ARCHIVAL REPORT

Reciprocal Duplication of the Williams-Beuren Syndrome Deletion on Chromosome 7q11.23 Is Associated with Schizophrenia


Background: Several copy number variants (CNVs) have been implicated as susceptibility factors for schizophrenia (SZ). Some of these same CNVs also increase risk for autism spectrum disorders, suggesting an etiologic overlap between these conditions. Recently, de novo duplications of a region on chromosome 7q11.23 were associated with autism spectrum disorders. The reciprocal deletion of this region causes Williams-Beuren syndrome.

Methods: We assayed an Ashkenazi Jewish cohort of 554 SZ cases and 1014 controls for genome-wide CNV. An excess of large rare and de novo CNVs were observed, including a 1.4 Mb duplication on chromosome 7q11.23 identified in two unrelated patients. To test whether this 7q11.23 duplication is also associated with SZ, we obtained data for 14,387 SZ cases and 28,139 controls from seven additional studies with high-resolution genome-wide CNV detection. We performed a meta-analysis, correcting for study population of origin, to assess whether the duplication is associated with SZ.

Results: We found duplications at 7q11.23 in 11 of 14,387 SZ cases with only 1 in 28,139 control subjects (unadjusted odds ratio 21.52, 95% confidence interval: 3.13–922.6, p value 5.5 × 10⁻⁵; adjusted odds ratio 10.8, 95% confidence interval: 1.46–79.62, p value .007). Of three SZ duplication carriers with detailed retrospective data, all showed social anxiety and language delay premorbid to SZ onset, consistent with both human studies and animal models of the 7q11.23 duplication.

Conclusions: We have identified a new CNV associated with SZ. Reciprocal duplication of the Williams-Beuren syndrome deletion at chromosome 7q11.23 confers an approximately tenfold increase in risk for SZ.

Key Words: Autism, 7q11.23 duplication syndrome, psychiatric genetics, schizophrenia, schizophrenia genetics, Williams-Beuren syndrome

Schizophrenia (SZ) is a severe psychiatric disorder that represents a significant public health burden, affecting 1% of the population worldwide (1). It has long been recognized that genetic factors must play a role in susceptibility, but until recently, identification of such risk factors has proven elusive (1). Landmark studies of genomic structural variation in...
SZ, first published in 2008, established that there is an excess of large, rare copy number variants (CNVs) in SZ populations (2–5). Since then, this has become one of the most exciting and consistently replicated findings in psychiatric genetics. Currently, at least 10 specific CNV loci have been replicated in multiple reports and can thus be regarded as confirmed risk factors (3,5–14). The first of these reports included two large studies with thousands of patients, where recurrent deletions were found at three new loci, 1q21, 15q11, and 15q13, in addition to the previously identified 22q11 deletion (3,5). Several studies soon followed, implicating deletions at 17q12 (15) and 3q29 (7,8) and duplications at 16p11 (12). These variants have the following properties in common: they are all large, involving many genes; they are rare, at a frequency far less than 1% even in SZ populations; and they all carry substantial risk for SZ, with estimated odds ratios between 3 and 7 (7,14). Smaller variants have been identified in specific genes, including deletions in neurexin1 (9,10,16) and contactin-associated protein-like 2, another member of the neurexin family (11). Duplication at the vasoactive intestinal peptide receptor 2 locus is also associated with high risk for schizophrenia (7,13). One surprising finding is that many of the CNVs associated with SZ are also significantly more common in individuals with intellectual disability (ID), autism, and epilepsy (15,17–20), advancing the concept of a neurodevelopmental link between these disorders (21).

In the current study, we initially assessed a sample of 554 independent SZ cases and 1014 control subjects, all of Ashkenazi Jewish (AJ) descent. We limited our analysis to large rare CNVs in keeping with previous reports. We replicate previous findings of rare and de novo CNVs, finding a significant excess of these events in SZ cases compared with control subjects. Among these rare events, we discovered two duplications on chromosome 7q11.23, in addition one confirmed de novo event. A subsequent meta-analysis of 14,387 SZ cases and 28,139 control subjects confirmed the overrepresentation of this duplication in SZ cases, with an estimated odds ratio of 10.8 (95% confidence interval: 1.46–79.62, p value .007). De novo duplications at this identical locus were previously reported in an autism population (22), further supporting a shared etiology between autism and schizophrenia.

Methods and Materials

Study Subjects

**SZ Cases.** Ashkenazi Jewish individuals affected with SZ (n = 615) were recruited nationally over a 6-year period. Cases were eligible for inclusion in these analyses if the proband met DSM-IV criteria for a SZ diagnosis and all four grandparents were of Ashkenazi Jewish descent. When available, parental DNAs were also collected. Proband were assessed for psychiatric illness according to an established consensus-based procedure, as described in Fallin et al. (23) and in Supplement 1. No subject in our study had a previous clinical genetic diagnosis.

**Control Subjects.** Control subjects were selected from three cohorts: a study of Crohn’s disease in the Ashkenazim (n = 258), a study of neuromuscular disease (Parkinson’s and dystonia) in the Ashkenazim (n = 266), and the Ashkenazi Jewish Control Registry hosted at Johns Hopkins University (n = 538). Control subjects from the Crohn’s and neuromuscular cohorts were not screened for psychiatric disease; Ashkenazi Jewish Control Registry control subjects were administered a questionnaire about psychiatric conditions.

**Meta-Analysis.** Seven additional samples were incorporated into our meta-analysis, ultimately totaling 14,387 SZ cases and 28,139 unaffected control subjects. Details of each sample, including ascertainment criteria and genotyping platform, are included in Supplement 1.

For the Ashkenazi Jewish sample ascertained at Johns Hopkins University, all recruitment methods and protocols for collection of clinical data and blood samples were approved by the Johns Hopkins Institutional Review Board, and informed consent was obtained from all individuals. All other data, including data for the meta-analysis, were fully anonymized before receipt at Emory University.

**Genotyping and Identification of CNVs.** DNA from the Ashkenazi Jewish sample was extracted using the Genta Puregene kit (Qiagen, Hilden, Germany) at Johns Hopkins University. All DNA used for this study was extracted from blood (no cell line DNA was used). Genotyping was performed using the Affymetrix Human Genome-Wide SNP Array 6.0 (Affymetrix, Santa Clara, California) at Emory University. Genotypes were called using the Birdseed algorithm, as implemented in Affymetrix power tool software (version 1.12.0). Single nucleotide polymorphisms (SNPs) with completion rates <90% were excluded, rendering 816,284 autosomal SNPs for analysis. For CNV analysis, normalization and log ratio data calculation were obtained using the Affymetrix power tools software (version 1.12.0). Log(2) ratio data for autosomes were extracted and analyzed using three algorithms: GLAD (24), GADA (25), and BEAST (G. Satten, et al., unpublished data). Copy number variants called by only a single algorithm were removed from analysis. Putative CNV intervals were filtered by size (>100 kilobase [kb]), number of SNPs in the CNV interval (>20 SNPs), and CNV-interval SNP homozygosity rates. Copy number variants >500 kb were validated by a second array (Illumina Human OmniExpress v1 genotyping array; Illumina, San Diego, California), quantitative real-time polymerase chain reaction, or polymerase chain reaction across deletion breakpoint. See Methods and Materials in Supplement 1 for specific details on validation methodologies.

**Definition of Rare CNV.** We filtered variants with the goal of excluding typical polymorphic events. To facilitate comparison with our earlier study (8), we excluded variants that had >50% overlap with a CNV in the database of genomic variants (http://projects.tcag.ca/variation/, Nov 02, 2010 update) for deletions and duplications separately. We also excluded any variant with a frequency >5% at any single locus.

**Statistical Analysis**

Permutation-corrected p values for overall CNV burden were calculated using PLINK (pngu.mgh.harvard.edu/~purcell/plink/). All odds ratios, associated confidence intervals, and p values were calculated using the R statistical software package. Meta-analysis statistics were calculated with the Cochran-Mantel-Haenszel exact test, stratified by study, in the R statistical package (cran.us-r-project.org) (26,27).

**Results**

**Rare and De Novo CNV in the AJ Population**

There was a 1.29-fold excess of rare CNVs >100 kb (Supplement 1), which became more pronounced for CNV >500 kb. In the 554 AJ SZ cases compared with 1014 control subjects, 5.6% of cases versus 2.4% of control subjects had at least one rare CNV >500 kb (odds ratio [OR]: 2.44, p value .001), consistent with previous reports (2–5). The OR was strongest for deletions >1 Mb (OR: 5.1, p value .004) (Table 1). These data harbor known susceptibility variants, including three 22q11 deletions and four 16p11 duplications, which are now considered established risk factors for SZ (see data and Table S4 in
For 292 of these SZ cases, both parental DNAs were available, enabling us to estimate the de novo rate for large (>500 kb) rare CNV in our sample. We find six de novo events or a rate of 2.1%. We compared this with the de novo rate in nonpsychiatric trios, reviewed by Kirov et al. (28), where a rate of .8% was reported (27 de novo CNV in 3495 trios). This difference is statistically significant (OR: 2.69, p value .038). Our de novo rate of 2.1% is identical to that reported in SZ (2.1% in the study by Kirov et al. [28]) and lower, but not significantly so, than the reported de novo rate in simplex autism spectrum disorder (ASD) trios (22) (2.1% vs. 3.9%, p value .13).

Meta-Analysis of the 7q11.23 Region

The six de novo CNV >500 kb in the AJ sample included one 1.3 Mb de novo duplication on chromosome 7q11.23. A duplication at this locus was also identified in an additional unrelated proband (parental DNAs were unavailable for inheritance testing) (Figure 1). Given the recurrent nature of this duplication and its involvement in ASD, we were motivated to investigate its frequency in additional SZ cohorts. This was the only variant tested in additional samples. We analyzed datasets where we could obtain the raw intensity files, to enable consistent data processing (Table S3 in Supplement 1). In total, we found 11 duplications in 14,387 cases (.076%) and one in 28,139 control subjects (.0035%) (Table 2, Figure 2), for an overall odds ratio of 21.5 (95% confidence interval: 3.13–922.6, p value 5.5 × 10–5). Although such a large CNV would be found with any of the array platforms used and there was no reason to suspect population differences for a CNV with such a high pathogenic effect and de novo rate, we nevertheless also calculated the

![Figure 1](http://www.sobp.org/journal)

**Figure 1.** Raw log(2) ratio data are shown for 15 Mb on chromosome 7q (65 Mb–80 Mb), flanking the duplication region, for two unrelated Ashkenazi Jewish schizophrenia probands carrying the 7q11.23 duplication (A, B). Shading indicates the duplicated region. The parents of schizophrenia proband 8015-2, who do not carry the duplication, are also shown (C, D).

### Table 1. Excess Rare Variants in 554 SZ Cases Versus 1014 Control Subjects

<table>
<thead>
<tr>
<th>Type of Variant</th>
<th>Number of Cases with at Least One Variant</th>
<th>Number of Control Subjects with at Least One Variant</th>
<th>p Value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare CNV &gt;500 kb</td>
<td>31 (5.6%)</td>
<td>24 (2.4%)</td>
<td>.0013</td>
<td>2.44 (1.37–4.4)</td>
</tr>
<tr>
<td>Deletions &gt;500 kb</td>
<td>13 (2.3%)</td>
<td>8 (.8%)</td>
<td>.018</td>
<td>3.02 (1.15–8.46)</td>
</tr>
<tr>
<td>Duplications &gt;500 kb</td>
<td>18 (3.2%)</td>
<td>16 (1.6%)</td>
<td>.044</td>
<td>2.09 (1.00–4.43)</td>
</tr>
<tr>
<td>Rare CNV &gt;1 Mb</td>
<td>19 (3.4%)</td>
<td>10 (1%)</td>
<td>.0012</td>
<td>3.56 (1.56–8.64)</td>
</tr>
<tr>
<td>Deletions &gt;1 Mb</td>
<td>11 (2%)</td>
<td>4 (.4%)</td>
<td>.0043</td>
<td>5.11 (1.51–22.1)</td>
</tr>
<tr>
<td>Duplications &gt;1 Mb</td>
<td>8 (1.4%)</td>
<td>6 (.8%)</td>
<td>.097</td>
<td>2.46 (74–8.65)</td>
</tr>
</tbody>
</table>

All odds ratios and p values calculated using a two-sided Fisher’s exact test in R. CI, confidence interval; CNV, copy number variant; kb, kilobase; Mb, megabase; SZ, schizophrenia.
Mantel-Haenszel corrected OR for this duplication, leading to a corrected OR of 10.8 (\(p\) value .007). These data therefore indicate the 7q11.23 duplication is a significant new risk factor for SZ.

**Discussion**

We have identified a new risk factor for schizophrenia, a 1.4 Mb duplication on chromosome 7q11.23. Two prior studies reported single 7q11.23 duplication carriers in their SZ case population patients (28,29). In this current study, we found the duplication in .076% of SZ patients and established a statistically significant enrichment compared with control subjects. The 7q11.23 duplication syndrome has previously been described (Online Mendelian Inheritance in Man [OMIM] #609757) in the context of intellectual disability and autism (22,30,31). It is found in .1% to .12% (39/32,587 [20]; 16/15,749 [32]) of patients referred for cytogenetic testing because of developmental delay/congenital malformations/ASD (20,32). We note that prior studies of the 7q11.23 duplication phenotype involved mainly pediatric patients. As the typical age of onset for psychosis in schizophrenia is in early adulthood, risk for psychosis in 7q11.23 duplication carriers was therefore not captured. Studies including adult patients are limited and omit psychiatric evaluation. For example, a 2009 study of 12 7q11.23 duplication carrier probands with intellectual disability revealed 7 were inherited; phenotypic descriptions of the parents neglected an evaluation for psychosis (30). Similarly, a 2011 study did not conduct psychiatric assessments on the eight adults identified with 7q11.23 duplication syndrome (31). We therefore may have uncovered a previously unrecognized aspect of the natural history of 7q11.23 duplication syndrome: adult risk for schizophrenia. This is reminiscent of 22q11 deletion syndrome, which is typically identified as a pediatric condition but carries substantial risk for schizophrenia in early adulthood (33,34). A longitudinal study of 7q11.23 duplication carriers would ideally assess the true risk for schizophrenia in this population.

It is possible we have ascertained adult individuals with autism rather than schizophrenia. However, the frequency of the 7q11.23 duplication in ASD patients is estimated at 4 in 3816 or .1048% (22). Our study observed the 7q11.23 duplication 11 times in 14,573 individuals with schizophrenia. If we assume for the moment that all 11 duplication carriers have ASD, not SZ, and that this duplication is at the reported frequency of .1048 in the

<table>
<thead>
<tr>
<th>Sample</th>
<th>Cases</th>
<th>Ashkenazi</th>
<th>MGS (41)</th>
<th>ISC (3)</th>
<th>Bulgarian Trios (28)</th>
<th>Japanese (42)</th>
<th>UK (4,14)</th>
<th>CATIE (43)</th>
<th>Sweden (44)</th>
<th>Totals</th>
<th>Control 7q11.23</th>
<th>Control Subjects</th>
<th>MH-Corrected OR</th>
<th>(95%) CI: 1.46–79.62, (p) value .007</th>
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<tr>
<td></td>
<td>Cases</td>
<td>Duplications</td>
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<tr>
<td>Ashkenazi</td>
<td>554</td>
<td>2(^{a})</td>
<td>1014</td>
<td>0</td>
<td>3945</td>
<td>4</td>
<td>3611</td>
<td>1</td>
<td>3063</td>
<td>1</td>
<td>3181</td>
<td>0</td>
<td>662</td>
<td>1(^{b})</td>
</tr>
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<td>MGS (41)</td>
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<td>1</td>
<td>3181</td>
<td>0</td>
<td>662</td>
<td>1(^{b})</td>
<td>638</td>
<td>0</td>
<td>575</td>
<td>0</td>
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<td>ISC (3)</td>
<td>3063</td>
<td>1</td>
<td>3181</td>
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<td>638</td>
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<td>575</td>
<td>0</td>
<td>564</td>
<td>0</td>
<td>471</td>
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<tr>
<td>Bulgarian Trios (28)</td>
<td>662</td>
<td>1(^{b})</td>
<td>638</td>
<td>0</td>
<td>575</td>
<td>0</td>
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<td>0</td>
<td>471</td>
<td>0</td>
<td>13,036</td>
<td>0</td>
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<tr>
<td>Japanese (42)</td>
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<td>0</td>
<td>564</td>
<td>0</td>
<td>471</td>
<td>0</td>
<td>13,036</td>
<td>0</td>
<td>738</td>
<td>1</td>
<td>289</td>
<td>0</td>
<td>4379</td>
<td>2</td>
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<tr>
<td>UK (4,14)</td>
<td>471</td>
<td>0</td>
<td>13,036</td>
<td>0</td>
<td>738</td>
<td>1</td>
<td>289</td>
<td>0</td>
<td>4379</td>
<td>2</td>
<td>5806</td>
<td>0</td>
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<td>11</td>
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<tr>
<td>CATIE (43)</td>
<td>738</td>
<td>1</td>
<td>289</td>
<td>0</td>
<td>4379</td>
<td>2</td>
<td>5806</td>
<td>0</td>
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<td>Totals</td>
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<td>Raw OR</td>
<td>21.52 ((95%) CI: 3.13–922.6, (p) value 5.5 \times 10^{-5})</td>
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CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; CI, confidence interval; ISC, International Schizophrenia Consortium; MGS, Molecular Genetics of Schizophrenia; MH, Mantel-Haenszel; OR, odds ratio; SZ, schizophrenia; UK, United Kingdom.

\(^{a}\)One de novo event.

\(^{b}\)De novo event.

Mantel-Haenszel corrected OR for this duplication, leading to a corrected OR of 10.8 (\(p\) value .007). These data therefore indicate the 7q11.23 duplication is a significant new risk factor for SZ.

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**Figure 2.** Eleven duplications found in schizophrenia (SZ) patients are shown against the context of previously reported events at the 7q11.23 locus, including typical and atypical Williams-Beuren syndrome (WBS) deletions (with highly social or not highly social phenotypes noted), de novo duplications in autism spectrum disorder (ASD) patients, and genes in the WBS region.

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AD population, that would imply 72% of all our SZ are actually misclassified ASD. Ascertainment procedures of SZ patients for the studies included herein are methodical, detailed, and comprehensive, and a 72% misclassification rate is highly unlikely. Assuming a more reasonable misclassification rate of 10% would imply 1 or 2 out of the 11 deletions are due to mischaracterized ASD. Since we observed the duplication 11 times, we conclude that any adult autism patients included in our sample cannot account for the enrichment we observe.

The 1.4 Mb region on chromosome 7q11.23 is flanked by segmental duplications (Figure 2), which are likely mediating nonallelic homologous recombination, giving rise to the duplication and reciprocal deletion. These rearrangements are typically de novo events: Sanders et al. (22) found that 4 out of 4 duplications were de novo; Girirajan et al. (20) found of 9 informative duplications, 5 were de novo (an additional 30 duplications in this study did not have parental DNAs available for inheritance testing). The reciprocal deletion gives rise to the well-characterized Williams-Beuren syndrome (OMIM #194050), first described in the early 1960s (35,36). The duplication syndrome has only been described more recently. In 2005, a single patient with the duplication and severe language delay was described (37); later, description of the microduplication syndrome (OMIM #609757) was expanded to include speech delay and other variable characteristics, such as ID, hypotonia, congenital heart defects, social interaction difficulties, and, less often, epilepsy (30). More recently, de novo duplication of this region was linked to ASD, where hallmarks of the phenotype are diminished development of language and poor social communication (22,38). In one of the largest and most comprehensive studies to date, Velleman and Mervis (31) describe the cognitive and behavioral profile of 7q11.23 duplication syndrome derived from both literature reports and their own direct evaluation of 30 children with the duplication. They confirm both language delay and social anxiety in 7q11.23 duplication carriers and find separation anxiety to feature prominently among these individuals (31,39). In fact, these authors suggest that this separation anxiety, which can manifest with selective mutism, could re semble an autism phenotype (31). In a research setting, the authors document social phenomena including eye contact, pleasureable engagement with a parent, imaginative play, and other reciprocal social interactions inconsistent with autism (31). While further study will be required to confirm or refute the autism-7q11.23 duplication relationship, our current data support a link between social anxiety, language delay, and the 7q11.23 duplication. Both SZ duplication carriers in the Ashkenazi sample reported severe social anxiety and language delay (data in Supplement 1).

Similarly, a Bulgarian duplication carrier with SZ also had speech delay and was described as socially withdrawn (28). The mean age at onset of the 11 SZ duplication carriers we report here was 20.7 years (SD = 8.3 years); however, 2 cases had an onset in childhood (aged 7 and 8 years), suggesting that the age at onset could be quite early in a proportion of carriers. In light of the Williams-Beuren syndrome phenotype, it is possible there may be a quantitative relationship between dosage of the 7q11.23 region and verbal and social skills, though more detailed phenotypic data will be necessary to investigate this hypothesis.

Heterogeneity is a hallmark of schizophrenia. Among any population of SZ patients, there is a wide spectrum of differences in clinical presentation, course, and outcome. It has long been suspected that this spectrum reflects heterogeneity in underlying etiology, and current CNV data support this notion. In our sample, we note that the two unrelated patients in the AJ cohort had similar early childhood morbidity, including obsessions and compulsions, eating disorders, and language delay. Though more research is required, including detailed phenotypic studies and collection of retrospective data on duplication carriers, our findings nevertheless suggest the 7q11.23 region may define a specific subtype of SZ. Categorizing patients by etiologic variants like this may ultimately serve to reduce the vast heterogeneity seen in this disorder.

We find duplications at 7q11.23 in SZ cases at a frequency of .08%, similar to the frequency of this duplication in ASD (.1%, 4 out of 3816 cases) (22). In two large samples of individuals referred for array comparative genomic hybridization testing with a heterogeneous mixture of phenotypes, including congenital abnormalities, developmental delay, and intellectual disability, this duplication was seen in 39 out of 32,587 individuals (.12%) (20) and 16 of 15,749 individuals (.1%) (32), respectively. Thus, this duplication is seen with similar frequencies in patients with either SZ, ASD, or ID, echoing results from other CNVs associated with both SZ and ASD. Notably, thus far, only a single duplication has been described in control subjects; most carriers are found in ID, autism, or SZ cohorts, underscoring the high pathogenicity of this duplication, which is similar to the 3q29 or 22q11 deletions (7,14).

In summary, we find that the 7q11.23 duplication is a new risk factor for the development of SZ. This duplication shares the hallmarks of other SZ-associated CNVs: it is rare, has a large effect size, and is associated not only with schizophrenia but also with autism and ID, supporting an etiologic link between these phenotypes. Future study incorporating comprehensive data collection will be required to understand the apparently different behavioral manifestations of the 7q11.23 deletion and duplication.

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