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A meta-analysis of rare copy number variants associated with autism and schizophrenia

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Abstract

A meta-analysis of rare copy number variants associated with autism and schizophrenia

By Brooke MacDonald

Autism spectrum disorder (ASD) and schizophrenia have been associated with considerable phenotypic overlap and substantial heterogeneity within diagnostic categories, complicating current diagnostic practices. Genomic studies have identified shared sets of rare copy number variant (CNV) loci associated with these disorders. Recently, an increasing number of whole-genome analyses of large sample sizes have been conducted. To better understand the underlying genetic architecture of these disorders, a meta-analysis was conducted to synthesize data from rare variant analyses of CNV loci associated with increased risk of ASD and schizophrenia. A search of PubMed for case-control studies identifying CNVs associated with the disorders identified 369 schizophrenia studies and 346 ASD studies. Seven ASD studies and 19 schizophrenia studies remained after implementation of inclusion criteria. Data were extracted for 11 CNV loci and effect sizes expressed as CMH odds ratios. Duplications at 22q11.2 (p-value SCZ = 2.2E-16; ASD = 0.0058) and deletions at 15q11.2-13 (p-value SCZ = 0.0018; ASD = 2.8E-06) were associated with increased risk for both schizophrenia and autism. Reciprocal relationships were observed for mutations at 16p11.2 (p-value SCZ duplication = 9.7E-16; ASD deletion = 0.026) and 1q21.1 (p-value SCZ deletion = 6.9E-14; ASD duplication = 0.03). For ASD, 22q11.2 deletions (CMH OR: 11.2, 95% CI: 1.6 – 486.8) displayed the strongest association, while 3q29 deletions (CMH OR: 38.8, 95% CI: 5.2 – 1873.3) displayed the strongest association with schizophrenia. These analyses further support an overlap in CNV loci associated with ASD and schizophrenia and provide further evidence to support the need for an evaluation of the current system of psychiatric classification. However, further analysis of the underlying genetic architecture associated with phenotypes common to both autism and schizophrenia as well as potential environmental influences is necessary in order to better understand the relationship between ASD and schizophrenia.

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Background/Literature Review

Schizophrenia is a chronic psychiatric illness affecting approximately 1% of the population when considered in isolation (1). Diagnosis is mostly dependent on the presence of positive symptoms (delusions and hallucinations), negative symptoms (impaired motivation, social withdrawal, etc.), and cognitive impairment (1). The first episode of psychosis usually occurs within late adolescence or early adulthood. While positive symptoms tend to relapse and remit, negative and cognitive symptoms tend to be chronic, with long-term effects on social function. This severe psychiatric disorder profoundly impacts not only the affected individual, but society as well, with a reported economic burden of $155.7 billion in 2013 (1, 2). Around 20% of diagnosed individuals have chronic symptoms and disability, with an unemployment rate of around 80-90% and life expectancy that is reduced by 10-20 years (1).

Autism spectrum disorder (ASD) is predominantly seen as a set of early-onset neurodevelopmental conditions. Like schizophrenia, autism also exhibits a worldwide population prevalence of about 1% (3). The operational definitions of both autism and schizophrenia have evolved with the subsequent revisions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). The latest edition, DSM-V, uses the broad term autism spectrum disorder, replacing defined subtypes, and reorganizes the triad of features emphasized in DSM-IV, into a dyad: difficulties in social communication and interaction; and restricted and repetitive behavior, interests, or activities (3). Autism affects around 4-5 times more males than females. Some speculate this diagnostic bias could be due to gender stereotypes or better compensation among females (3), however, this bias has also been linked to hormonal fluctuations in pregnancy and their involvement in genetic control and determining gender (4).

Diagnosis of psychiatric disorders traditionally relies on a set of reproducible diagnostic criteria, restricted to categorical classifications (5). This method of diagnosis, based on clinical and behavioral characteristics, fails to account for an increasingly apparent overlap of diagnostic categories among various psychiatric disorders as well as the high degree of heterogeneity within diagnostic categories. For example, occurrence of psychotic symptoms such as hallucinations and delusions, mood changes, and alterations in speech, activity level, behavior and sleep can point to a diagnosis of bipolar disorder or schizophrenia, illustrating the arbitrary boundaries existing between diagnoses and hindering the ability of medical professionals to make a clear-cut diagnosis (6). The current classification system in psychiatry, although standardized, remains highly subjective, especially when compared to diagnostic systems used in most other branches of medicine (6). Strict adherence to these categories makes it easy for physicians to overlook common comorbidities among psychiatric conditions, or simply assign a diagnosis they feel carries greater weight within this hierarchical system (6).

Many psychiatric disorders and the symptoms accompanying them have been found to aggregate within families, providing evidence for a genetic role in the risk of developing them (7). Most psychiatric disorders display high heritability estimates, ranging from 0.4-0.8 (8). However, studies on the genomic architecture of these disorders have shown that they are highly polygenic, meaning that no single variant explains more than a small fraction of the genetic risk (8). Psychiatric disorders also exhibit pleiotropy, when the altered function of a gene influences multiple traits, providing evidence for cross-disorder effects of genetic variation. These traits of psychiatry genetics further complicate research that attempts to understand biological mechanisms of psychiatric phenotypes stemming from underlying genetic variation.

Risk of schizophrenia increases when relatives with the disorder are present. Depending on the degree of relation, the risk increases from about 2-4% for second-degree relatives to 10-15% for first-degree relatives, to even 45% for monozygotic twins (9). However, about 90% of individuals with schizophrenia have no parent with the disorder. Therefore, the majority of cases seem sporadic even though schizophrenia has proven highly heritable, with estimates up to 80% (10).

Advances in psychiatry genetics in recent years have been made as the result of genome-wide association studies (GWAS) and studies of copy number variation (CNV) (8). A GWAS can be described as a survey of the entire human genome for genetic variants that predispose to a certain outcome, such as a disease (12). These studies involve the analysis of single nucleotide polymorphisms (SNPs) – a variation of a single base pair within the genomic sequence (9). SNPs are generally common and easily accessible, allowing for rapid and cost efficient analysis of the entire genome (9). More than 100 loci have been identified by GWAS for schizophrenia (1). These loci are very common and have very small effect size, individually explaining only a small fraction of total genetic risk (8). However, taken together, they capture approximately 23% of variation in liability to schizophrenia (9). While there is emerging evidence that variance in liability to ASD can be attributed to common genetic variation, individual loci have not been identified with sufficient evidence (6).

Copy number variants (CNV) are deletions or duplications of large regions of the genome leading to a change in the number of copies of the genetic elements encoded within these regions. Unlike SNPs, CNVs individually confer large effects on risk of disease (10). Recently, whole-genome analysis of large cohorts has generated large collections of data, indicating that CNVs may contribute to susceptibility of individuals with these genomic alterations (13). CNVs associated with an increased risk of schizophrenia include 1q21.1

deletion and duplication, *NRXN1* exonic deletion, 3q29 deletion, 7q11.23 duplication, 15q11.2 deletion, 15q11.2-13 duplication, 15q13.3 deletion, 16p13.11 duplication, 16p11.2 duplication, and 22q11.2 deletion (13-15). The available data from large-scale studies on CNVs associated with autism are far fewer than that available for schizophrenia. However, certain CNVs have been identified that increase the probability of an individual developing ASD, including 1q21 duplication, 5p15.2 deletion, 7q11.23 duplication, 15q11-13 deletion and duplication, 15q13 duplication, 16p11.2 deletion and duplication, 17p11.2 duplication, and 22q11.2 deletion and duplication (13-16).

Over time, various models have evolved in an attempt to explain the apparent core relationship between autism and schizophrenia(15). While some have described autism as an early subtype of schizophrenia, others depict the conditions as separate and completely unrelated, or even opposite. However, evidence does support a fourth explanation: autism and schizophrenia partially overlap, sharing some risk factors and phenotypes but not others (15). Identifying the true, underlying relationship between autism and schizophrenia, two major psychiatric disorders presents profound implications for diagnoses and, therefore, treatment, both psychologically and pharmacologically.

Strong evidence exists that there is a relationship between ASD and schizophrenia, including overlapping CNVs. However, current diagnostic practices do not account for cross-disorder phenotypes or heterogeneity within diagnostic categories. Adequate treatment ultimately depends on a thorough understanding of the underlying biological mechanisms associated with observed phenotypes. This requires a comprehensive analysis of all available genome-wide association data for ASD and schizophrenia to determine the source of shared phenotypes and biological mechanisms within the genome. Toward this

purpose, a meta-analysis of case-control studies involving genome analysis was performed, focusing on rare CNVs associated with ASD and schizophrenia.

Methods

Selection of Genomic Disorders

Genomic disorders were chosen for analysis based on a case-control study by Cooper *et al.* on CNVs in children with intellectual disability, a trait known to be common to schizophrenia as well as ASD, compared with unaffected controls (17). Selections were made based on a documented p-value less than or equal to 0.05, also including 3q29 deletions, resulting in a total of 23 deletions and 13 duplications. The list of CNVs for analysis was further narrowed down to 11 loci based on prior evidence of an association with either autism or schizophrenia, considering both deletions and duplications for each (14-16). The disorders used for analysis are listed with their coordinates in Table 1.

Search Strategy

Conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, the author independently searched PubMed for studies up to 31 March 2016. Two groups of keywords were used in the search: "[autism OR schizophrenia] CNV" and "rare chromosomal [autism OR schizophrenia]". A manual search of reference lists was also conducted to identify any additional eligible studies.

Selection Criteria and Study Selection

Only case-control studies were considered. Studies included in this meta-analysis adhered to the following inclusion criteria: (1) sampling of cases and controls in the primary study (studies with no control group, as well as case reports were excluded); (2) incidence of at least 1 genomic interval in either cases or controls; and (3) at least 100 cases and 100 controls included in analysis. Studies were excluded for the following reasons: (1) the study was a case report; (2) the study was about a psychiatric disorder other than schizophrenia and/or autism; (3) the study was a review and did not contain primary data; or (4) too few participants were included in the study. Studies that contained data from a common source,

as well as studies on progressively larger sample sizes – where data from the earlier study was included in the later study, were compared, and the study with the largest, most complete sample was used in the analysis.

Data Extraction

The author independently extracted the following information from each study: (1) first author's name; (2) title; (3) year of publication; (4) location where study was performed; (5) sources of cases; (6) male/female ratio (when available); (7) selection of controls; and (8) number of total cases, total controls, exposed cases, and exposed controls.

Data Analysis

After extracting data on deletions and duplications of each region from qualifying studies, Cochran-Mantel-Haenszel (CMH) analyses were performed for deletions and duplications, separately, as well as combined. For regions with significant p-values (< 0.05) for both autism and schizophrenia, further sensitivity analyses were conducted. Leave-one-out analyses were used to assess the magnitude of influence of each study on the pooled CMH odds ratio. The statistical analyses were conducted using R-Studio statistical software (version 0.99.903, RStudio, Inc., Boston MA).

Results

Literature Search

Figure 1 illustrates the detailed literature search strategy implemented for this meta-analysis. A search of PubMed up to 31 March 2016 for the keywords 'schizophrenia CNV' and 'autism CNV' resulted in 167 and 192 studies, respectively. A second search for 'rare chromosomal schizophrenia' and 'rare chromosomal autism' resulted in 202 and 215 studies, respectively, with some overlapping the initial search. Duplicate studies were removed. Studies were then excluded on the basis of title and abstract. Implementation of inclusion criteria resulted in 7 autism studies and 19 schizophrenia studies. Descriptions of the studies included in the meta-analysis are displayed in Table 2.

Study Characteristics

Most studies on schizophrenia selected controls based on ethnicity ("EM" = ethnically matched). One study (Malhotra *et al.*) used unaffected siblings of autism cases from Simons Simplex Collection (SSC), one used a combination of sources (McCarthy *et al.*), and another study provided no information on selections of controls (Vacic *et al.*). Only 2 autism studies ethnically matched controls to cases (Wang *et al.* and Guilmatre *et al.*). One study used unaffected family members (Sanders *et al.*), and one sampled from BioServe, a collection more than 12,000 control samples (Prasad *et al.*).

Main Analysis

Deletions

For autism, analysis of the 16p11.2 (CMH OR: 3.1, 95% CI: 1.1 – 11.0; p-value = 0.026)) and 22q11.2 (CMH OR: 11.2, 95% CI: 1.6 – 486.8; p-value = 0.0058)) regions resulted in significant odds ratios, with the 22q11.2 region results proposing an 11.2-fold increase in risk (Table 3).

For schizophrenia, analysis of the 1q21.1 (CMH OR: 8.9, 95% CI: 4.6 – 18.2; p-value = 6.9E-14), 1p36 (CMH OR = 3.3, 95% CI: 0.8 – 19.1; p-value = 0.08), 3q29 (CMH OR: 38.8, 95% CI: 5.2 – 1873.3; p-value = 1.1E-07), 15q11.2-13 (CMH OR: 2.3, 95% CI: 1.8 – 3.1; p-value = 6.2E-10), and 22q11.2 (CMH OR: 23.3, 95% CI: 8.8 – 87.5; p-value = 2.2E-16) regions resulted in significant odds ratios, with the 3q29 region results proposing a 38.8-fold increase in risk.

Duplications

The CMH-adjusted odds ratios for 1q21.1 (CMH OR: ∞, 95% CI: 1.2 – ∞; p-value = 0.03) and 15q11.2-13 (CMH OR: ∞, 95% CI: NaN – NaN; p-value = 2.8E-06) were significant, with odds ratios of infinity due to a lack of exposed controls. For schizophrenia, odds ratios for duplications at 1p36 (CMH OR: 4.7 , 95% CI: 1.5 – 19.5; p-value = 0.0039), 3q29 (CMH OR: 8.4, 95% CI: 1.4 – 103.6; p-value = 0.0079), 7q11.23 (CMH OR: 8.4, 95% CI: 1.4 – 103.6; p-value = 0.0079), 15q11.2-13 (CMH OR: 2.5, 95% CI: 1.4 – 4.8; p-value = 0.0018), 16p11.2 (CMH OR: 5.8, 95% CI: 3.5 – 10.2, p-value = 9.7E-16) with both 3q29 and 7q11.23 results proposing 8.4-fold increases in risk.

Deletions and Duplications Combined

For autism, 1q21.1 (CMH OR: ∞, 95% CI: 1.72 - ∞; p-value = 0.007), 15q11.2-13 (CMH OR: 28.4, 95% CI: 4.7 – 115.2; p-value = 5.8E-08) , 16p11.2 (CMH OR: 2.9, 95% CI: 1.4 – 6.4; p-value = 0.0018), and 22q11.2 (CMH OR: 7.1, 95% CI: 1.6 – 5.2; p-value = 0.0032) resulted in significant CMH-adjusted odds ratios, with the 15q11.2-13 region conferring a 28.4-fold increase in risk. For schizophrenia, 1q21.1 (CMH OR: 5.0, 95% CI: 3.0 – 8.3; p-value = 9.3E-13), 1p36 (CMH OR: 4.0, 95% CI: 1.7 – 11.2; p-value = 7.3E-04), 3q29 (CMH OR: 11.3, 95% CI: 3.8 – 46.8; p-value = 1.9E-08), 7q11.23 (CMH OR: 4.8, 95%

CI: 1.1 – 33.5; p-value = 0.03), 15q11.2-13 (CMH OR: 2.4, 95% CI: 1.9 – 3.1; p-value = 2.5E-12), 16p11.2 (CMH OR: 4.5, 95% CI: 2.9 – 7.1; p-value 6.4E-15), and 22q11.2 (CMH OR 6.0, 95% CI: 3.5 – 11.0; p-value = 5.2E-15) resulted in significant CMH-adjusted odds ratios. Results of the 3q29 region (CMH OR: 11.3, 95% CI: 3.8 – 46.8) propose an 11.3-fold increase in risk for schizophrenia.

Autism and schizophrenia shared significant odds ratios for 15q11.2-13, 16p11.2 and 22q11.2 deletions and duplications combined, as well as for 22q11.2 deletions and 15q11.2-13 duplications. However, the magnitude of risk of each region varied by disorder (Table 4). For example, while results of this analysis indicate that the 22q11.2 deletion confers a 23.3-fold increase in risk for schizophrenia, it only indicates an 11.2-fold increase in risk for autism. In addition, for 16p11.2, autism is differentially associated with deletions (CMH OR: 3.1, 95% CI 1.1 – 11.0, p-value 0.026) and schizophrenia with duplications (CMH OR: 5.8, 95% CI 3.5 – 10.2, p-value 9.7e-16). 1q21.1 exhibited the opposite relationship between the disorders. Autism is differentially associated with duplications (CMH OR: ∞, 95% CI: 1.2 - ∞, p-value -0.03), while schizophrenia is associated with deletions (CMH OR: 8.9, 95% CI: 4.6 – 18.2, p-value 6.9E-14).

Sensitivity Analysis

To examine the magnitude of influence of each study on the pooled results for regions where autism and schizophrenia shared significant CMH-adjusted odds ratios, leave-one-out analyses were performed on all but 15q11.2-13 duplications or 1q21.1 due to odds ratios of infinity.

For autism, Glessner *et al.* appears to influence the pooled results for both 15q11.2-13 and 16p11.2, while Wang *et al.* influences the pooled results for 22q11.2 (Table 5).

For schizophrenia, the analysis resulted in a range of odds ratios for 15q11.2-13 of 2.00 (95% CI 1.50 – 2.70, p-value 9.84e-07) to 2.70 (95% CI 2.03 – 3.59, p-value 1.96e-12), indicating that no single study substantially modified the pooled odds ratio (Table 6). The leave-one-out analysis of 16p11.2 resulted in a moderately wide range of 3.84 (95% CI 2.42 – 6.25, p-value 2.26e-10) to 5.16 (95% CI 3.17 – 8.67, p-value 3.83e-14), with no single study substantially modifying the pooled estimates. For the 22q11.2 deletion, Costain *et al.*, Li *et al.* (cohort 1), and Szatkiewicz *et al.* substantially modified the overall CMH-adjusted odds ratios the most with values of 81.1 (95% CI 14.1 – 3189, p-value < 2.2e-16), 40.8 (95% CI 8.0 – 121.4, p-value < 2.2e-16), and 17.39 (95% CI 6.50 – 65.62, p-value < 2.2e-16), respectively.

Discussion

The results of this meta-analysis suggest that deletions and/or duplications at 1q21.1, 15q11.2-13, 16p11.2, and 22q11.2 are associated with an increased risk of developing both autism and schizophrenia. Duplications at 15q11.2-13 and deletions at 22q11.2 are associated with increased risk of both autism and schizophrenia. Schizophrenia risk factors also include deletions at 1p36, 3q29, and 15q11.2-13, as well as duplications at 1p36, 3q29, and 7q11.23.

1q21.1 and 16p11.2 display reciprocal relationships between autism and schizophrenia. While duplications at 1q21.1 are associated with increased risk of autism, deletions at 1q21.1 are associated with increased risk of schizophrenia. For 16p11.2, the opposite is true. While deletions at 16p11.2 are associated with increased risk of autism, duplications are associated with increased risk of schizophrenia. These same reciprocal relationships have been observed in previous studies, supporting a "diametric" model for the relationship between autism and schizophrenia (15). However, some research suggests that this relationship may be confounded by the inclusion of children premorbid for schizophrenia-spectrum conditions in genome-wide association studies of autism, diluting the detection of any significant findings supporting the diametric model (15).

Many studies have identified duplications at 15q11.2-13 and deletions at 22q11.2 as risk factors for both autism and schizophrenia (13, 16, 18). An "overlapping" model, as opposed to the diametric model, supports a relationship between autism and schizophrenia in which some risk factors and phenotypes are shared, but not others (15). The results of the combined data for each CNV only reveals whether or not there is a relationship with autism or schizophrenia. Therefore, comparing these results alone does not provide any information about the type of relationship. Results for the specific deletions and duplications must be considered.

These findings further challenge the traditional view that autism and schizophrenia are completely unrelated diagnoses. It is also understood that gene-environment interactions play a substantial role in development of the disease. Therefore, it is important to understand how these particular CNVs affect the underlying protein-coding structure of the genome and how this, in effect, interacts with other genetic and environmental risk factors to produce the phenotypes characteristic of ASD and schizophrenia.

This analysis provides insight into possible relationships between phenotypes associated with ASD and/or schizophrenia and the rare CNVs associated with the disorders. If children diagnosed with ASD and either a 22q11.2 deletion or 15q11.2-13 duplication are truly at an increased risk of schizophrenia, this implies that these CNVs could encompass genes associated with phenotypes common to both ASD and schizophrenia. With a greater understanding of the underlying mechanisms behind development of these disorders comes the possibility of identifying potentially modifiable risk factors. This is especially important if these modifiable risk factors could prevent the individual diagnosed with ASD from further developing schizophrenia by modifying exposure to associated environmental risk factors. Additionally, if children with ASD and either a deletion at 16p11.2 and duplication at 1q21.1 are not at an increased risk for schizophrenia, this implies that these CNVs, most likely, do not encompass genes associated with phenotypes common to ASD and schizophrenia. This is further supported by the reciprocal relationship displayed by mutations observed at these locations. While a loss of material at 16p11.2 is associated with autism, a gain of material is associated with schizophrenia. The inverse is true for 1q21.1. The importance of environmental influences and their interaction with these genetic risk factors must also be considered.

For both autism and schizophrenia, as with most psychiatric disorders, early identification is imperative because it allows for early intervention. Identifying whether there truly is a connection between autism and schizophrenia, or if it is actually confounded by a tendency to diagnose children premorbid for schizophrenia-spectrum conditions as ASD, has important implications for early identification of autism and schizophrenia as well as intervention among individuals with these rare CNVs. Improving the prognosis of individuals with this disorder through early intervention would lower the financial burden on society by decreasing the overall healthcare costs incurred by these individuals. Genetic testing of associated CNVs, with optional genetic counseling given a positive result, should be encouraged by healthcare professionals among children with a family history of autism or schizophrenia, due to the high heritability of the disorders.

Limitations

The major limitations of this meta-analysis stem from the low number of available genome-wide association studies on autism. There are far fewer available for autism (N = 5,414 cases) than for schizophrenia (N = 41,323 cases). Therefore, data for several CNVs lack any exposed controls, resulting in an odds ratio of infinity, preventing a comparison of magnitude of odds ratios for these CNVs given significance. In addition, many of these studies include ASD pooled with other diagnoses, preventing inference concerning exactly which, if any, of the conditions are associated with the CNV.

Strengths

In pooling the data from several case-control studies and performing a meta-analysis, a much larger sample size was obtained, which was especially important for autism, given the lack of genome-wide association studies. Also, a meta-analysis decreases the effect of bias from individual studies on the overall risk estimate. This is especially important for studies

where diagnosis was dependent on structured interviews. However, all included schizophrenia studies used the same criteria (DSM-IV) when determining a diagnosis.

While this meta-analysis provides evidence to support the diametric as well as the overlapping models of the autism-schizophrenia relationship, further analysis is required to distinguish between the two models. This includes more genome-wide association studies of autism, which would help gain a more precise view of the significant CNVs associated with autism, allowing a better assessment of any relationship with schizophrenia. These studies would need to focus on individuals with ASD, alone, independent of any other disorders.

Tables

Table 1. Intervals of selected copy number variants (CNVs)

Location	Chr	START	STOP
1q21.1	1	145044110	145861130
1p36	1	7765595	11019814
3q29	3	197240451	198829062
4p16.3	4	419224	2010962
5q35	5	175661584	176946567
7q11.23	7	72382390	73780449
15q11.2-13	15	21309483	26230781
16p11.2	16	29557497	26230781
17p11.2	17	16723271	20234630
22q11.2	22	17400436	18676130
22q13	22	51115059	51160754

Abbreviations: Chr, chromosome. All coordinates are according to build36.

Table 2. Descriptions of each study included in analysis.

Reference	Ethnicity	Male/Female Ratio	Selection of Controls
Autism			
Girirajan *et al.* (19)	Mixed	No information	Matched on age, sex, and broad geographic region
Glessner *et al.* (20)	European ancestry	No information	No information (recruited from Children's Hospital of Philadelphia and AGRE)
Griswold *et al.* (21)	Mixed	6.7:1 (Cases); 1:1 (Controls)	No information (sampled from John. P. Hussman Institute for Human Genomics and preterm birth study)
Guilmatre *et al.* (22)	French	4.1:1 (Cases); 1:1.3 (Controls)	EM
Prasad *et al.* (23)	Mixed	4.6:1 (Cases)	BioServe*
Sanders *et al.* (24)	Mixed	6.1:1	Unaffected family members
Wang *et al.* (25)	Croatian	3.7:1 (Cases); 2.6:1 (Controls)	EM
Schizophrenia			
Buizer-Voskamp *et al.* (26)	Dutch	No Information	EM
Costain *et al.* (27)	European ancestry	2.3:1 (SZ); 1:1 (Controls)	EM
Guilmatre *et al.* (22)	French	2:1 (SZ); 1:1.3 (Controls)	EM
International Schizophrenia Consortium (28)	Mixed European	1.3:1 (Total)	EM
Li *et al.* (29)	Chinese	No information	EM
Magri *et al.* (30)	Italian	No information	EM
Malhotra *et al.* (31)	Mixed	1.46:1 (SZ); 1:1 (Controls)	Unaffected siblings of autism cases from SSC

McCarthy *et al.* (32)	European American, African American	2.3:1 (SZ); 1:1 (Controls)	Combination of many different sources
Mulle *et al.* (33)	Ashkenazi Jewish	2.6: 1 (SZ)	EM
Need *et al.* (34)	German/Scottish	No information	EM
Priebe *et al.* (35)	German	1:2.9 (SZ); 1:2 (Controls)	EM
Rees *et al.* (36)	Mixed	2.6:1 (SZ)	EM
Rodriguez-Santiago *et al.* (37)	Spanish	2.2:1 (SZ); 1.3:1 (Controls)	EM
Stefansson *et al.* (38)	European	No information	EM
Szatkiewicz JP *et al.* (39)	Swedish	No information	EM
Szatkiewicz JP *et al.* (40)	Swedish	1.7:1 (SZ); 1.9:1 (Controls)	EM
Vacic *et al.* (41)	European American, African American, Hispanic	No information	No information
Van den Bossche *et al.* (42)	Belgian, Swedish, Scottish	No information	EM
Xu *et al.* (43)	Afrikaner SZ trios	No information	Afrikaner control trios

*a collection of >12,000 control samples originally banked by Genomics Collaborative, Inc. (acquired by BioServe in 2007) for the purpose of large scale genomic studies
Abbreviations: AGRE, Autism Genetics Research Exchange; EM, Ethnically Matched; SZ, Schizophrenia; SSC, Simons Simplex Collection

Table 3. CMH-adjusted odds ratios for each region separated by deletion/duplication classification as well as combined.
a. Autism

	Deletion CMH OR (95% CI, p-value)	**Duplication** CMH OR (95% CI, p-value)	**Combined** CMH OR (95% CI, p-value)
1q21.1	∞ (0.2 – ∞, 0.2)	**∞ (1.2 – ∞, 0.03)**	**∞ (1.72 – ∞, 0.007)**
1p36			
3q29	∞ (NaN – ∞, 0.3)	∞ (NaN – ∞, 0.2)	∞ (0.3 – ∞, 0.1)
4p16.3			
5q35			
7q11.23		∞ (0.92 – ∞, 0.06)	∞ (0.92 – ∞, 0.06)
15q11.2-13	4.5 (0.5 – 205.3, 0.25)	**∞(NaN – NaN , 2.8E-06)**	**28.4 (4.7 – 115.2, 5.8E-08)**
16p11.2	**3.1 (1.1 – 11.0, 0.026)**	2.5 (0.9 – 8.0, 0.076)	**2.9 (1.4 – 6.4, 0.0018)**
17p11.2			
22q11.2	**11.2 (1.6 – 486.8, 0.0058)**	2.7 (0.1 – 164., 0.57)	**7.1 (1.6 – 5.2, 0.0032)**
22q13	∞ (0.9 – ∞, 0.06)		∞ (0.9 – ∞, 0.06)

b. Schizophrenia

	Deletion CMH OR (95% CI, p-value)	**Duplication** CMH OR (95% CI, p-value)	**Combined** CMH OR (95% CI, p-value)
1q21.1	**8.9 (4.6 – 18.2, 6.9E-14)**	1.9 (1.0 – 4.0, 0.056)	**5.0 (3.0 – 8.3, 9.3E-13)**
1p36	**3.3 (0.8 - 19.1, 0.08)**	**4.7 (1.5 - 19.5, 0.0039)**	**4.0 (1.7 – 11.2, 7.3E-04)**
3q29	**38.8 (5.2 – 1873.3, 1.1E-07)**	**8.4 (1.4 – 103.6, 0.0079)**	**11.3 (3.8 – 46.8, 1.9E-08)**
4p16.3	∞ (NaN – ∞, 0.25)	0 (0 – NaN, 0.13)	0.7 (0.1 – 4.0, 0.6)
5q35	1.0 (0.1 – 15.9, 1)	1.0 (0.2 – 4.1, 1)	1.0 (0.3 – 3.6, 1)
7q11.23	0 (0 – NaN, 0.5)	**8.4 (1.4 – 103.6, 0.0079)**	**4.8 (1.1 – 33.5, 0.03)**
15q11.2-13	**2.3 (1.8 – 3.1, 6.2E-10)**	**2.5 (1.4 – 4.8, 0.0018)**	**2.4 (1.9 – 3.1, 2.5E-12)**
16p11.2	1.6 (0.5 – 4.7, 0.45)	**5.8 (3.5 – 10.2, 9.7E-16)**	**4.5 (2.9 – 7.1, 6.4E-15)**
17p11.2	0 (0 – NaN, 0.5)	∞ (NaN – ∞, 0.1)	3.0 (0.3 – 28.8, 0.3)
22q11.2	**23.3 (8.8 – 87.5, 2.2E-16)**	0.3 (0.1 – 1.1, 0.075)	**6.0 (3.5 – 11.0, 5.2E-15)**
22q13	1.0 (0.2 – 4.2, 1)		1.0 (0.2 – 4.2, 1)

Abbreviations: CMH, Cochran-Mantel-Haenszel; OR, odds ratio; CI, confidence interval

Table 4. Pooled data for regions with shared significant CMH-adjusted odds ratios.

a. Autism

Reference	**Cases**	**Controls**	*1q21.1*		*15q11.2-13*		*16p11.2*		*22q11.2*	
Girirajan *et al.*	243	223	1/0	0/0	0/0	0/0	0/4	0/0	0/0	0/0
Glessner *et al.*	2195	2519	0/0	0/0	8/9	4/4	0/15	0/0	0/0	0/0
Griswold *et al.*	813	592	0/2	0/0	1/2	0/0	5/2	0/0	0/1	0/0
Guilmatre *et al.*	260	236	0/0	0/0	0/0	0/0	0/1	0/0	9/0	1/0
Prasad *et al.*	676	1000	0/0	0/0	0/1	0/0	0/0	0/0	2/1	0/0
Sanders *et al.*	1124	872	0/2	0/0	7/4	1/2	1/1	1/0	0/0	0/0
Wang *et al.*	103	203	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1
Total	5414	5645	1/5	0/0	16/16	5/6	6/23	1/0	11/2	1/1
CMH OR (95% CI, p-value)			∞ (1.72 – ∞, 0.007) ∞ (1.2 – ∞, 0.03)*		28.4 (4.7 – 115.2, 5.8e-08) ∞(NaN – NaN , 2.8E-06)*		2.9 (1.4 – 6.4, 0.002) 3.1 (1.1 – 11.0, 0.026)†		7.1 (1.6 – 5.2, 0.003) 11.2 (1.6 – 486.8, 0.006)†	

*duplications only; †deletions only

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; OR, odds ratio; del, deletion; dup, duplication

b. Schizophrenia

Reference	**Cases**	**Controls**	*1q21.1*		*15q11.2-13*		*16p11.2*		*22q11.2*	
Buizer-Voskamp *et al.*	834	672	0/0	0/0	3/1	1/0	0/0	0/0	2/1	0/0
Costain *et al.*	420	416	1/3	0/3	0/22	5/6	1/7	0/4	3/0	2/5
Guilmatre *et al.*	236	236			0/1	0/0	0/0	0/3	0/0	0/0
International Schizophrenia Consortium	3391	3181	10/3	1/1	0/1	0/0	1/5	3/1	11/0	0/1
Li *et al.*	2992	5176	8/2	2/2	17/2	14/0	2/8	0/3	1/0	1/1
	3596	2636	6/1	0/1	4/3	3/0	0/5	1/0	5/0	0/1
Magri *et al.*	172	160	0/0	0/0	2/1	0/0	0/0	0/0	0/0	0/0
Malhotra *et al.*	177	426	0/0	0/0	0/0	0/0	0/0	0/0	1/0	0/0
McCarthy *et al.*	2645	2420	0/0	0/0	0/0	0/0	0/9	0/1	0/0	0/0
Mulle *et al.*	245	490	0/0	0/0	0/0	0/0	1/0	0/0	2/0	0/0
Need *et al.*	1013	1084	2/0	0/0	0/0	2/0	0/0	0/0	4/0	0/1
Priebe *et al.*	1637	1627	3/0	1/0	2/0	3/0	0/1	0/0	2/0	0/0
Rees *et al.*	6882	6316	12/8	1/5	44/0	26/0	0/27	2/0	20/0	0/0
Rodriguez-Santiago *et al.*	654	604	0/0	0/0	0/1	0/0	0/0	0/0	0/3	0/0
Stefansson *et al.*	4718	41194	11/1	8/13	33/0	87/0	2/0	11/0	0/0	0/0
Szatkiewicz JP *et al.*	4719	5917	5/2	1/1	7/1	2/2	2/12	1/6	6/0	0/3
Vacic *et al.*	4899	4250	0/0	0/0	18/0	1/0	0/22	0/1	13/0	0/0
Van den Bossche *et al.*	1259	1173	3/0	1/1	6/8	2/8	0/2	0/2	0/0	0/0
Xu *et al.*	834	672	0/0	0/0	0/0	0/0	0/0	0/0	3/0	0/0
Total	41323	78650	61/20	15/27	172/116	146/16	9/98	18/21	84/4	3/12
CMH OR (95% CI, p-value)			5.0 (3.0 – 8.3, 9.3E-13) 8.9 (4.6 – 18.2, 6.9E-14)†		2.4 (1.9 – 3.1, 2.5e-12) 2.5 (1.4 – 4.8, 0.0018)*		4.5 (2.9 – 7.1, 6.4e-15) 5.8 (3.5 – 10.2, 9.7E-16)*		5.8 (3.3 – 10.9, 9.6e-14) 27.97 (9.2 – 138.6, <2.2e-16)†	

*dupications only; †deletions only

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; OR, odds ratio

Table 5. Leave-one-out sensitivity analysis results for pooled autism data.

a. 15q11.2-13

Reference	Autism Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Sanders *et al.*	1124	1/1	872	1/0	Inf (6.8 – Inf, 1.3e-08)
Glessner *et al.*	2195	0/15	2519	0/0	11.3 (1.7 – 476.2, 0.003)
Girirajan *et al.*	243	0/4	223	0/0	24.7 (4.0 – 1009.9, 7.6e-07)
Griswold *et al.*	813	5/2	592	0/0	23.2 (3.7 – 954.3, 1.6e-06)
Guilmatre *et al.*	260	0/1	236	0/0	27.5 (4.5 – 1119.7, 1.1e-07)

b. 16p11.2

Reference	Autism Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Sanders *et al.*	1124	7/4	872	1/2	2.9 (1.2 – 7.7, 0.008)
Glessner *et al.*	2195	8/9	2519	4/4	4.0 (1.1 – 21.8, 0.02)
Griswold *et al.*	813	1/2	592	0/0	2.7 (1.3 – 6.0, 0.004)
Prasad *et al.*	676	0/1	1000	0/0	2.8 (1.4 – 6.2, 0.003)

c. 22q11.2 deletion

Reference	Autism Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Wang *et al.*	103	0/0	203	0/1	
Griswold *et al.*	813	0/1	592	0/0	
Guilmatre *et al.*	260	9/0	236	1/0	8.4 (1.1 – 67.0, 0.016)
Prasad *et al.*	676	2/1	1000	0/0	Inf (p-value 0.129)

d. 22q11.2 deletion and duplication combined

Reference	Autism Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Wang *et al.*	103	0/0	203	0/1	13.5 (2.0 – 573.9, 0.002)
Griswold *et al.*	813	0/1	592	0/0	6.7 (1.5 – 62.1, 0.005)
Guilmatre *et al.*	260	9/0	236	1/0	5.6 (0.5 – 281.2, 0.2)
Prasad *et al.*	676	2/1	1000	0/0	4.9 (1.0 – 47.0, 0.04)

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; OR, odds ratio; del, deletion; dup, duplication

Table 6. Leave-one-out sensitivity analysis results for pooled schizophrenia data.

a. 1q21.1

Reference	SZ Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Costain *et al.*	420		416		5.44 (3.11 – 9.86, 2.15e-11)
International Schizophrenia Consortium	3391		3181		4.59 (2.61 – 8.36, 6.95e-09)
Li *et al.* (2)	3596		2636		4.75 (2.75 – 8.44, 4.67e-10)
Need *et al.*	1013		1084		4.65 (2.74 – 8.14, 2.37e-10)
Priebe *et al.*	1637		1627		4.87 (2.84 – 8.63, 1.29e-10)
Rees *et al.*	6882		6316		5.61 (3.01 – 10.85, 1.36e-09)
Stefansson *et al.*	4713		41194		3.32 (1.91 – 6.08, 2.67e-06)
Szatkiewicz *et al.*	4719		5917		4.81 (2.76 – 8.68, 7.59e-10)
Van den Bossche *et al.*	1270		1145		5.19 (3.00 – 9.28, 3.90e-11)

b. 15q11.2-13 duplication

Reference	SZ Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Costain *et al.*	420		416		1.79 (0.79 – 4.34, 0.1395)
Guilmatre *et al.*	236		236		2.45 (1.33 – 4.72, 0.0026)
International Schizophrenia Consortium	3391		3181		2.46 (1.34 – 4.73, 0.0018)
Li *et al.* (1)	2992		5176		2.34 (1.27 – 4.50, 0.0039)
Li *et al.* (2)	3596		2636		2.37 (1.28 – 4.57, 0.0036)
Magri *et al.*	172		160		2.46 (1.34 – 4.73, 0.0018)
Rodriguez-Santiago *et al.*	654		604		2.46 (1.34 – 4.73, 0.0018)
Szatkiewicz *et al.*	4719		5917		2.77 (1.47 – 5.55, 0.0008)
Buizer-Voscamp *et al.*	834		672		2.46 (1.34 – 4.74, 0.0018)
Van den Bossche *et al.*	1270		1145		4.29 (1.92 – 10.84, 5.315e-05)

c. 15q11.2-13 deletion and duplication combined

Reference	SZ Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Costain *et al.*	420	0/22	416	5/6	2.43 (1.86 – 3.16, 1.6e-11)
Guilmatre *et al.*	236	0/1	236	0/0	2.37 (1.85 – 3.05, 3.6e-12)
International Schizophrenia Consortium	3391	0/1	3181	0/0	2.37 (1.85 – 3.05, 3.6e-12)
Li *et al.* (1)	2992	17/2	5176	14/0	2.41 (1.87 – 3.10, 2.48e-12)
Li *et al.* (2)	3596	4/3	2636	3/0	2.41 (1.87 – 3.10, 2.48e-12)
Magri *et al.*	172	2/1	160	0/0	2.35 (1.83 – 3.02, 5.16e-12)
Need *et al.*	1013	0/0	1084	2/0	2.43 (1.89 – 3.13, 8.15e-13)
Priebe *et al.*	1637	2/0	1627	3/0	2.43 (1.90 – 3.14, 9.46e-13)
Rees *et al.*	6882	44/0	6316	26/0	2.70 (2.03 – 3.59, 1.96e-12)
Rodriguez-Santiago *et al.*	654	0/1	604	0/0	2.37 (1.85 – 3.05, 3.61e-12)
Stefansson *et al.*	4713	33/0	41194	87/0	2.00 (1.50 – 2.70, 9.84e-07)
Szatkiewicz *et al.*	4719	7/1	5917	2/2	2.38 (1.84 – 3.07, 7.78e-12)
Vacic *et al.*	4899	18/0	4250	1/0	2.22 (1.72 – 2.88, 3.54e-10)
Buizer-Voscamp *et al.*	834	3/1	672	1/0	2.37 (1.84 – 3.05, 4.00e-12)
Van den Bossche *et al.*	1270	6/8	1145	2/8	2.51 (1.94 – 3.26, 8.49e-13)

d. 16p11.2

Reference	SZ Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Costain *et al.*	420	1/7	416	0/4	4.93 (3.12 – 8.04, 5.32e-15)
Guilmatre *et al.*	236	0/0	236	0/3	4.39 (2.85 – 6.92, 2.83e-14)
International Schizophrenia Consortium	3391	1/5	3181	3/1	5.04 (3.20 – 8.20, 1.64e-15)
Li *et al.* (1)	2992	2/8	5176	0/3	4.36 (2.77 – 7.06, 5.16e-13)
Li *et al.* (2)	3596	0/5	2636	1/0	4.53 (2.93 – 7.21, 2.26e-14)
McCarthy *et al.*	2645	0/9	2420	0/1	4.35 (2.80 – 6.94, 1.77e-13)
Mulle *et al.*	245	1/0	490	0/0	4.48 (2.92 – 6.88, 1.18e-13)
Priebe *et al.*	1637	0/1	1627	0/0	4.46 (2.91 – 7.04, 1.05e-14)
Rees *et al.*	6882	0/27	6316	2/0	3.84 (2.42 – 6.25, 2.26e-10)
Stefansson *et al.*	1438	2/0	33246	11/0	4.52 (2.90 – 7.32, 2.76e-14))
Szatkiewicz *et al.*	4719	2/12	5917	1/6	5.16 (3.17 – 8.67, 3.83e-14)
Vacic *et al.*	8290	0/22	7431	0/1	3.88 (2.48 – 6.26, 5.22e-11)
Van den Bossche *et al.*	1270	0/2	1145	0/2	4.79 (3.08 – 7.66, 1.97e-15)

e. 22q11.2 deletion

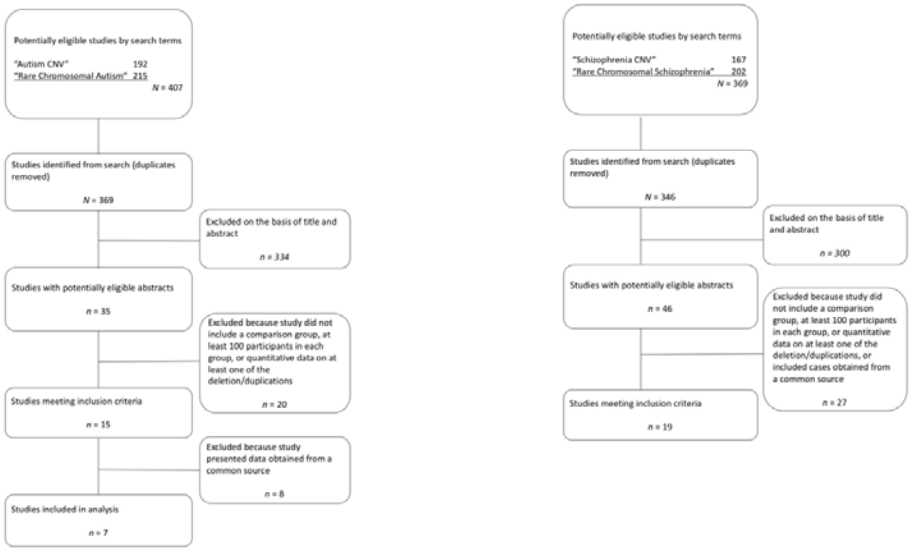
Reference	SZ Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Costain *et al.*	420	3/0	416	2/5	81.1 (14.1 – 3189.4, <2.2e-16)
International Schizophrenia Consortium	3391	11/0	3181	0/1	24.5 (8.0 – 121.4, <2.2e-16)
Li *et al.* (1)	2992	1/0	5176	1/1	40.8 (10.9 – 342.6, <2.2e-16)
Li *et al.* (2)	3596	5/0	2636	0/1	26.7 (8.8 – 132.5, <2.2e-16)
Malhotra *et al.*	177	1/0	426	0/0	27.2 (9.0 – 134.7, <2.2e-16)
Mulle *et al.*	245	2/0	490	0/0	26.7 (8.8 – 132.1, <2.2e-16)
Need *et al.*	1013	4/0	1084	0/1	26.6 (8.8 – 132.0, <2.2e-16)
Priebe *et al.*	1637	2/0	1627	0/0	27.3 (9.0 – 135.3, <2.2e-16)
Rees *et al.*	6882	20/0	6316	0/0	21.8 (7.1 – 108.9, <2.2e-16)
Rodriguez-Santiago *et al.*	654	0/3	604	0/0	
Szatkiewicz *et al.*	4719	6/0	5917	0/3	17.39 (6.50 – 65.62, <2.2e-16)
Vacic *et al.*	4899	13/0	4250	0/0	20.7 (6.7 – 103.7, 2.85e-15)
Xu *et al.*	152	3/0	156	0/0	26.9 (8.9 – 133.5, <2.2e-16)
Buizer-Voscamp *et al.*	834	2/1	672	0/0	26.9 (8.9 – 133.5, <2.2e-16)

f. 22q11.2 deletion and duplication combined

Reference	SZ Cases	Case (del/dup)	Controls	Control (del/dup)	OR (95% CI, p-value)
Costain *et al.*	420	3/0	416	2/5	10.6 (5.1 – 25.5, <2.2e-16)
International Schizophrenia Consortium	3391	11/0	3181	0/1	5.5 (3.1 – 10.6, 8.9e-12)
Li *et al.* (1)	2992	1/0	5176	1/1	6.5 (3.6 – 12.8, 2.9e-14)
Li *et al.* (2)	3596	5/0	2636	0/1	6.0 (3.4 – 11.5, 3.2e-13)
Malhotra *et al.*	177	1/0	426	0/0	5.7 (3.3 – 10.7, 3.1e-13)
Mulle *et al.*	245	2/0	490	0/0	5.6 (3.2 – 10.5, 5.7e-13)
Need *et al.*	1013	4/0	1084	0/1	6.0 (3.4 – 11.5, 2.3e-13)
Priebe *et al.*	1637	2/0	1627	0/0	5.7 (3.3 – 10.7, 2.8e-13)
Rees *et al.*	6882	20/0	6316	0/0	4.6 (2.6 – 8.7, 2.5e-09)
Rodriguez-Santiago *et al.*	654	0/3	604	0/0	5.7 (3.2 – 10.6, 4.5e-13)
Szatkiewicz *et al.*	4719	6/0	5917	0/3	6.7 (3.6 – 13.4, 1.3e-13)
Vacic *et al.*	4899	13/0	4250	0/0	4.4 (2.5 – 8.3, 1.1e-08)
Xu *et al.*	152	3/0	156	0/0	5.6 (3.2 – 10.5, 8.3e-13)
Buizer-Voscamp *et al.*	834	2/1	672	0/0	5.7 (3.2 – 10.6, 4.2e-13)

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; OR, odds ratio; del, deletion; dup, duplication; SZ, schizophrenia

Figures



a. b.

Figure 1. Flowcharts of search strategy and study identification for (a) autism and (b) schizophrenia

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