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Abstract

Schizophrenia occurs in about one in four individuals with 22q11.2 deletion syndrome (22q11.2DS). The aim of this International Brain and Behavior 22q11.2DS Consortium (IBBC) study was to identify genetic factors that contribute to schizophrenia, in addition to the similar to 20-fold increased risk conveyed by the 22q11.2 deletion. Using whole-genome sequencing data from 519 unrelated individuals with 22q11.2DS, we conducted genome-wide comparisons of common and rare variants between those with schizophrenia and those with no psychotic disorder at age >= 25 years. Available microarray data enabled direct comparison of polygenic risk for schizophrenia between 22q11.2DS and independent population samples with no 22q11.2 deletion, with and without schizophrenia (total n = 35,182). Polygenic risk for schizophrenia within 22q11.2DS was significantly greater for those with schizophrenia (p(adj) = 6.73 x 10(-6)). Novel reciprocal case-control comparisons between the 22q11.2DS and population-based cohorts showed that polygenic risk score was significantly greater in individuals with psychotic illness, regardless of the presence of the 22q11.2 deletion. Within the 22q11.2DS cohort, results of gene-set analyses showed some support for rare variants affecting synaptic genes. No common or rare variants within the 22q11.2 deletion region were significantly associated with schizophrenia. These findings suggest that in addition to the deletion conferring a greatly increased risk

to schizophrenia, the risk is higher when the 22q11.2 deletion and common polygenic risk factors that contribute to schizophrenia in the general population are both present.

Palabras clave

KeyWords Plus:COPY-NUMBER VARIATION; PSYCHIATRIC-DISORDERS; VARIANTS; INDIVIDUALS; BRAIN; ASSOCIATION; CONSORTIUM; MUTATIONS; BEHAVIOR; DATABASE

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