



Opening the 'black box' of biological mechanisms behind complex disease, and the hornet's nest of media hype: Complex variation in C4 as a risk factor for schizophrenia

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Over the last decade, DNA sequencing has become exponentially more affordable. This development has raised hopes for the future of personalized medicine, where treatments will be primarily preventative, and tailored to individual needs. However, determining disease risk from DNA sequence has turned out to be very challenging, especially for complex diseases, which involve many genes and complex environmental interactions. Schizophrenia, a serious mental illness estimated to affect ~1% of adult populations, represents one such complex disease. For such human health challenges, Genome Wide Association Studies (or GWAS) have identified hundreds or thousands of genetic variants associated with the complex disease, usually without pinpointing any clear cause. A recent GWAS on schizophrenia reported in *Nature* (Sekar et al. 2016) came to national attention for identifying a genetic variant that isn't just statistically associated with the disease, but might also point to a biological mechanism and pathways for the development of novel treatments. This study has also received some criticism for the level of hype it has attracted in the press! Translating GWAS results into biological insights is a subject of widespread interest among geneticists, as is the process by which science gets translated for the wider public by journalists, so we decided to take the debate to our bi-weekly Genetics Journal Club.

Sekar et al. came across the gene C4, encoding a protein of the complement system, while following up on a previous GWAS study, from 2014, which identified a strong association between schizophrenia and the MHC locus of the human genome. However, the association didn't correspond to any known variant. This led them to C4, which varies between people in a complex way that might mask standard screens for variation. There are two standard versions of C4 that exist in humans - C4A and C4B - and people can have zero to three copies of one or both variants. C4 is also further complicated by a transposable element sometimes found in this gene, which makes either C4A or C4B substantially longer when it's present. Sekar et al. demonstrate that most people have one of four combinations of C4A and C4B, and that different combinations can lead to different amounts of C4A and/or C4B protein. Measurements in post-mortem samples of brains showed that people with schizophrenia were more likely to have C4A/C4B combinations that corresponded to significantly higher levels of C4A production. Previous screens for genetic variation in people with schizophrenia show the same trend across very large sample sizes in many populations.

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This result is important for two reasons. First of all, the authors show physiological evidence from a mouse genetic model that C4 is necessary for synaptic pruning, which has been frequently brought up as potentially key in the development of schizophrenia. Second, if levels of C4 are critical for the etiology of schizophrenia, it would be a logical target for drug development. Most members of our journal club did feel that press releases describing it as the “first-ever insight” into the biological basis of schizophrenia are probably overblown, and that the results although exciting are not conclusive. However, we look forward to seeing over the next few years if their findings do lead to new biological insights. Regardless, Sekar et al. is a very interesting read, and an excellent demonstration of how GWAS results can be complicated and elucidated by an understanding of structural and copy number variation of genes in populations.

Anne Sonnenschein is a sixth-year graduate student in the Genetics Program (@MSUGenetics), working in the laboratory of Dr. David N. Arnosti at Michigan State University. She can be found on Twitter at @Anne_Sunenshine.

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