Low frequency of schizophrenia, not nervous system-linked genes carrying harmful variants in schizophrenia patients: Inferences for negative symptoms

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Research on the impact of schizophrenia-associated genes on clinical presentation, particularly negative symptoms, is limited. Positive symptoms are better understood and respond well to medications targeting neurotransmitter pathways, while negative symptoms remain treatment resistant[1]. We analyzed exome sequencing data from the Sweden-Schizophrenia Population-Based Case-Control cohort (dbGaP: phs000473.v2.p2, protocol #24624[2]) to examine schizophrenia-associated genes. Data were annotated using SnpEff and SnpSift, variants called with FreeBayes, and rsIDs retrieved from dbSNP. Population frequency came from GnomAD 2.9, clinical significance from ClinVar, and predictor values from dbNSFPv4.2a. Variants deemed Benign or Likely Benign and those with allele frequency>5% were excluded. Deleterious variants were algorithmically identified based on allele frequency, predictors, conservation, and clinical significance. Genes were linked to DisGeNET[3], mapped to organ systems via UMLS Metathesaurus, and ranked by gene-disease association (GDA≥0.5). To validate the algorithm, we compared the presence of epilepsy-related genes in an epilepsy cohort (N=193, phs001489.v3.p2[2]) and a Crohn's disease cohort (N=111, phs001076.v1.p1[2]). We found 173 cases (89.2%) in the epilepsy cohort and 13 cases (11.7%) in the Crohn's cohort, yielding a sensitivity of 89.6%, specificity of 88.3%, and accuracy of 89.1%. In the schizophrenia cohort, only 27/142 cases (18.6%) had deleterious variants in schizophrenia-associated genes (e.g. *DISC1, CACNA1C, PRODH*), while 122/142 cases (84.1%) carried deleterious variants in genes linked to nervous system diseases, with no overlap between the two groups. This suggests many schizophrenia patients may have undiagnosed neurological conditions presenting as schizophrenia. To better understand the role of nervous system-associated genes, we used Varelect to identify those linked to neuropathological processes, such as cortical atrophy, mitochondrial damage, and gliosis, often associated with schizophrenia. Functional enrichment analysis via g:Profiler, a functional enrichment analysis tool, revealed subgroups of nervous system genes, including those associated with lysosomal damage (e.g. *ARSA, ATP7B, GBA*) and cortical neuronal loss (e.g. *SPG7, VPS13A*). These genes were linked to terms like dementia, diminished motivation, and abnormal reality perception. In contrast, schizophrenia-associated genes were linked to synaptic modulation and glutamatergic transmission, while Crohn's-associated genes (e.g. *ABCB1, IL10RB*) were tied to interleukin production and gastrointestinal inflammation, with no association with cognitive phenotypes. In summary, many deleterious variants in the schizophrenia cohort are linked to neuropathological processes, potentially shedding light on the mechanisms underlying negative symptoms. Further research using DNA sequencing is needed to fully understand the molecular pathology of treatment-resistant schizophrenia.

References

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The NIH has determined that these data can be used for general research purposes and IRB approval is not required.

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