)	*p*	# impaired/total
FSIQ-2	97.4 (11.7)	97.1 (13.1)	95.0 (9.8)	.81	1/12
Vocabulary	49.5 (6.6)	49.4 (7.5)	47.3 (2.5)	.66	0/12
Matrix reasoning	47.8 (11.4)	47.6 (13.3)	47.3 (9.1)	.97	2/12
ABAS-III	Total (*n* = 8)	DRS (*n* = 5)	RRS (*n* = 2)	*p*	# impaired/total
GAC	88.1 (12.7)	84.2 (6.8)	105.0 (9.9)	.02	3/8
Conceptual	91.8 (11.5)	86.2 (5.8)	108.5 (6.4)	.01	0/8
Social	92.0 (15.7)	90.2 (11.6)	107.5 (14.8)	.15	1/8
Practical	85.8 (11.6)	82.2 (5.4)	101.5 (9.2)	.01	3/8
Beery Buktenica	Total (*n* = 12)	DRS (*n* = 8)	RRS (*n* = 3)	*p*	# impaired/total
VMI	88.0 (17.6)	92.5 (13.5)	76.3 (27.8)	.21	2/12
BRIEF	Total (*n* = 13)	DRS (*n* = 8)	RRS (*n* = 4)	*p*	# impaired/total
GEC	54.8 (13.2)	59.8 (14.5)	46.3 (5.6)	.11	3/13
BRI	51.8 (10.9)	55.4 (12.4)	45.5 (5.2)	.16	2/13
MI	55.9 (14.0)	61.6 (15.0)	46.0 (5.1)	.08	4/13

Note: All reported scores are *M* (*SD*). Scores are standard scores with *M* = 100 and *SD* = 15 (FSIQ-2, ABAS-III, VMI) or *t*-scores with *M* = 50 and *SD* = 10 (WASI-II Vocabulary and Matrix Reasoning; BRIEF). Total *n* includes DRS, RRS, and the *GPC4 variant*. *p*-values reflect comparisons between DRS and RRS. Impairment refers to scores below the 10th percentile (WASI-II, ABAS-III, VMI) or *t*-scores ≥65 on the BRIEF.

Abbreviations: ABAS-III, Adaptive Behavior Assessment System, Third Edition; BRI, Behavior Regulation Index; BRIEF, Behavior Rating Inventory of Executive Function; DRS, autosomal-dominant Robinow syndrome; FSIQ-2, Full Scale IQ 2 subtest; GAC, Global Adaptive Composite; GEC, Global Executive Composite; MI, Metacognition Index; RRS, autosomal-recessive Robinow syndrome; VMI, visuomotor integration; WASI-II, Wechsler Abbreviated Scale of Intelligence, Second Edition.

reported moderate emotional problems (symptoms of depressed mood and anxiety), and 2/5 reported emotional problems in the high to very high range. None of the five adults who completed the PROMIS scales indicated significant current symptoms of depression or anxiety, though one did report a prior history of depression and anxiety. A history of behavior problems was reported in 1/7 children and 1/5 adults.

Problems with bullying were reported in 3/7 children and 2/5 adults, while 4/5 youth reported a high to very high level of peer problems on the Strengths & Difficulties Questionnaire (Table 2). More participants in the DRS group reported being bullied (5/8) than in the RRS group (0/3), but this difference did not reach significance ($p = .44$, *Fisher's exact test*). Concerns regarding social skills development were reported by parents of 5/7 children. Despite these problems, most respondents indicated having positive social relationships on the PROMIS scales, though a lack of positive peer relations or companionship was reported for 1/4 children and 1/4 adults. In terms of long-term relationships, one adult was married with children, and four were single with no children. Living arrangements varied: one lived alone, one with parents, one with roommates, and two with a partner or family. Incomes were not reported by most participants and so are not included here.

3.6 | *GPC4* variant

The individual with a variant affecting *GPC4* had average intellectual functioning, but very low adaptive functioning in the social and practical domains (Table 3). Visuomotor skills were below average, and he had a history of OT, PT, and speech/language therapies. He did not have reported problems with attention or executive functioning, or any psychosocial concerns.

4 | DISCUSSION

This is the first study to report formal data on the cognitive, adaptive, and behavioral characteristics of individuals with RS. Overall, intellectual functioning in our cohort was within the average range, with a distribution of scores similar to the normative population. Only one of 12 participants had an IQ score below the 10th percentile, and none were in the range of intellectual disability. Visuomotor integration was slightly below average overall, possibly reflecting the hand anomalies that characterized our participants (see Abu-Ghname et al., 2020).

Adaptive functioning, which was obtained for the children only, fell in the low average range overall, with over a third of participants (37.5%) falling in the very low range (i.e., below the 10th percentile). Practical skills were a particular area of weakness, possibly as a result of the speech and motor deficits that characterized most of these individuals. However, four of five adults reported good current physical functioning on the PROMIS scales, suggesting physical problems may resolve over time, or that individuals are better able to compensate for these deficits as adults.

Learning problems may be especially prevalent in RS. Four of 12 participants (33%) had a reported history of learning disability,

which is higher than the prevalence of about 7% in the general population (National Survey of Children's Health, 2016–2017). Similarly, 4/12 participants (25%) had a reported history of attention problems and 4/13 (31%) had executive dysfunction. As we only screened for these problems, we do not know if these individuals would meet full diagnostic criteria for ADHD, making it difficult to compare prevalence to the general population. Interestingly, all of the participants with attention problems or executive dysfunction in our study were children; none of the adults reported similar concerns. When examined just within the children, 4/7 (57%) had significant parent-reported attention problems, and 4/9 (44%) had parent-reported executive dysfunction on the BRIEF. It is unclear why these problems were prevalent in the children but not the adults, though during testing we observed attention problems and impulsivity in a number of the adults, suggesting that these problems might have been underreported. If correct, attention problems and executive dysfunction might be more prevalent in RS across the lifespan than the present data indicate.

There was no difference in IQ between participants with DRS and RRS, but there were group differences in multiple other domains. Participants with DRS had significantly lower adaptive functioning than individuals with RRS, and they had a higher prevalence of learning and attention problems. In addition, impairments in intellectual, adaptive, and executive functioning were evident only in participants with DRS (Table 3)—no participants with RRS showed impairment in any area other than visuomotor integration. Learning problems were especially evident in participants carrying *DVL1* pathogenic variants, 3/5 (60%) of whom had a reported learning disability, compared to 1/3 with pathogenic variant affecting *WNT5A*, and 0/3 with RRS. Similarly, 3/5 individuals with a *DVL1* pathogenic variant had attention problems (compared to 0/4 with other mutations), and 3/5 had executive dysfunction (compared to 1/9 with other mutations). These findings are consistent with previous report of higher prevalence of developmental delay in DRS compared to RRS (Mazzeu et al., 2007), and suggest that DRS—especially *DVL1* variants—may confer heightened risk for neurodevelopmental disability. The one possible exception was in visuomotor integration, which was lower in the RRS group, but this conclusion has to be viewed with caution given the especially small number of participants with RRS.

Our findings also revealed a high degree of psychosocial problems among the children but not the adults. Four of the five youth who completed the SDQ self-report measure indicated moderate to high symptoms of depression and/or anxiety (this measure combines internalizing symptoms into one scale). As predicted, peer problems were especially prevalent. Problems with bullying were reported in over 40% of participants (children and adults), which is almost twice the prevalence of bullying reported in the general population (National Survey of Children's Health, 2016–2017), and 4/5 youth (80%) reported significant peer problems on the SDQ. Our findings are in line with studies looking at teasing and bullying in individuals with disparate craniofacial conditions, where reported prevalence estimates range from 40–65% (Feragen & Stock, 2017; Pinquart, 2016). Pinquart (2016) suggested that differences in facial appearance might place individuals at especially high risk for discrimination. Individuals with various skeletal dysplasias also report a high degree of stigmatization due to their appearance (Dhiman et al., 2017). Despite these difficulties, most participants reported having positive social relationships and having someone to share enjoyable activities with, though only one of five adults was married or partnered. Taken together, these findings raise concern about the social lives and long-term social prospects of individuals with RS.

4.1 | Limitations and future directions

This study has a number of limitations. Most importantly, we had a very small sample size due to the rarity of RS, which limits our ability to make subgroup comparisons, reduces power, and at the same time increases the likelihood of false positives. Thus, the findings need to be interpreted with caution. In particular, we cannot rule out the possibility that the observed differences between individuals with DRS and RRS were due to chance effects. It is notable that the DRS group (and, in particular, participants with *DVL1* variants) had lower functioning across all of the domains that we assessed, but it is possible that the relatively few individuals in either group had atypically higher or lower functioning than the RS population as a whole. Our sample was also restricted in terms of gender and racial/ethnic diversity, limiting the generalizability of the findings.

Second, method variance was introduced by using parent proxy report for minor participants and self-report for adults. As discussed above, parents reported a high incidence of attention problems and executive dysfunction in their children, whereas the adults did not report similar concerns for themselves. Thus, it is possible that parents over-reported or adult participants underreported these problems. Also, in contrast with the children, adults reported no current problems with depression or anxiety. It is unclear whether this accurately reflects their psychological functioning, or whether they were underreporting symptoms here as well. Longitudinal studies that follow children with RS into adulthood might help clarify this issue.

Third, not all measures were completed by all participants. In particular, we only obtained a measure of adaptive functioning for the children, limiting conclusions that can be drawn about adaptive functioning across different ages. Fourth, due to time limitations, we were unable to complete formal test-based assessments of many neurocognitive domains (e.g., attention, memory, language) and academic skills, which would provide more fine-grained information about strengths and weaknesses in the RS cognitive profile. Similarly, we were unable to formally evaluate for ADHD and learning disabilities, and in both cases had to rely on parent- or self-report. Fifth, we only used screening measures of psychosocial functioning to minimize response burden. As a result, our findings may under- or overestimate the prevalence of psychological and peer difficulties in RS. Further research with more comprehensive measures of psychological and social functioning will be important. Finally, it is possible that other genetic and familial factors may have contributed to the findings. For example, attention problems and learning disabilities are

highly heritable, and the effect of these factors could have been magnified within our small sample. Future studies might benefit from looking more closely at family histories of neurodevelopmental conditions in RS.

4.2 | Clinical implications and conclusion

Overall, the findings from the present study suggest that RS is characterized by average intellectual functioning, mild delays in adaptive skills (especially practical skills), and a heightened incidence of learning and attention problems and executive dysfunction. Neurocognitive deficits were more likely in participants with DRS, and *DVL1* variants in particular may carry heightened risk for neurodevelopmental disabilities. Nonetheless, we believe that all children with RS should be screened for learning and attention problems at an early age (e.g., prior to third grade), so as to facilitate early intervention.

Peer problems were reported for a majority of the children and youth with RS. It may be that their skeletal abnormalities and atypical facial features make them targets for bullying in childhood. Caregivers and schools should be vigilant for bullying, and school personnel should intervene proactively whenever bullying occurs. Bullying is often a precipitant for internalizing problems as children get older, and we did find relatively high rates of anxiety and depressive symptoms in the older youth in our study. Screening for symptoms of depression and anxiety is therefore also important for youth with RS, though it is unclear if internalizing symptoms are less common or were underreported in the adults.

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CONFLICT OF INTEREST

The authors do not have any financial conflicts of interest to report.

AUTHOR CONTRIBUTIONS

D. D. S., R. H. F., and M. E. A. conceived and designed the study and collected the data. C. M. B. C. coordinated the study and data collection. D. D. S. analyzed the data and wrote the manuscript with input from R. H. F. and M. E. A., who also helped edit each draft. C. M. B. C., V. R. S., and J. F. M. provided input into the study and helped revise the initial manuscript. All of the authors (D. D. S., R. H. F., C. M. B. C., V. R. S., J. F. M., and M. E. A.) were involved in revising manuscript drafts and reviewed the final manuscript.

DATA AVAILABILITY STATEMENT

The submission numbers for identified variants were deposited into ClinVar with the preliminary identifiers: SUB8111875. The dbGAP accession number for all exome sequences reported in this paper and for which informed consent for data sharing in controlled-access databases has been provided is dbGAP:phs000711.v5.p1. Additional data that support the findings of this study are available from the corresponding author upon reasonable request.

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