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Rare Genome-Wide Copy Number Variation and Expression of Schizophrenia in 22q11.2 Deletion Syndrome.

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Abstract

OBJECTIVE: Chromosome 22q11.2 deletion syndrome (22q11.2DS) is associated with a more than 20-fold increased risk for developing schizophrenia. The aim of this study was to identify additional genetic factors (i.e., "second hits") that may contribute to schizophrenia expression.

METHOD: Through an international consortium, the authors obtained DNA samples from 329 psychiatrically phenotyped subjects with 22q11.2DS. Using a high-resolution microarray platform and established methods to assess copy number variation (CNV), the authors compared the genome-wide burden of rare autosomal CNV, outside of the 22q11.2 deletion region, between two groups: a schizophrenia group and those with no psychotic disorder at age ≥25 years. The authors assessed whether genes overlapped by rare CNVs were overrepresented in functional pathways relevant to schizophrenia.

RESULTS: Rare CNVs overlapping one or more protein-coding genes revealed significant between-group differences. For rare exonic duplications, six of 19 gene sets tested were enriched in the schizophrenia group; genes associated with abnormal nervous system phenotypes remained significant in a stepwise logistic regression model and showed significant interactions with 22q11.2 deletion region genes in a connectivity analysis. For rare exonic deletions, the schizophrenia group had, on average, more genes overlapped. The additional rare CNVs implicated known (e.g., GRM7, 15q13.3, 16p12.2) and novel schizophrenia risk genes and loci.

CONCLUSIONS: The results suggest that additional rare CNVs overlapping genes outside of the 22q11.2 deletion region contribute to schizophrenia risk in 22q11.2DS, supporting a multigenic hypothesis for schizophrenia. The findings have implications for understanding expression of psychotic illness and herald the importance of whole-genome sequencing to appreciate the overall genomic architecture of schizophrenia.