

Study provides clues to relationship between schizophrenia and rheumatoid arthritis

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Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

An in-depth computational analysis of genetic variants implicated in both schizophrenia and rheumatoid arthritis by researchers at the University of Pittsburgh points to eight genes that may explain why susceptibility to one of the disorders could place individuals at lower risk

for the other, according to the results of a study published today in the journal *npj Schizophrenia*.

"There is a wealth of genomic data on both [schizophrenia](#) and rheumatoid arthritis. Analyzing it jointly with known [protein interaction](#) information could provide invaluable clues to the relationship between the diseases and also shed light on their shared roots," said Madhavi Ganapathiraju Ph.D., associate professor of biomedical informatics at the University of Pittsburgh School of Medicine and senior author of the study.

While schizophrenia is a psychiatric disorder of unknown origin and rheumatoid arthritis is an autoimmune disease of the joints that occurs as a result of the body's immune system attacking its own cells, both disorders are thought to be influenced by multiple genetic risk factors modified by the environment.

"Several previous research studies have hinted at a potential inverse relationship in the prevalence and risk for the two disorders, so we wondered if individual genetic variants may exist that could have opposing effects on the risk of schizophrenia and rheumatoid arthritis," said co-senior author Vishwajit Nimgaonkar M.D., Ph.D., professor of psychiatry at Pitt's School of Medicine and human genetics at Pitt's Graduate School of Public Health.

The researchers first analyzed two large databases of genetic variants significantly associated with either schizophrenia or rheumatoid arthritis. They identified 18 unique variants, also known as [single nucleotide polymorphisms](#) (SNPs) that were located in the HLA region of the genome that harbors genes associated with [immune function](#). The variants appeared to confer different risk for schizophrenia or rheumatoid arthritis. As the SNPs were located near eight known genes in this region, the authors suggested those genes might lead to

dysfunction in both schizophrenia and rheumatoid arthritis. Proteins encoded by two of these eight genes, HLA-B and HLA-C, are present in both brain and immune cells.

Analysis of proteins that interact with these eight genes using a computational model developed last year by Ganapathiraju's team called High-Precision Protein Interaction Prediction found more than 25 signaling pathways with proteins common to both rheumatoid arthritis and schizophrenia signaling. Moreover, several of these pathways were associated with immune system function and inflammation.

The findings are encouraging because they support associations of the HLA gene region and immune function with schizophrenia and rheumatoid arthritis that were known over four decades ago, said Ganapathiraju. Increasing evidence also suggests that a dysfunctional [immune system](#) could play a role in the development of schizophrenia.

"We believe that the research community studying these two disorders will find our results extremely helpful," Nimgaonkar said.

The authors note that the study only focused on SNPs in known gene regions, and other mechanisms apart from the ones they described may also contribute to the diseases. However, the study has significantly narrowed the list of potential [genes](#) for examining the schizophrenia/[rheumatoid arthritis](#) relationship. Studying the functional relevance of the gene candidates in cells and tissues will provide insights into the two disorders, according to the researchers.

More information: Tulsi A. Malavia et al. Generating testable hypotheses for schizophrenia and rheumatoid arthritis pathogenesis by integrating epidemiological, genomic, and protein interaction data, *npj Schizophrenia* (2017). [DOI: 10.1038/s41537-017-0010-z](https://doi.org/10.1038/s41537-017-0010-z)

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