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The 3q29 deletion confers greater than 40-fold increase in risk for schizophrenia

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The 1.4 Mb deletion on chromosome 3q29 was first described in 2005 and is associated with a range of neurodevelopmental phenotypes, including developmental delay, intellectual disability (ID), and autism[1]. Prior data has implicated this same deletion as a suggestive or significant risk factor for schizophrenia (SZ)[2-4], but the low frequency of the deletion has rendered individual samples underpowered to confirm this association, and prohibited an accurate estimate of risk. However, since the initial reports many more SZ samples with copy number variation (CNV) data have been published, and in aggregate is possible to arrive at a more accurate estimate of SZ risk for this genetic lesion. Toward this goal, a meta-analysis was conducted according to MOOSE guidelines[5]: a search of PubMed on 11/19/2014 for the keywords “schizophrenia CNV” resulted in 195 studies. A second search for “rare chromosomal schizophrenia” revealed 154 studies largely but not completely overlapping the initial set. Only case-control studies were considered. Criteria for inclusion into this meta-analysis included: sampling of cases and controls in the primary study (case-only studies and case reports were excluded); interrogation of the 3q29 genomic interval in cases and controls (by genome-wide methods, region-specific probes, or other assays directly targeting the region); and reporting of all rare CNV found in both cases and controls (in the primary paper or a supplement). Reasons studies were commonly excluded were: the study was a case report; the study was about a psychiatric disorder other than schizophrenia; or the paper was a review and did not contain primary data. Frequently, multiple papers were published on a progressively larger sample, where data from earlier papers are contained in later papers with additional study subjects included (for example, Rees 2014[6] and Rees 2014[7]; Szatkiewicz 2013[8] and Szatkiewicz 2014[4]; Mulle 2010[2] and Mulle 2014[9].) In these instances, to avoid “double-counting” of the data and inflating the risk estimate, we included for analysis purposes the paper with the largest and most complete data collection (in these three cases, the most recent paper). Sixteen studies, contributing seventeen distinct samples, fit all inclusion criteria. [3,4,6,9-21]. From the final list of these qualifying papers, data for the 3q29 region were extracted (Table 1), representing 25,314 SZ cases and 62,432 controls. Overlapping data were identified in one instance: 590 cases (including 1 deletion carrier) and 439 controls were reported in[4] and [20]; data were subtracted from the totals

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reported in the more recent publication. In most papers, controls were ethnically matched to cases (Table 1, “EM”). Three papers used population-based, unscreened controls[14,15,17]; another used publicly available data as a comparison sample[6], and the remainder used controls that were screened in some way for psychiatric illness. Determination of cases status was highly heterogeneous among studies; most studies used one or more standardized instruments along with case notes, medical records, history of hospitalizations, and/or informant interviews to arrive at a diagnosis. A single study used childhood onset cases[13] (“COS” in Table 1) and a second study used SZ cases with ID.[11] For two studies, clinical trial participants were included.[6,10] The size of the reported variant was consistent among studies, with most reports indicating a 1.3 to 1.6 Mb deletion which removes all 24 genes in the interval. One report indicated a slightly smaller 837 kb deletion (though all but 1 gene in the typical deletion interval was removed)[9] and two reports could not resolve the size because individual probes[15] or limited markers[17] were used for detection. For this meta-analysis, an overall (raw) odds ratio and a Cochran-Mantel-Haenszel (CMH) adjusted odds ratio were calculated. The results of this analysis indicate that the 3q29 deletion confers a 41.1-fold increased risk for schizophrenia (p-value 5.8×10^{-8}, 95% CI 5.6 – 1953.6). To assess whether any one sample was exerting undue influence on the risk estimate, each sample was removed and the CMH-adjusted odds ratio was recalculated. The range of OR estimates (33.3 – 41.1) suggests that larger samples may be exerting upward influence on the estimate of risk, but no one sample is driving the observed effect size. Typical estimates for effect sizes of other SZ-associated CNV range from 5-30[22]; thus, the 3q29 deletion may be the single largest risk factor for schizophrenia, surpassing even the 22q11.2 deletion. The 24 genes in the 3q29 deletion interval deserve scrutiny as molecular targets which, when haploinsufficient, may underlie at least one form of schizophrenia. Several candidate genes have been implicated in the region, including DLG1, PAK2 and FBXO45. This meta-analysis highlights the utility of large samples to identify rare genetic variants with high risk for severe psychiatric disease.

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Table 1

Ref.	Ethnicity	Selection of Controls	SZ cases	Case 3q29 del	Controls	Control 3q29 del	CMH OR (95% CI, p-value) with this sample removed
2	European American	EM	2,667	4	2,648	0	36.4 (4.7 -1799.3, 8.4e-07)
2	African American	EM	1,273	1	963	0	40.2 (5.4 – 1924.3, 1.0e-07)
3	Swedish	EM	4,129	5	5,478	0	33.4 (4.2 – 1695.3, 3.4e-06)
5	Mixed (95% European ancestry)	EM	6,882	4	11,255	0	33.3 (4.2 – 1691.5, 2.6e-06)
8	Ashkenazi Jewish	EM	554	1	1,014	0	39.0 (5.2 – 1882.6, 1.6e-07)
9	Mixed (78% Caucasian)	EM	150	1	256	0	39.1 (5.3 – 1887.4, 1.5e-07)
10	No information (recruited from Iowa)	No information (recruited from Iowa)	166	0	52	0	41.1 (5.6 – 1953.6, 5.8e-08)
11	Scottish (ID with SZ)	Scottish (ID w/o SZ)	64	0	66	0	41.1 (5.6 – 1953.6, 5.8e-08)
12	COS: “highly heterogeneous”	Unaffected sibs of cases	126	0	69	0	41.1 (5.6 – 1953.6, 5.8e-08)
13	German	EM	1,637	0	1,627	0	41.1 (5.6 – 1953.6, 5.8e-08)
14	Belgian, Swedish, Scottish	EM	1,259	2	1,173	0	38.9 (5.2 – 1881.2, 2.1e-07)
15	Dutch	EM	834	1	672	0	40.1 (5.4 – 1922.3, 1.0e-07)
16	Northern European/European	EM	1,438	0	33,246	1	∞ (6.7 - ∞, 2.7e-08)
17	Italian	EM	172	1	160	0	40.0 (5.4 – 1917.5, 1.1e-07)
18	Afrikaner SZ trios (*de novo* CNV)	Afrikaner control trios (*de novo* CNV)	152	0	156	0	41.1 (5.6 – 1953.6, 5.8e-08)
19	Mixed European	EM	3,391	2	3,181	0	38.9 (5.2 – 1880.7, 2.1e-07)
20	European ancestry	EM	420	0	416	0	41.1 (5.6 – 1953.6, 5.8e-08)
Total			25,314	22	62,432	1	
Raw OR			**54.3 (95% CI: 8.8 – 2215.7, p-value 2.2e-11)**				
MHC OR			**41.1 (95% CI: 5.6 – 1953.6 p-value 5.8e-08)**				