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LETTER TO THE EDITOR

The 3q29 deletion confers >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 the 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 Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines:[5] a search of PubMed on 19 November 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 for excluding the studies were: the study was a case report; the study was about a psychiatric disorder other than SZ; 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 *et al.*[6,7]; Szatkiewicz *et al.*[4,8]; Mulle *et al.*[2,9]) 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 17 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 one deletion carrier) and 439 controls were reported in Szatkiewicz *et al.*[4] and International Schizophrenia Consortium[20]; data were subtracted from the total reported in the more recent publication. In most papers, controls were ethnically matched to cases (Table 1, 'ethnically matched'). 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

Table 1. Meta-analysis of 3q29 deletion and schizophrenia

Ref.	*Ethnicity*	*Selection of controls*	*SZ cases*	*Case 3q29 del*	*Controls*	*Control 3q29 del*	*CMH OR (95% CI, P-value) with this sample removed*
Levinson *et al.*[3]	European American	EM	2667	4	2648	0	36.4 (4.7 –1799.3, 8.4e – 07)
Levinson *et al.*[3]	African American	EM	1273	1	963	0	40.2 (5.4–1924.3, 1.0e – 07)
Szatkiewicz *et al.*[4]	Swedish	EM	4129	5	5478	0	33.4 (4.2–1695.3, 3.4e – 06)
Rees *et al.*[6]	Mixed (95% European ancestry)	EM	6882	4	11 255	0	33.3 (4.2–1691.5, 2.6e – 06)
Mulle *et al.*[9]	Ashkenazi Jewish	EM	554	1	1014	0	39.0 (5.2–1882.6, 1.6e – 07)
Walsh *et al.*[10]	Mixed (78% Caucasian)	EM	150	1	256	0	39.1 (5.3–1887.4, 1.5e – 07)
Rudd *et al.*[11]	No information (recruited from Iowa)	No information (recruited from Iowa)	166	0	52	0	41.1 (5.6–1953.6, 5.8e – 08)
Derks *et al.*[12]	Scottish (ID with SZ)	Scottish (ID w/o SZ)	64	0	66	0	41.1 (5.6–1953.6, 5.8e – 08)
Ahn *et al.*[13]	COS: 'highly heterogeneous'	Unaffected sibs of cases	126	0	69	0	41.1 (5.6–1953.6, 5.8e – 08)
Priebe *et al.*[14]	German	EM	1637	0	1627	0	41.1 (5.6–1953.6, 5.8e – 08)
Van Den Bossche *et al.*[15]	Belgian, Swedish, Scottish	EM	1259	2	1173	0	38.9 (5.2–1881.2, 2.1e – 07)
Buizer-Voskamp *et al.*[16]	Dutch	EM	834	1	672	0	40.1 (5.4–1922.3, 1.0e – 07)
Stefansson *et al.*[17]	Northern European/European	EM	1438	0	33,246	1	∞ (6.7–∞, 2.7e – 08)
Magri *et al.*[18]	Italian	EM	172	1	160	0	40.0 (5.4–1917.5, 1.1e – 07)
Xu *et al.*[19]	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)
International Schizophrenia Consortium[20]	Mixed European	EM	3391	2	3181	0	38.9 (5.2–1880.7, 2.1e – 07)
Costain *et al.*[21]	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)			
CMH OR				41.1 (95% CI: 5.6–1953.6, *P*-value 5.8e – 08)			

Abbreviations: CI, confidence interval; CNV, copy number variation; CMH, Cochran–Mantel–Haenszel; COS, childhood-onset schizophrenia; EM, ethnically matched; ID, intellectual disability; OR, odds ratio; SZ, schizophrenia.

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] ('childhood-onset schizophrenia' 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 1.3–1.6 Mb deletion, which removes all 22 protein-coding genes in the interval. One report indicated a slightly smaller 837 kb deletion (although all but two genes in the typical deletion interval were 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 SZ (*P*-value 5.8×10^{-8}, 95% confidence interval 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 ranged from 5 to 30[22]; thus, the 3q29 deletion may be the single-largest risk factor for SZ, surpassing even the 22q11.2 deletion. The 22 protein-coding genes in the 3q29 deletion interval deserve scrutiny as molecular targets that, when haploinsufficient, may underlie at least one form of SZ. 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.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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