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Schizophrenia Studies Find Genetic Risk Spread Across Shared Pathways

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By a GenomeWeb staff reporter

NEW YORK (GenomeWeb News) – A pair of papers published online today in *Nature* described the outcome of two large exome sequencing studies aimed at finding new and/or rare genetic contributors to schizophrenia.

In each case, the groups involved found that schizophrenia risk did not reside in any one gene, but across a few, recurrent — often brain-related — pathways.

"Taken as a group … genes involved in neural function and development showed greater rates of disruptive mutations in patients," Broad Institute researcher Shaun Purcell, a co-author on both of the papers, said in a statement, calling the findings "sobering but also revealing."

"[I]t suggests that many genes underlie risk for schizophrenia and so any two patients are unlikely to share the same profile of risk genes," he said.

For the first of the studies, Purcell was part of an international team led by investigators in the UK and US that did exome sequencing on more than 600 individuals with schizophrenia and their unaffected parents. Amongst the mutations found in affected individuals but not their parents were *de novo* alterations affecting pathways implicated in synaptic function, brain development, cognition, memory, and the like.

That group used Agilent or Nimblegen arrays to grab protein-coding sequences from members of 623 schizophrenia-affected parent-child trios, subsequently sequencing each of the exomes to depths of 10 reads or more across 93 percent of the sequences targeted, on average.

In the 617 trios that made it through the quality control steps, researchers identified 637 *de novo* alterations that could be verified by Sanger sequencing.

Delving into the genes affected by those mutations offered a window into some of the biological processes that may go awry when individuals develop schizophrenia, including pathways implicated in neuronal signaling, synaptic plasticity, and synaptic function.

In affected members of the trios, for instance, the researchers saw an over-representation of relatively small *de novo* mutations in genes coding for components of two synapse-related complexes: the so-called "activity-regulated cytoskeleton-associated" (ARC) protein complex and the N-methyl-D-aspartate receptor (NMDAR) complex.

Genes coding for proteins that interact with such complexes to dial synapse strength up or down were often affected too, as were genes previously found to be prone to rare mutations in individuals with schizophrenia.

These and other findings broadly fit with patterns detected by authors of another*Nature* study who considered exome sequence data from thousands of schizophrenia cases and controls.

For that analysis, researchers from the Icahn School of Medicine, the Broad Institute, and elsewhere compared exome sequences from 2,536 Swedish individuals with schizophrenia and 2,543 individuals from the same population who were not affected by the disease.

When they sifted through the rare single nucleotide changes and small insertions and deletions that were more common in the cases than the controls, members of that team found that those types of genetic glitches affected a wide set of genes, consistent with a polygenic risk model for schizophrenia.

Such changes were especially common amongst genes linked to the condition in the past. They also tended to turn up in ion channel genes and genes from synaptic pathways identified in the *de novo* mutations study, including the ARC and NMDAR complexes.

"Although the complexity of the genetics is sobering, these types of studies should provide a firm base from which we can chart a course toward the ultimate goal of subtyping patients and offering a more personalized treatment path than the one-size-fits-all approach currently used," Purcell said in a statement.

While the case-control study did not show overlap between individual genes involved in schizophrenia and risk genes already reported in autism spectrum disorder or intellectual disability, the results indicated that at least some of the same pathways are affected in all three conditions.

Authors of the *de novo* mutation study, on the other hand, saw more pronounced overlap between genes and pathways contributing to ASD, intellectual disability, and schizophrenia.

"The fact we've been able to identify a degree of overlap between the underlying causes of schizophrenia and those in autism and intellectual disability suggests that these disorders might share some common mechanisms and lends further weight to calls for research that integrates findings across multiple disorders," that study's co-senior author Michael O'Donovan, a researcher at Cardiff University's Medical Research Centre for Neuropsychiatric Genetics and Genomics, said in a statement.