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PSYCHIATRIC DISORDERS

Linking genetic risk to pruning

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Studies have linked variations at more than 100 different genomic loci with increased schizophrenia risk, yet we know little about the responsible alleles or how they might give rise to neurobiological dysfunction. Sekar *et al.* now demonstrate an association between schizophrenia risk and a complex form of genome structural variation that alters the expression of particular forms of complement component 4 (*C4*) and that may affect synaptic pruning.

The *C4* locus resides within a region of chromosome 6 (the major histocompatibility complex (MHC) locus) that is strongly linked to schizophrenia risk and exhibits a complicated form of structural variation: it contains variable numbers of copies of two isotypes of the C4 gene (*C4A* and *C4B*), each of which exists in either 'long' or 'short' form. The authors developed droplet-based PCR assays to determine the structure and copy number — the 'structural haplotype' — of these forms of *C4* in 222 healthy individuals, revealing four 'common' *C4* structural haplotypes that are present in 90% of individuals. Moreover, they showed that the *C4* structural haplotype of an individual predicted the expression levels of *C4A* and *C4B* in post-mortem brain samples.


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By performing a new analysis of a set of previously obtained single-nucleotide polymorphism (SNP) data from 28,799 individuals with schizophrenia and 35,986 controls, the authors found a strong association between schizophrenia risk and *C4* structural variation. Crucially, the level of risk associated with each of the common *C4* structural haplotypes correlated with the extent to which it predicted increased *C4A* expression. This suggested that increased *C4A* expression in the brain might contribute to schizophrenia pathophysiology. Indeed, the authors showed that *C4A* RNA expression levels were increased in the brain tissue of 35 patients with schizophrenia (compared to 70 controls).

Using immunohistochemistry, the authors showed that CNS C4 expression frequently colocalized with synaptic markers in the brains of patients with schizophrenia. Other components of the complement cascade have been implicated in developmental synaptic 'pruning'. Here, the authors showed that the loss of C4 resulted in reduced pruning in a mouse model of retino-geniculate synapse refinement, indicating a probable role for C4 in this process.

It has been proposed that disrupted synaptic refinement during development and adolescence contributes to schizophrenia pathophysiology. By providing a direct link between synaptic pruning and variations in a gene associated with schizophrenia risk, this study supports this idea. In addition, the strategy to assess complex structural variations in the genome may enable the identification of other genetic loci contributing to neurological disorders.

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