Full article title: Neuropsychiatric Phenotypes in 3q29 Deletion Syndrome and Novel Features of ASD: Results from the 3q29 Registry

Authors: Rebecca M Pollak[1], Melissa M Murphy[2], Michael P Epstein[2], Michael E Zwick[2,3], Cheryl Klaiman[3,4], Celine A Saulnier[3], Jennifer G Mulle[2,5]

Affiliations: [1]Genetics and Molecular Biology, Laney Graduate School, Emory University, [2]Department of Human Genetics, School of Medicine, Emory University, [3]Department of Pediatrics, School of Medicine, Emory University, [4]Marcus Autism Center, Children's Healthcare of Atlanta and Emory University School of Medicine, [5]Department of Epidemiology, Rollins School of Public Health, Emory University

Corresponding author information: Jennifer Gladys Mulle, MHS, PhD, Whitehead 305M, 615 Michael Street, Atlanta, GA 30322; (404) 727-3042; jmulle@emory.edu

Running title: Neuropsychiatric Phenotypes in 3q29 Deletion Syndrome

Keywords: autism, copy number variants, 3q29 deletion, psychiatric genetics, SRS, developmental delay

Abstract word count: 248

Main text word count: 3551

Number of figures: 3

Number of tables: 2

Number of supplements: 1

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 (3q29Del, “cases”, n=94, 58.5% male) and typically developing controls (n=64, 51.6% male) through the 3q29 registry (https://3q29deletion.patientcrossroads.org). Self-report of neuropsychiatric illness was evaluated for 94 cases. Subsets of records were evaluated with the Social Responsiveness Scale (SRS), Social Communication Questionnaire (SCQ), Autism Spectrum Screening Questionnaire (ASSQ), and Achenbach Behavior Checklists.

Results

3q29Del cases report increased prevalence of autism diagnosis versus the general population (29.8% vs. 1.47%, $p<2.22E-16$). Cases also report increased frequency of generalized anxiety disorder and attention deficit/hyperactivity disorder, which is mirrored by elevated scores on the Achenbach DSM-oriented sub-scales ($p<0.001$). Finally, cases showed a novel constellation of ASD features on the SRS, with elevated mean scores on 5 of the 6 sub-scales; however, the mean score for Social Motivation was in the mild range.

Conclusions

Our sample of 3q29Del is significantly enriched for ASD diagnosis, especially among females, and features of autism may be present even when an ASD diagnosis is not reported. 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 3q29Del. From a research perspective, the novel ASD subtype present in 3q29Del is an ideal entry point for expanding understanding of ASD.

INTRODUCTION

3q29 deletion syndrome (3q29Del) is a rare (~1 in 30,000) (1), poorly understood genomic disorder characterized by a 1.6 Mb typically *de novo* deletion on chromosome 3 (2-4) . 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 (5). The 3q29 deletion is associated with schizophrenia (SZ) (6-8), and studies with large sample sizes indicate that the 3q29 deletion is enriched in ASD samples (9). However, no systematic evaluation of the ASD phenotype in 3q29 deletion syndrome exists. Case reports also indicate other neuropsychiatric phenotypes may exist, including attention deficit/hyperactivity disorder (ADHD) and bipolar disorder (2, 3, 10-14). Previous work by our team in examining self-report data from 44 individuals with 3q29Del also shows an association with generalized anxiety disorder (4).

The range of neuropsychiatric manifestation in 3q29Del is consistent with other CNV disorders. For example, the 22q11.2 deletion has a well-known association with schizophrenia but is also associated with intellectual disability (ID), ASD, anxiety, mood disorders, and ADHD (15, 16). A similar constellation of phenotypes, including ASD, ADHD, ID, SZ, and anxiety, has been identified in 16p11.2 deletion and duplication syndromes (17, 18), 7q11.23 duplication syndrome (19), and 1q21.1 deletion syndrome (20). 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 more targeted intervention planning and potentially improve long-term

outcomes. Additionally, this careful description of the phenotypic spectrum of 3q29Del can provide inroads to identifying mechanisms underlying 3q29Del 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 3q29Del ever assembled.

METHODS AND MATERIALS

Sample

Individuals with 3q29Del and unrelated typically developing controls were ascertained through the internet-based 3q29 deletion registry (https://3q29deletion.patientcrossroads.org) (4). Participant recruitment, informed consent and assent, and data collection are all performed through the website. This study was approved by Emory University's Institutional Review Board (IRB00064133). 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 3q29Del 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 (4).

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 (21). The Social Communication Questionnaire (SCQ) (22) 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 (23). 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 (24, 25). Data from the CBCL and ABCL were pooled for analysis. All standardized questionnaires were adapted for the online 3q29 deletion registry and were completed by the participant or 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 were imported into R (26) and were 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.

To compare responses for 3q29Del cases and controls, linear models and logistic regression models were implemented using the stats (26) R package, and cumulative link proportional-odds models were implemented using the ordinal (27) R package. All statistical models included age, race, and sex as covariates. To compare rates of self-reported diagnoses in 3q29Del cases to self-reported diagnoses in controls and to population prevalence values, and to compare demographic parameters, Fisher's exact test was implemented using the stats (26) R package. To compare sex distribution in 3q29Del participants and controls, Pearson's chi square was implemented using the stats (26) R package. To compare age distribution in 3q29Del participants and controls, two sample t-test was implemented using the stats (26) R package. To compare scores in 3q29Del participants versus mean values for children with idiopathic ASD, one sample t-test was implemented using the stats (26) R package. Figures were generated using the plotly (28) and ggplot2 (29) R packages.

Sensitivity Analysis

The questionnaires for 90 participants with 3q29Del (95.7%) were completed by a parent or guardian ("parent-registered"), while 4 participants with 3q29Del (4.3%) completed all questionnaires themselves ("self-registered"). All control participants were parent-registered. To assess whether responses from the self-registered 3q29Del participants were influencing the results, the dataset was stratified to remove self-registrants and re-analyzed. Self-registrants were not found to have a significant effect on the analyses (Tables S5 and S6). All results include both parent- and self-registrants.

RESULTS

Self-report of neuropsychiatric diagnosis in 3q29Del

Self-report of neuropsychiatric diagnoses in our 3q29Del study subjects revealed a high prevalence of diagnoses of neuropsychiatric disorders, including ASD (29.8%), ID (58.5%), and anxiety (26.6%) (Table 2), confirming prior work by our group (4). 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, since 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 (30-34) and the frequency of bipolar disorder is ~1.8 times higher than expected (35). A summary of neuropsychiatric diagnoses can be found in Table 2.

Features of ASD self-report in 3q29Del

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 3q29Del.

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 3q29Del scored significantly higher than typically developing controls on all 4 scales ($p < 3.0E-12$, Table S4).

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 3q29Del and an ASD diagnosis scored significantly higher than both controls and individuals with 3q29Del without an ASD diagnosis ($p < 0.001$, Figure 2B). We were interested to observe that individuals with 3q29Del without an ASD diagnosis also scored significantly higher than controls ($p < 0.001$, Figure 2B). In addition to the contribution of diagnosed ASD to inflated SRS scores, we also examined possible sex differences in scores. We found that both males and females with 3q29Del scored significantly higher than controls ($p < 0.001$), 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 3q29Del without an ASD diagnosis had significantly higher scores than controls ($p < 0.001$, Figure 2D). Taken together, this implies that increased SRS scores in individuals with 3q29Del are not being driven by sex or ASD diagnosis status; rather, the presence of the deletion itself confers a greater risk for features of ASD. Furthermore, these data show 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 3q29Del, 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 3q29Del

While total scores on the SRS, SCQ, ASSQ, and CBCL/ABCL can give an indication of the overall level of impairment of individuals, sub-scores can reveal nuances of 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). These common DSM-oriented sub-scales from the CBCL and ABCL align with common neuropsychiatric diagnoses reported by individuals with 3q29Del (4). 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 3q29Del showed high scores across all sub-scales. The mean scores for five of the six sub-scales were elevated: four mean scores were in the moderate range (Social Awareness, Social Cognition, Social Communication, and Social Communication and Interaction), and one was in the severe range (Restricted Interests and Repetitive Behaviors). Notably, 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 (3q29Del vs. idiopathic ASD Social Motivation p=7.66E-11) (36). 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 3q29Del 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 3q29Del scored significantly higher than typically developing controls on all three scales ($p < 0.001$, Figure 3C), supporting previous reports of increased risk for neuropsychiatric diagnoses associated with the 3q29 deletion (4).

Confounding due to heart defects and/or ID

A previous study of 3q29Del by our group showed that approximately 25% of individuals reported a congenital heart defect (4). Early hypoxic insult due to a heart defect has been hypothesized to contribute to later neuropsychiatric and neurodevelopmental outcomes (37-42). 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 (43) . Congenital heart defects are not associated with self-reported ASD or ID diagnoses or age at walking ($p > 0.05$, Table S5). Individuals with 3q29Del 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 ($p < 0.015$, Table S6), 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 3q29Del 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 (44). Taken together, this suggests that the 3q29 deletion is approaching the severe end of the spectrum of ASD-associated mutations.

We have shown that compared to typically developing children, our 3q29Del sample is significantly enriched for ASD features and other behavioral problems, whether or not they have a clinical ASD diagnosis. This finding is particularly concerning; while individuals with 3q29Del that have an ASD diagnosis do tend to score higher on symptomology scales overall, 3q29Del individuals without an ASD diagnosis still score significantly higher than typically developing children. This indicates several possible explanations: a) an enrichment for ASD features or social disability that falls short of diagnostic criteria, b) possible undiagnosed ASD in our study population, or c) non-specificity of the SRS, and potentially SCQ, for phenotypes other than ASD, such as anxiety. The possibility of undiagnosed ASD in our study population 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, our data suggest that gold-standard ASD evaluations should be standard of care for individuals diagnosed with 3q29Del. If implemented, this practice would enable patients to gain access to early interventions, treatments, and therapeutic programs that are known to improve later outcomes.

It is possible that the score inflation observed in individuals with 3q29Del may be due to the high prevalence of developmental delay or congenital heart defects associated with the 3q29 deletion (4); however, these factors do not contribute significantly to scores in our study population. Our results suggest that the early hypoxic insult from a congenital heart defect is not related to neurodevelopmental outcomes in 3q29Del, and that these phenotypes are arising via different biological mechanisms. As the 3q29 interval encompasses 21 genes (2) 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 3q29Del.

Based on the SRS sub-scales, participants with 3q29Del display a strikingly different behavioral profile than what is observed in children with idiopathic ASD (36). Male and female 3q29Del 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 difference between 3q29Del and idiopathic ASD is further supported by the scores on the Withdrawn sub-scale of the CBCL and ABCL; while 3q29Del participants score significantly higher than controls, their mean score is still in the normal range

(Figure S2). Previous studies utilizing the CBCL in idiopathic ASD have found that mean scores for participants with ASD are in the borderline range, with over 50% of subjects scoring in the borderline or clinical range (45, 46). Only 27% of 3q29Del participants score in the borderline or clinical range, indicating another dimension where 3q29Del differs from idiopathic ASD. This profile is consistent with our direct, 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 3q29Del, as well as an investigative inroad to a novel subtype of ASD. Because social motivation appears to be relatively well-preserved in 3q29Del, 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 3q29Del to date, it is not without limitations. All of the data used in the present study were collected from questionnaires completed by the parents and guardians of individuals with 3q29Del, which introduces several potential sources of bias. Some studies have questioned the validity and reliability of parent-report data (47); 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 (48). 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 3q29Del 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 3q29Del. 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 3q29Del 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 (4), which is a relatively mild heart defect; however, the low number of participants with different types of heart defects rendered analyses to assess their associations with neurodevelopment underpowered. Ongoing studies by the Emory 3q29 Project, including in-person patient evaluations (genome.emory.edu/3q29; (49)) aim to address some of the weaknesses of the present work by performing gold-standard evaluations by trained clinicians.

There are significant strengths of this study as compared to previous studies of 3q29Del. First, this is the largest cohort of individuals with 3q29Del ever assembled. This is a critical step in capturing the true phenotypic spectrum associated with the 3q29 deletion. Our use of standardized questionnaires and best practices allowed rigorous assessment of phenotypes in 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, these attributes make the present study an excellent complement to previously published case reports on individuals with 3q29Del; by capturing a larger patient base with systematic assessments, 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 3q29Del, 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 3q29Del 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.

Acknowledgements

Funded by NIH 1R01MH110701-01A1 (Mulle), the Treasure Your Exceptions Project (Zwick), and NIH T32 GM0008490 (Pollak).

This manuscript is currently available on the bioRxiv preprint server (https://doi.org/10.1101/386243).

Disclosures

Rebecca Pollak reports no relevant biomedical financial interests or potential conflicts of interest.

Dr. Murphy reports no relevant biomedical financial interests or potential conflicts of interest.

Dr. Epstein reports no relevant biomedical financial interests or potential conflicts of interest.

Dr. Zwick reports no relevant biomedical financial interests or potential conflicts of interest.

Dr. Klaiman reports no relevant biomedical financial interests or potential conflicts of interest.

Dr. Saulnier reports receiving royalties from Pearson Clinical for the Vineland-3.

Dr. Mulle reports no relevant biomedical financial interests or potential conflicts of interest.

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Tables/Figures

Table 1: Characteristics of study participants with 3q29Del and controls. Demographic data collected from the custom Medical & Demographic Questionnaire completed by participants upon enrollment in the online 3q29 Registry. P values were calculated with Student's t test (age), Fisher's exact test (race, heart defect, age at walking), and Pearson's chi square test (sex).

	3q29 Deletion Syndrome	Control	P value
Age, years (mean ± SD)	12.7 ± 11	10.6 ± 7.2	0.822
Sex (n, %)			0.484
Male	55 (58.5%)	33 (51.6%)	
Female	39 (41.5%)	31 (48.4%)	
Race (n, %)			5.85E-05
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, %)			2.06E-07
Yes	21 (22.3%)	0 (0%)	
No	57 (60.6%)	61 (95.3%)	
Unsure	16 (17%)	3 (4.7%)	
Age at Walking (n, %)			1.14E-09
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: Self-reported neuropsychiatric diagnoses. Characteristics of self-reported neuropsychiatric diagnoses in study participants with 3q29Del and controls. P values were calculated with Fisher's exact test.

		3q29 Deletion Syndrome			Control			P value; 3q29Del 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%)	<2.2E-16
	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%)	7.57E-8
	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%)	

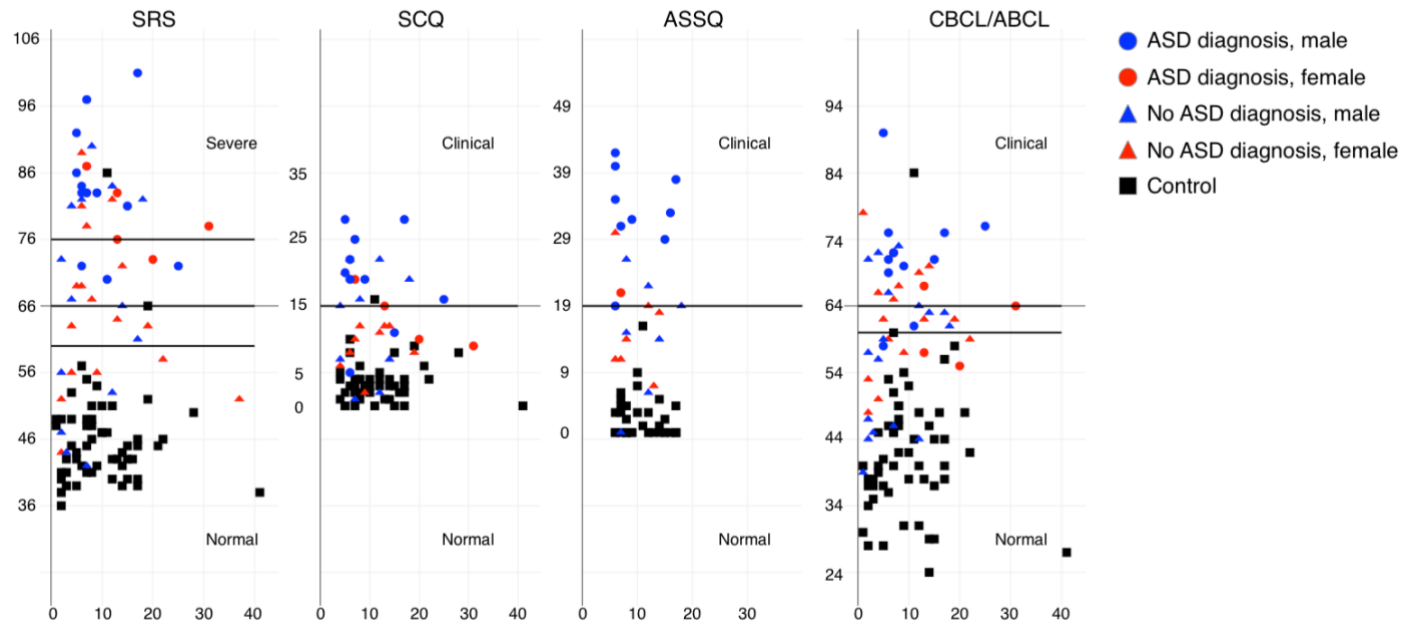

Figure 1. Total scores on the SRS (n=48 3q29Del, 59 control), SCQ (n=33 3q29Del, 46 control), ASSQ (n=24 3q29Del, 35 control), and CBCL/ABCL (n=48 3q29Del, 57 control) for registry participants. Self-reported diagnosis of ASD is denoted by shape (circle/ASD, triangle/no ASD), and gender of participant is denoted by color (red/female, blue/male). Controls are shown in black.

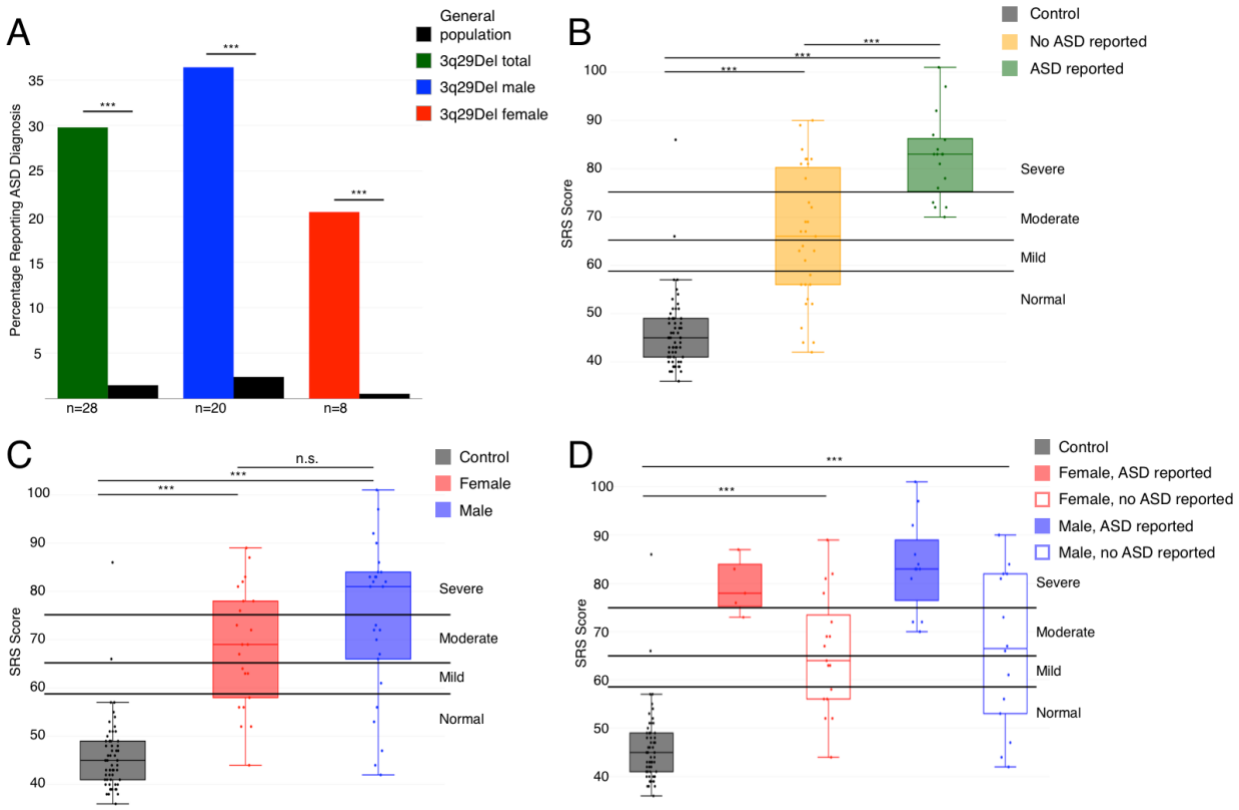

Figure 2. A) Proportion of participants with 3q29Del self-reporting a diagnosis of ASD (not all respondents completed symptom questionnaires); 28 cases report an ASD diagnosis (green), comprised on 20 males (blue) and 8 females (red). Compared to general population frequencies (black), cases report significantly higher incidence of ASD. **B)** SRS scores split by control (n=59), 3q29Del not reporting an ASD diagnosis (n=31), and 3q29Del 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), 3q29Del female (n=22), and 3q29Del male (n=26), showing a lack of gender bias in scores for 3q29Del participants. **D)** SRS scores split by gender and self-reported diagnostic status, with control (n=59), 3q29Del female reporting ASD (n=5), 3q29Del female not reporting ASD (n=17), 3q29Del male reporting ASD (n=12), and 3q29Del male not reporting ASD (n=14), showing inflated scores for 3q29Del participants irrespective of gender or diagnostic status. ***, $p<0.001$

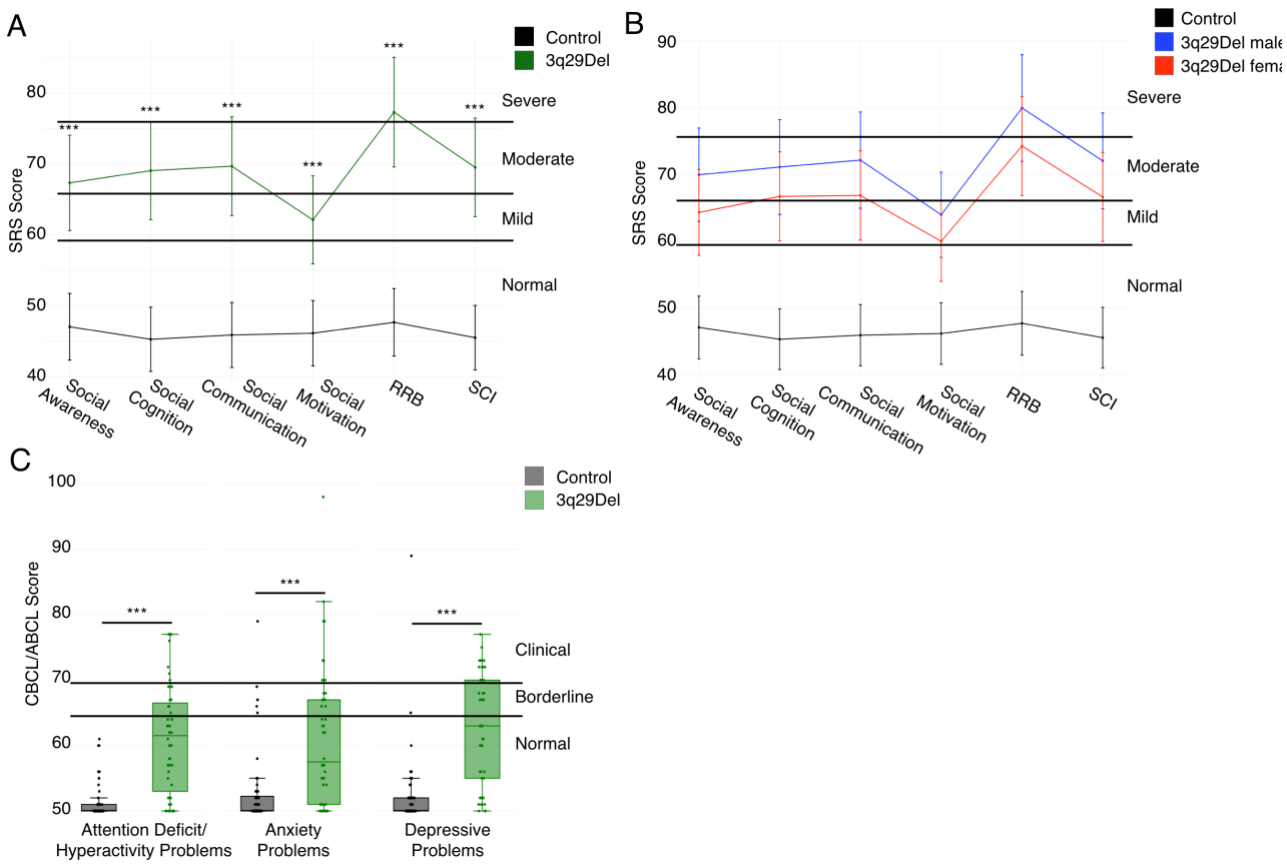

Figure 3. A) Profile of individuals with 3q29Del (n=48) and controls (n=59) across SRS sub-scales, showing moderate to severe impairment of 3q29Del participants in all domains except Social Motivation (RRB, Restricted Interests and Repetitive Behaviors; SCI, Social Communication and Interaction). **B)** Profile of 3q29Del males (n=26) and females (n=22) and controls (n=59) across SRS sub-scales, showing that 3q29Del 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 3q29Del participants (n=48) and controls (n=57) across 3 DSM-oriented sub-scales from the CBCL and ABCL, showing significantly increased pathology in 3q29Del participants in all 3 domains. ***, $p<0.001$