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Schizophrenia-Relevant Collections of Genes from the Rest of the Genome Contribute to Schizophrenia Expression in 22q11.2DS

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Background: Understanding the ~25-fold increased risk for schizophrenia imparted by the 22q11.2 deletion is a major goal of the International 22q11DS Brain Behavior Consortium (IBBC). In this ground-breaking study, whole genome sequencing (WGS) data were generated for previously ascertained individuals with neuropsychiatric phenotypic data and DNA samples from an international cohort of patients with 22q11.2 deletion syndrome (22q11.2DS). In this IBBC study we aimed to discover DNA variation and gene pathways that influence the expression of schizophrenia, in addition to the 22q11.2 deletion itself. **Methods:** We first performed extensive quality control efforts to refine the genotypic and phenotypic data available for 1,411 individuals aged 7 -67 years, identifying duplicate subjects, delineating the genomic extent of the 22q11.2 deletion region using multiple methods including available MLPA and microarray data, and determining genotypic ethnicity and relatedness status for individuals. For the current study, we investigated genome-wide common and rare sequence variants in 519 unrelated 22q11.2DS subjects, comparing WGS results for 259 with schizophrenia (SZ) to those for 260 with no psychotic disorder (NP) at age 25 or older. We analyzed the hemizygous 22q11.2 deletion region separately, and excluded variants in the HLA region and sex chromosomes from genome-wide analyses. All WGS data were called and annotated using PEMapper and Bystro. For rare variants (minor allele frequency (MAF) <1%), we focussed on those affecting protein coding (exome), and further classified those most likely to cause loss of function (LOF: deleterious missense (CADD>15), stop gain (nonsense), splice variants, etc.). Collectively, common variants were investigated using a polygenic risk score (PRS) method and rare variants using standard gene-set (pathway) burden, leveraging from data/methods in large general schizophrenia population data-sets. Individual variant or gene-based analyses used SKAT. Standard methods were used (e.g., genome-wide cut-offs, permutation FDR) to determine significance, accounting for multiple testing. **Results:** As expected, no individual variant or gene reached genome-wide significance, for common or rare variants, genome-wide or in the intact 22q11.2 allele region. There was however evidence for collective variant burden genome-wide. The highest proportion of variance in schizophrenia explained by the PRS was 7.7% (corrected p = 6.73x10-6, for pT=0.05). Results were similar using microarray data, despite a smaller 22q11.2DS sample (n=322), that allowed comparison to a >30x larger cohort of idiopathic SZ (n=10,791) where the effect of PRS was greater (OR=1.36, 95% CI: 1.14-1.62, p= 5.55x10-4). There was also evidence that for rare variants, the 22q11.2DS-SZ group was enriched for gene-set burden relevant to neuronal function, including the "Kirov-ARC" gene-set (genes encoding neuronal activity-regulated cytoskeleton-associated proteins). **Discussion**: The results suggest that, collectively, for both common and rare variants, sequence variants relevant to schizophrenia in the general population increase the likelihood of schizophrenia in 22q11.2DS, in addition to effects of the 22q11.2 deletion itself. These results provide further support for 22q11.2DS as a powerful model to study schizophrenia.