Neuropsychiatric Phenotypes in 3q29 Deletion Syndrome

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Background

The 1.6 Mb 3q29 deletion is associated with a 40-fold increased risk for schizophrenia. However, additional behavioral phenotypes, including autism spectrum disorder (ASD), are not well characterized.

Methods

We ascertained individuals with 3q29 deletion syndrome (3q29DS, “cases”, n=94) and typically developing controls (n=64) through the 3q29 registry (https://3q29deletion.patientcrossroads.org). Self-report of neuropsychiatric illness was evaluated for 94 cases. Subsets of case and control records were evaluated with the SRS, SCQ, ASSQ, and Achenbach Behavior Checklists.

Results

Cases report increased prevalence of autism diagnosis versus the general population (29.8% vs. 1.47%, $p<2.22e-16$). 3q29DS also report increased frequency of generalized anxiety disorder and attention deficit/hyperactivity disorder, which is mirrored by elevated scores on the Achenbach DSM-oriented subscales ($p<0.001$). The SRS reveals that individuals with 3q29DS demonstrate less compromised social motivation than other ASD sub-domains, which is strikingly different from idiopathic ASD.

Conclusions

Our sample of 3q29DS is significantly enriched for ASD diagnosis, especially among females, and features of autism may be present even when individuals with 3q29DS do not report an ASD diagnosis. Further, the presentation of ASD in this population is novel, with substantially less impaired social motivation compared to idiopathic ASD. Our study implies that ASD evaluation should be the standard of care for individuals with 3q29DS. From a research perspective, the

novel ASD subtype present in 3q29DS is an ideal entry point for expanding our understanding of ASD.

INTRODUCTION

3q29 deletion syndrome (3q29DS) is a rare (~1 in 30,000) (Stefansson), poorly understood genomic disorder characterized by a 1.6 Mb typically *de novo* deletion on chromosome 3 (1-3) . The interval contains 21 distinct protein-coding genes, 3 antisense transcripts, 1 long noncoding RNA, and 1 microRNA. Initial reports of the syndrome found developmental delay/intellectual disability universal among 3q29 deletion carriers, though some case reports have since identified individual without cognitive impairment (4). The 3q29 deletion is associated with schizophrenia (SZ) (5-7), and studies with large sample sizes indicate that the 3q29 deletion is enriched in ASD samples (8). However, no systematic evaluation of the ASD phenotype in 3q29 deletion syndrome exists. Case reports implicate ASD and other neuropsychiatric phenotypes, including attention deficit/hyperactivity disorder (ADHD) and bipolar disorder. Previous work by our team in 44 individuals with 3q29DS shows an association with generalized anxiety disorder (3).

The range of neuropsychiatric manifestation in 3q29DS is consistent with other CNV disorders. For example, the 22q11.2 deletion has a well-known association with schizophrenia, but is also associated with ID, ASD, anxiety, mood disorders, and ADHD (9, 10). A similar constellation of phenotypes, including ASD, ADHD, ID, SZ, and anxiety, has been identified in other CNV disorders, including in 16p11.2 deletion and duplication syndromes (11, 12), 7q11.23 duplication syndrome (13), and 1q21.1 deletion syndrome (14). Furthermore, individuals with any of these CNV disorders have a highly heterogeneous clinical presentation. The causes of this variation remain unexplained.

Developing a clearer and more comprehensive picture of 3q29 deletion-associated phenotypes will aid in patient management and potentially improve long-term outcomes. Additionally, this careful description of the phenotypic spectrum of 3q29DS can provide inroads

to identifying mechanisms underlying 3q29DS and similar disorders caused by CNVs. The present study aims to improve the current understanding of 3q29 deletion-associated neuropsychiatric and neurodevelopmental phenotypes by examining data from comprehensive, standardized questionnaires in the largest cohort of individuals with 3q29DS ever assembled.

METHODS AND MATERIALS

Sample

Individuals with 3q29DS and typically developing controls were ascertained through the internet-based 3q29 deletion registry (https://3q29deletion.patientcrossroads.org), a previously described IRB-approved, HIPAA-compliant website (Glassford). Participant recruitment, informed consent and assent, and data collection are all performed through the website. Data were de-identified and securely downloaded for analysis. After data cleaning of the electronic records (removing spam accounts, duplicate records, and related individuals), 94 3q29 DS registrants (58.5% male) were included in the present study, ranging in age from 1.5-79.9 years (mean=12.7±11 years). 64 typically developing controls (51.6% male) were included, ranging in age from 1.7-41.7 years (mean=10.6±7.2 years). Controls reporting a clinical diagnosis of any neurodevelopmental disorder were excluded (n=1). Description of the study sample can be found in Table 1.

Questionnaires

Upon registration, the participant or his/her parent completes a custom medical and demographic questionnaire. This questionnaire includes questions on the gender, birthdate, race, and ethnicity of the participant, as well as a detailed medical history, including developmental milestones and prior clinical diagnoses of any neuropsychiatric or neurodevelopmental disorders.

Four standardized questionnaires were used to assess ASD-related symptomology and general behavioral problems in the participants. The Social Responsiveness Scale (SRS; preschool, school-age, and adult forms) is a 65-item, 4 point Likert-scaled questionnaire designed to assess ASD-related symptoms along a normative continuum (15). The Social Communication Questionnaire (SCQ) (16) is a 40-item, yes/no questionnaire designed to assess ASD-related symptoms keyed to DSM criteria . The Autism Spectrum Screening Questionnaire (ASSQ) is a 27-item, yes/somewhat/no questionnaire designed to assess ASD-related symptoms in high-functioning individuals with no to mild ID (17). The Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL) are 100-, 113-, or 126-item (CBCL preschool, CBCL school-age, and ABCL, respectively), 3 point Likert-scaled questionnaires designed to assess behavioral or developmental problems (18, 19). Data from the CBCL and ABCL was pooled for analysis. All standardized questionnaires were adapted for the online 3q29 deletion registry and were completed by the parent/guardian of the participant upon registration. Demographic characteristics of the respondents for each questionnaire can be found in Table S1.

Analysis

Data from standardized questionnaires was imported into R (20) and was recoded and scored according to the publisher's guidelines. Features of interest from the medical history questionnaire (heart defects, age at walking, ASD diagnosis, ID diagnosis) were recoded for analysis as follows: for heart defects, yes/no; for age at walking, binned as normal (≤18 months), delayed (19-24 months), and extremely delayed (>24 months); for ASD diagnosis, yes/no; for ID diagnosis yes (reported diagnosis of global developmental delay and/or mental retardation)/no. Linear models and generalized linear models were implemented using the stats (20) R package,

cumulative link models were implemented using the ordinal (21) R package, and figures were generated using the plotly (22) and ggplot2 (23) R packages.

RESULTS

Self-report of neuropsychiatric diagnosis in 3q29DS

Study participants with 3q29DS self-reported diagnoses of a variety of neuropsychiatric disorders, including ASD, ID, and anxiety (Table 2), confirming prior work by our group (3). In addition to ASD, cases report significantly higher incidence of ID, anxiety, and panic attacks than controls. Reported rates of conduct disorder and oppositional defiant disorder were similar to those observed in the general population (3.2% vs. 3.5%). While a small proportion of participants reported diagnoses of bipolar/manic depression (5.3%), depression (6.4%), and schizophrenia (4.3%), we have focused on ASD due to the young age (mean=12.7 years) of our study population, meaning many study participants have not reached the age of risk for schizophrenia and other adult-onset disorders. Despite this young age, we note that the frequency of schizophrenia is 6.7-17.2 times higher than expected (24-28) and the frequency of bipolar disorder is ~1.8 times higher than expected (29). A summary of neuropsychiatric diagnoses can be found in Table 2.

Features of ASD self-report in 3q29DS

Cases reported a significantly higher incidence of ASD than the general population frequency (29.8% vs. 1.47%, $p<2.22e-16$, Figure 2A). This increased frequency of ASD diagnosis is observed in both males (36.4%, $p=6.55e-6$) and females (20.5%, $p=1.24e-5$), (Figure 2A). In comparison to the 4:1 male bias observed in ASD in the general population, the male:female ratio observed in our study population is 1.8:1, reflecting the increase in female ASD in 3q29DS.

SRS, SCQ, ASSQ, and CBCL/ABCL scores

In 3q29 deletion carriers, the mean SRS score was in the moderate range (*T-score* = 71.75), the mean ASSQ score was in the clinical range (mean = 22.167), and the mean CBCL/ABCL score was in the borderline range (*T-score* = 62.5). The mean SCQ score in 3q29 deletion carriers was at the extremely high end of the normal range (mean = 13.88, clinical cutoff = 15) and elevated as compared to controls (mean = 3.52). Mean scores for typically developing controls were all in the normal range (SRS *T-score* = 46.05, ASSQ mean = 2.23, CBCL/ABCL *T-score* = 41.75, SCQ mean = 3.52) (Figure 1). Participants with 3q29DS scored significantly higher than typically developing controls on all 4 scales ($p < 0.05$, Table S2).

Standardized scores stratified by ASD diagnosis

Next, we examined the relationship between SRS scores and the presence of an ASD diagnosis, to determine whether the score inflation we observed in our study population as a whole was largely due to the increased prevalence of ASD. As expected, we observed that individuals with 3q29DS and an ASD diagnosis scored significantly higher than both controls and individuals with 3q29DS without an ASD diagnosis ($p<0.05$, Figure 2B). We were interested to observe that individuals with 3q29DS without an ASD diagnosis also scored significantly higher than controls ($p<0.05$, Figure 2B). In addition to the contribution of diagnosed ASD to inflated SRS scores, we also interrogated possible sex differences in scores. We found that both males and females with 3q29DS scored significantly higher than controls ($p<0.05$), but they did not score significantly differently from each other ($p>0.05$, Figure 2C). After stratifying our study population further by ASD diagnosis status, we determined that both males and females with 3q29DS without an ASD diagnosis had significantly higher scores than controls ($p<0.05$, Figure 2D). Taken together, this implies that increased SRS scores in individuals with 3q29DS

are not being driven by sex or ASD diagnosis status; rather, the presence of the deletion itself confers a greater risk for autistic features. Furthermore, this data shows an enrichment for female ASD in our study population, based on the reduction in male bias and the highly similar scores between males and females with 3q29DS, irrespective of ASD diagnosis status. Similar features were observed in the contribution of sex and ASD diagnosis to SCQ scores (Figure S1).

ASD presentation and behavioral features of 3q29DS

While total scores on the SRS, SCQ, ASSQ, and CBCL/ABCL can give an indication of the overall level of impairment of individuals, it is also important to take advantage of sub-scores to assess impairment in specific behavioral domains. To this end, we analyzed all SRS sub-scales (Social Awareness, Social Cognition, Social Communication, Social Motivation, Restricted Interests and Repetitive Behaviors, and Social Communication and Interaction) and a subset of CBCL and ABCL DSM-oriented sub-scales that were common across all age groups (Attention Deficit/Hyperactivity Problems, Anxiety Problems, and Depressive Problems). Coincidentally, these common DSM-oriented sub-scales from the CBCL and ABCL align with common neuropsychiatric diagnoses reported by individuals with 3q29DS (3). We first analyzed the SRS sub-scales to better understand the presentation of autistic features in our study population; our goal was to determine whether our observed total score inflation was due to a specific severe deficit in a few domains, or if individuals with 3q29DS showed high scores across all sub-scales. The mean scores for 4 of the 6 sub-scales were in the moderate range (Social Awareness, Social Cognition, Social Communication, and Social Communication and Interaction), the mean score for Restricted Interests and Repetitive Behaviors was in the severe range, and the mean score for Social Motivation was in the mild range (Figure 3A). This sub-score profile is strikingly different from that observed in studies of idiopathic ASD, where children tend to score equally

high on all sub-scales (30). To determine whether this unusual profile was influenced by sex, we examined profiles of male and female 3q29 deletion carriers separately. We find the shape of the profiles are identical, with females scoring on average 5 points lower than males on every sub-scale ($p>0.05$, Figure 3B). This atypical behavioral profile is supported by clinical data; direct assessment of individuals with 3q29DS by clinicians affiliated with the Emory 3q29 Project (http://genome.emory.edu/3q29/) show less impaired social motivation as compared to children with idiopathic ASD (personal communication, Saulnier, Klaiman). To further assess behavioral features associated with the 3q29 deletion, we examined the DSM-oriented Attention Deficit/Hyperactivity Problems, Anxiety Problems, and Depressive Problems sub-scales from the CBCL and ABCL. Individuals with 3q29DS scored significantly higher than typically developing controls on all three scales (Figure 3C), supporting previous reports of increased risk for neuropsychiatric diagnoses associated with the 3q29 deletion (3).

Confounding due to heart defects and/or ID

A previous study of 3q29DS by our group showed that approximately 25% of individuals reported a congenital heart defect (3). Early hypoxic insult due to a heart defect has been hypothesized to contribute to later neuropsychiatric and neurodevelopmental outcomes (31-36). To determine if the high frequency of heart defects in our study population was driving adverse neurodevelopmental outcomes, we implemented generalized linear and cumulative link models to assess the relationship between congenital heart defects and clinical ASD diagnosis, ID diagnosis (based on parent-reported mental retardation and global developmental delay diagnoses), and age at walking, which has been reported to be a good proxy for intellectual disability (37) . Congenital heart defects are not associated with self-reported ASD or ID diagnoses or age at walking (Table S3). Individuals with 3q29DS are also commonly diagnosed

with mild to moderate intellectual disability. To ask whether ASD phenotypes or ASD features were disproportionately overrepresented in individuals with more pronounced ID and/or heart defects, we stratified the data according to these phenotypes. Scores for 3q29 deletion carriers remain significantly higher than controls after stratifying the data based on these factors (Table S4), indicating that they are not driving the increased scores; rather, the 3q29 deletion itself is a major contributor to ASD and neuropsychiatric phenotypes.

DISCUSSION

The present study has confirmed previous reports that individuals with 3q29DS are at significantly increased risk for neurodevelopmental disorders, specifically ASD. Notably, the self-reported frequency of ASD in our study population is similar in males and females, with a male:female ratio of 1.8:1. This is a reduction from the 4:1 male bias observed in idiopathic ASD in the general population. A substantial reduction in male bias in ASD prevalence has been observed in studies of other CNVs; a recent study has shown that as the severity of a CNV increases, the sex ratio in ASD prevalence approaches 1:1 (38). Taken together, this suggests that the 3q29 deletion is approaching the severe end of the spectrum of ASD-associated mutations.

Additionally, we have shown that the 3q29DS population is significantly enriched for ASD features and other behavioral problems versus typically developing children, irrespective of clinical ASD diagnosis. This is a particularly concerning finding; while individuals with 3q29DS that have an ASD diagnosis do tend to score higher on symptomology scales overall, 3q29DS individuals without an ASD diagnosis still score significantly higher than typically developing children. This indicates several possible explanations: a) an enrichment for ASD features not reaching diagnostic criteria, b) possible undiagnosed ASD in our study population, or c) non-specificity of the SRS in particular for phenotypes other than ASD. It is also possible that the

score inflation observed in individuals with 3q29DS may be due to the high prevalence of developmental delay or congenital heart defects associated with the 3q29 deletion (3); however, these factors do not contribute significantly to scores in our study population. This is aligned with anecdotal reports from parents of our study participants, where they have reported concerns about atypical social development that do not appear to have been addressed using gold-standard ASD evaluations. Based on the elevated symptomology scores in our study population, the substantially increased risk for ASD associated with the 3q29 deletion, and the apparent severity of the 3q29 deletion, gold-standard ASD evaluations should be standard of care for individuals diagnosed with 3q29DS. This practice will help us to gain a better understanding of the prevalence of 3q29 deletion-associated phenotypes and will enable patients to gain access to the early interventions, treatments, and therapeutic programs that they are entitled to. These results suggest that the early hypoxic insult from a congenital heart defect is not related to neurodevelopmental outcomes in 3q29DS, and that these phenotypes are arising via different biological mechanisms. As the 3q29 interval encompasses 21 genes (1) it is not entirely surprising that multiple developmental circuits could be disrupted by the deletion; however, this does suggest that early hypoxic insult is not the major neurodevelopmental and neuropsychiatric risk factor in 3q29DS.

Based on the SRS sub-scales, participants with 3q29DS display a strikingly different behavioral profile than what is observed in children with idiopathic ASD (30). Male and female 3q29DS individuals show substantially less impaired social motivation in the context of an otherwise typical ASD profile, with the most severe deficits in the Restricted Interests and Repetitive Behaviors domain. This profile is aligned with what our team has observed from in-person evaluations of study participants, suggesting that 3q29 deletion-associated ASD is

qualitatively different from ASD in the general population. Notably, this qualitative difference from idiopathic ASD may serve as an inroad to therapeutic interventions in 3q29DS, as well as an investigative inroad to a novel subtype of ASD. Because social motivation appears to be relatively well-preserved in 3q29DS, this suggests that therapies such as cognitive-behavioral therapy to teach social skills and effective strategies for social interaction may be particularly successful in this patient population.

While this study is the most comprehensive study of behavioral phenotypes in 3q29DS to date, it is not without limitations. All of the data used in the present study was collected from questionnaires completed by the parents and guardians of individuals with 3q29DS, which introduces several potential sources of bias. Some studies have questioned the validity and reliability of parent-report data (39); however, a recent study in Williams syndrome patients has shown that parents are more accurate in predicting their child's social behaviors than the child themselves (40). The responses to the medical and demographic questionnaire are more likely to include error due to the fact that the data is retrospective. By limiting our study to only a few key points in the medical history (heart defects, age at walking, and ID/ASD diagnosis) we aimed to reduce recall errors; however, we only had proxies for ID, rather than reported ID diagnosis itself. Finally, there is likely ascertainment bias within our sample. First, our sample of 94 individuals with 3q29DS is 86.2% white, indicating that we are not adequately reaching minority populations. Second, parents that register their children and complete in-depth questionnaires are likely to be highly motivated – a potential indication that we are sampling from the extreme of the phenotypic distribution of 3q29DS. Thus, scores on the standardized questionnaires, as well as rates of heart defects and clinical psychiatric diagnoses, may be higher in our study sample than in the general 3q29DS population. Finally, the lack of observed association between

congenital heart defects and neurodevelopmental outcomes may be obscured by the high rate of patent ductus arteriosus in 3q29 deletion syndrome (3), which is a relatively mild heart defect; however, we did not have enough participants with different types of heart defects to analyze their associations with neurodevelopment separately. Ongoing studies by the Emory 3q29 Project, including in-person patient evaluations (genome.emory.edu/3q29; (41)) aim to address some of the weaknesses of the present work by performing gold-standard evaluations by trained clinicians.

After considering the limitations of the present study, there are still significant strengths of this study as compared to previous studies of 3q29DS. First, this is the largest cohort of individuals with 3q29DS ever assembled. This is a critical step in capturing the true phenotypic spectrum associated with the 3q29 deletion, which is supported by our use of standardized questionnaires. By adhering to standardized instruments and best practices, we were able to collect the most reliable data possible from our cohort. Additionally, our online patient registry allows for remote data collection, which has enabled us to expand our study population and reach patients outside of the continental United States. This study has shown that high-quality, comprehensive medical history and symptomology data can be collected through an online patient registry, effectively reducing the patient-ascertainment burden associated with studying rare disorders. Taken together, this makes the present study an excellent complement to previously published case reports on individuals with 3q29DS; by capturing a larger patient base, we are able to more accurately measure the presence of a variety of neuropsychiatric and neurodevelopmental phenotypes associated with the 3q29 deletion. These findings imply that comprehensive neuropsychiatric and neurodevelopmental assessments are merited for individuals diagnosed with 3q29DS, and that such assessments should be standard of care for

this patient population. Finally, the data in the present study make a compelling argument for the value of studying CNV disorders such as 3q29DS to gain a better understanding of neuropsychiatric and neurodevelopmental disorders. By studying a single genomic variant of large effect, we can effectively control for genetic etiology and potentially gain a better understanding of the mechanisms underlying the development of neuropsychiatric and neurodevelopmental disorders.

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Footnotes

None

Table/Figure Legends

Table 1. Characteristics of study participants with 3q29DS and controls.

Table 2. Characteristics of self-reported neuropsychiatric diagnoses in study participants with 3q29DS and controls. P values were calculated with Fisher's Exact Test.

Figure 1. Total scores on the SRS (n=48 3q29DS, 59 control), SCQ (n=33 3q29DS, 46 control), ASSQ (n=24 3q29DS, 35 control), and CBCL/ABCL (n=48 3q29DS, 57 control) for registry participants. Self-reported diagnosis of ASD is denoted by shape (circle/ASD, triangle/no ASD), and gender of participant is denoted by color (red/female, blue/male). Controls are shown in black.

Figure 2. A) Proportion of participants with 3q29DS self-reporting a diagnosis of ASD (not all respondents completed symptom questionnaires); 28 cases report an ASD diagnosis (green), comprised on 20 males (blue) and 8 females (red). Compared to general population frequencies (black), cases report significantly higher incidence of ASD. **B)** SRS scores split by control (n=59), 3q29DS not reporting an ASD diagnosis (n=31), and 3q29DS reporting an ASD diagnosis (n=17), showing a significant association between self-reported diagnostic status and SRS score. **C)** SRS scores split by gender, with control (n=59), 3q29DS female (n=22), and 3q29DS male (n=26), showing a lack of gender bias in scores for 3q29DS participants. **D)** SRS scores split by gender and self-reported diagnostic status, with control (n=59), 3q29DS female reporting ASD (n=5), 3q29DS female not reporting ASD (n=17), 3q29DS male reporting ASD (n=12), and 3q29DS male not reporting ASD (n=14), showing inflated scores for 3q29DS participants irrespective of gender or diagnostic status. ***, $p<0.001$

Figure 3. A) Profile of individuals with 3q29DS (n=48) and controls (n=59) across SRS subscales, showing moderate to severe impairment of 3q29DS participants in all domains except

Social Motivation (RRB, Restricted Interests and Repetitive Behaviors; SCI, Social Communication and Interaction). **B)** Profile of 3q29DS males (n=) and females (n=) and controls (n=59) across SRS subscales, showing that 3q29DS males and females both score significantly higher than controls and that there are no significant differences in score between males and females. **C)** Profile of 3q29DS participants (n=48) and controls (n=57) across 3 DSM-oriented subscales from the CBCL and ABCL, showing significantly increased pathology in 3q29DS participants in all 3 domains. ***, $p<0.001$

Figure 1

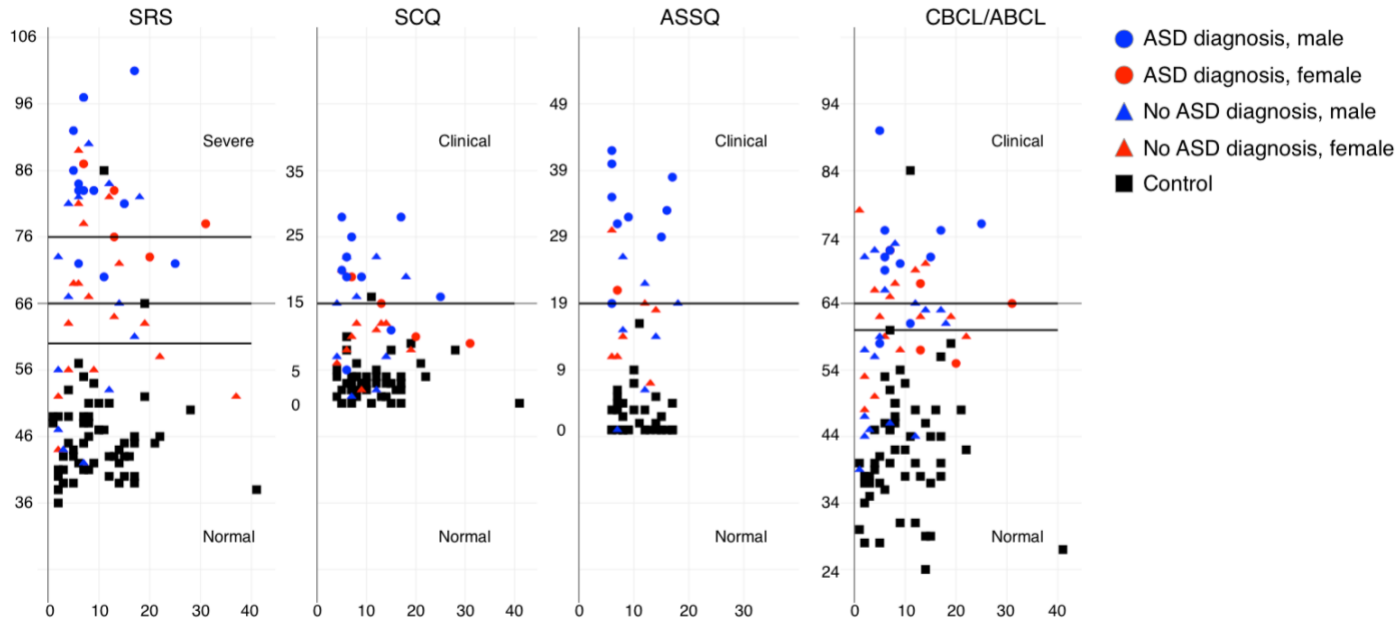

Figure 2

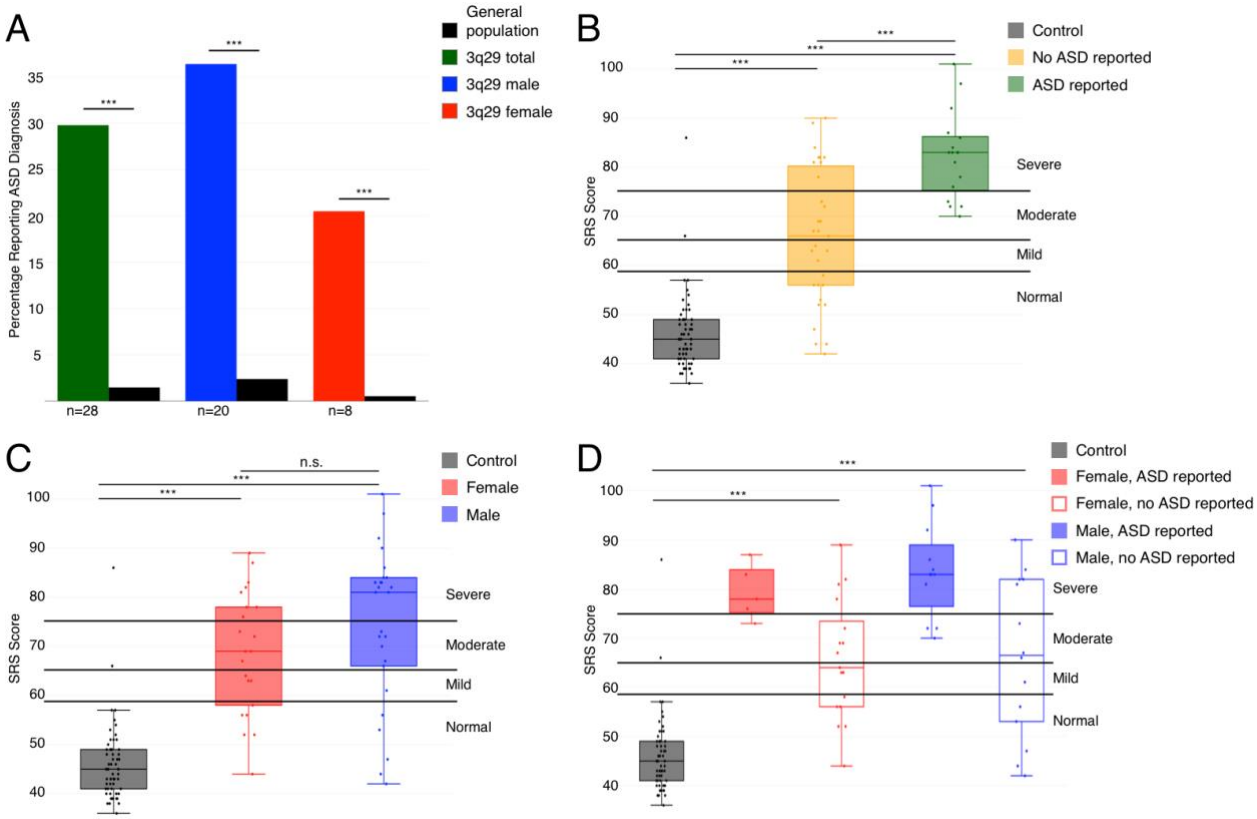

Figure 3

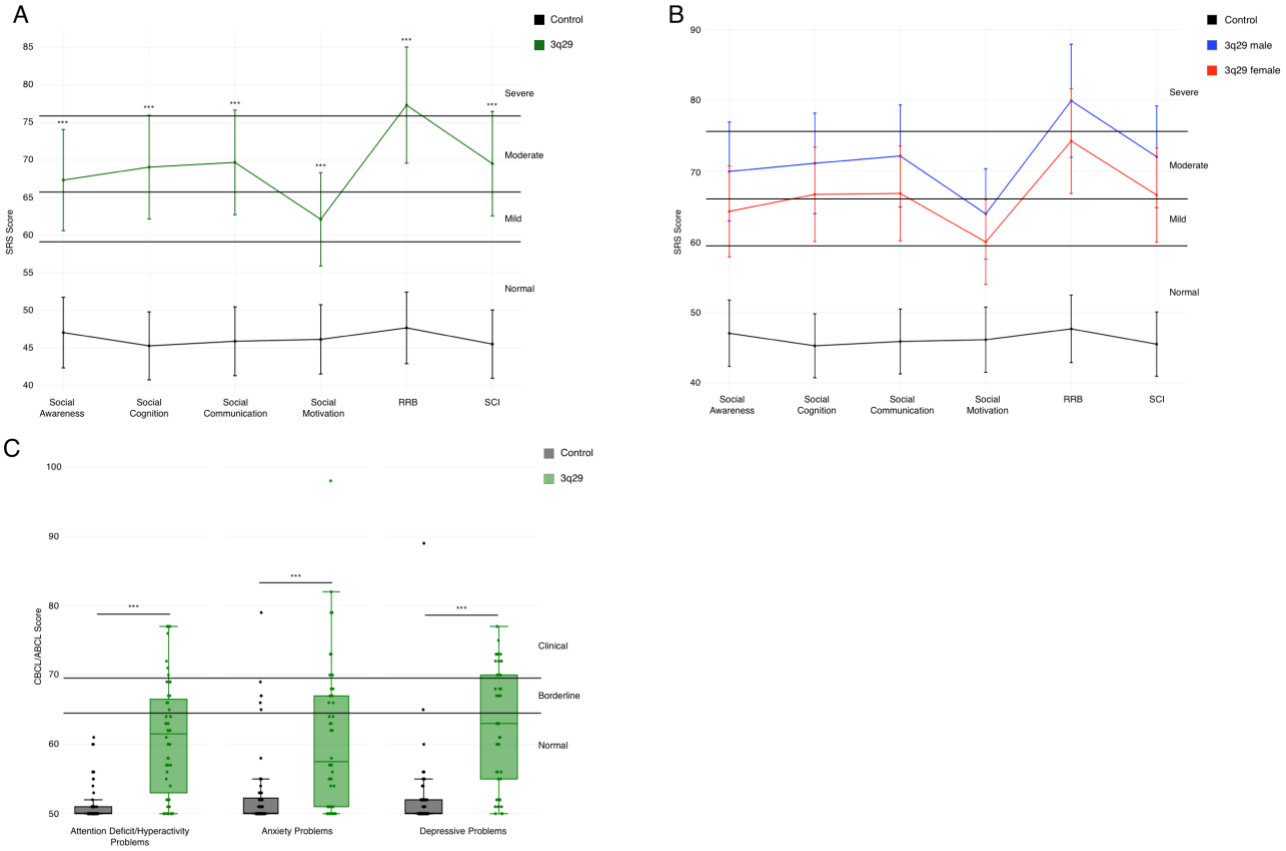
A
Control
3q29
SRS Score
Severe
Moderate
Mild
Normal
Social Awareness
Social Cognition
Social Communication
Social Motivation
RRB
SCI
B
Control
3q29 male
3q29 female
SRS Score
Severe
Moderate
Mild
Normal
Social Awareness
Social Cognition
Social Communication
Social Motivation
RRB
SCI
C
Control
3q29
CBCL/ABCL Score
Clinical
Borderline
Normal
Attention Deficit/Hyperactivity Problems
Anxiety Problems
Depressive Problems

Table 1

	3q29 Deletion Syndrome	Control
Age, years (mean ± SD)	12.7 ± 11	10.6 ± 7.2
Sex (n, %)		
Male	55 (58.5%)	33 (51.6%)
Female	39 (41.5%)	31 (48.4%)
Race (n, %)		
White	82 (87.2%)	41 (64.1%)
Black/African American	1 (1.1%)	13 (20.3%)
Other	10 (10.6%)	8 (12.5%)
Blank	1 (1.1%)	2 (3.1%)
Heart Defect (n, %)		
Yes	21 (22.3%)	0 (0%)
No	57 (60.6%)	61 (95.3%)
Unsure	16 (17%)	3 (4.7%)
Age at Walking (n, %)		
Normal	42 (44.7%)	60 (93.8%)
Delayed	22 (23.4%)	1 (1.6%)
Extremely Delayed	14 (14.9%)	1 (1.6%)
Unsure	11 (11.7%)	2 (3.1%)
Not applicable	5 (5.3%)	0 (0%)

Table 2

		3q29 Deletion Syndrome			Control			P value; 3q29DS vs. Control
		Total	Male	Female	Total	Male	Female	
ID (n, %)								
	Yes	55 (58.5%)	31 (56.4%)	24 (61.5%)	0 (0%)	0 (0%)	0 (0%)	7.57E-08
	No	39 (41.5%)	24 (43.6%)	15 (38.5%)	64 (100%)	33 (100%)	31 (100%)	
ASD (n, %)								
	Yes	28 (29.8%)	20 (36.4%)	8 (20.5%)	0 (0%)	0 (0%)	0 (0%)	<2.2E-16
	No	66 (70.2%)	25 (45.6%)	31 (79.5%)	64 (100%)	33 (100%)	31 (100%)	
Anxiety (n, %)								
	Yes	25 (26.6%)	14 (25.5%)	11 (28.2%)	4 (6.2%)	2 (6.1%)	2 (6.5%)	0.0014
	No	69 (73.4%)	41 (74.5%)	28 (71.8%)	60 (93.8%)	31 (93.9%)	29 (93.5%)	
Bipolar/Manic Depression (n. %)								
	Yes	5 (5.3%)	2 (3.6%)	3 (7.7%)	0 (0%)	0 (0%)	0 (0%)	0.081
	No	89 (94.7%)	53 (96.4%)	36 (92.3%)	64 (100%)	33 (100%)	31 (100%)	
Conduct Disorder (n, %)								
	Yes	3 (3.2%)	1 (1.8%)	2 (5.1%)	0 (0%)	0 (0%)	0 (0%)	0.272
	No	91 (96.8%)	54 (98.2%)	37 (94.9%)	64 (100%)	33 (100%)	31 (100%)	
Depression (n, %)								
	Yes	6 (6.4%)	2 (3.6%)	4 (10.3%)	4 (6.2%)	4 (12.1%)	0 (0%)	1.00
	No	88 (93.6%)	53 (96.4%)	35 (89.7%)	60 (93.8%)	29 (87.9%)	31 (100%)	
Oppositional Defiant Disorder (n, %)								
	Yes	3 (3.2%)	2 (3.6%)	1 (2.6%)	0 (0%)	0 (0%)	0 (0%)	0.272
	No	91 (96.8%)	53 (96.4%)	38 (97.4%)	64 (100%)	33 (100%)	31 (100%)	
Panic Attacks (n, %)								
	Yes	13 (13.8%)	9 (16.4%)	4 (10.3%)	2 (3.2%)	0 (0%)	2 (6.5%)	0.027
	No	81 (86.2%)	46 (83.6%)	35 (89.7%)	62 (96.8%)	33 (100%)	29 (93.5%)	
Schizophrenia (n, %)								
	Yes	4 (4.3%)	1 (1.8%)	3 (7.7%)	0 (0%)	0 (0%)	0 (0%)	0.15
	No	90 (95.7%)	54 (98.2%)	36 (92.3%)	64 (100%)	33 (100%)	31 (100%)	