Copy Number Variation and Endophenotypes in Psychiatric Disorders

Results in Brief

Advances in understanding psychiatric disease risk

A European, genome-wide association study of copy-number variants has advanced knowledge related to the pathophysiology of psychiatric disorders. Analyses of variant samples were used to generate data for schizophrenia, bipolar disorder and major depression.

HEALTH

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With the support of EU funding, the 'Copy number variation and endophenotypes in psychiatric disorders' (PSYCHGENE) project associated common variants conferring low risk of psychiatric disorders, as well as rare variants conferring high risk of such disorders. The collaboration of university centres and research institutes studied contributions from the sequence variants to endophenotypes and searched for at-risk biological pathways in psychiatric disorders through a systems biology approach.

Improved means of garnering information regarding the heritability of psychiatric disease has prompted more extensive research into genetic variations that potentially confer risk. Consortium members found that identified common variants explain only

a very small fraction of the heritability observed in psychiatric disorders. A likely explanation for this is the reduced reproduction associated with many psychiatric disorders. The high-risk variants, recurrent copy number variants (CNVs) and mutations in coding sequence offer more of an explanation of heritability. New knowledge in these areas of interest may help ascertain commonalities of conditions such as schizophrenia, autism and mental retardation.

Progress gained through systems biology approaches enabled PSYCHGENE to identify several sequence variants conferring risk of schizophrenia. Building on work in another EU-funded study entitled 'A large scale genome-wide association study of schizophrenia addressing variation in expressivity and contribution from environmental factors' (SGENE), the project associated a variant in the VRK2 gene and a second variant in the TCF4 gene with schizophrenia. These variants confer low or modest risk of schizophrenia and individually did not contribute strongly to endophenotypes.

Project research also provided support for the association of AHI1 markers with schizophrenia, while large meta-analyses of samples revealed the association of an additional five genomic regions with schizophrenia. Genome-wide significance was found for three loci in a large meta-analysis for bipolar disorders, while sparse evidence was found when sequence variants were tested for association with depression.

In their search for an overlap in the genetics of schizophrenia and diabetes, the consortium found association of a variant in the TCF7L2 gene with schizophrenia. The systems biology approach was also used successfully in a search for biological pathways conferring risk, demonstrating association with specific abnormalities of post-synaptic signalling complexes in the pathogenesis of schizophrenia.

Overall, PSYCHGENE contributed to the identification of several rare variants conferring high risk of schizophrenia and psychoses. Further exploration of such variants will reveal more information on risk of psychiatric disorders, with project findings contributing to improved understanding of the basis of the pathology of psychiatric disorders. This is also important for future work related to drug discovery.

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