Comment on: An Expanded View of Complex Traits: From Polygenic to Omnigenic

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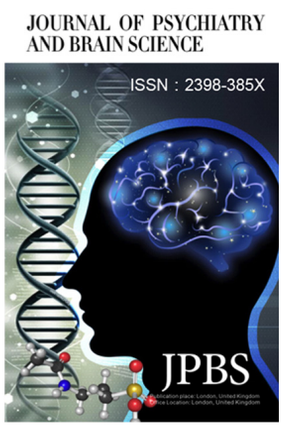
Pritchard and colleagues' finding that virtually all genes in cell types that are involved in a disease contribute to heritability of disease leads to his discussion of a focus on "core genes", a concept related to the "core networks" of Chakravarti and Turner (2016) [1]. The definition of core genes requires further thought, they note, and there may be diseases without core genes.

What is missing from that paper's discussion is the complexity of phenotypes, and the multiple phenotypes involved in disease and in the complex traits he considers. He does not consider that there may be "core phenotypes" within these traits, parallel to his consideration of core genes. In Schizophrenia, one of the three diseases he focuses on, there are known to be multiple component phenotypes, and recently the genetics of the components has become a focus of investigative interest. Ventricular enlargement [2] in the brain has been known to be associated with Schizophrenia for decades. In our own work, a specific SNP in the gene for LDL receptor related protein 1B accounted for 5 % of phenotypic variance in the Cavum Septum Pellucidum, a ventricular space that persists past infancy more often in patients with psychosis diagnosis than in controls. Although 5 % is not a large proportion of total variance, it is much larger than the phenotypic variance accounted for by any of the known genetic associations with Schizophrenia. Furthermore, the SNP is not significantly associated with Schizophrenia.

So we would argue that the complexity of molecular networks within cells is one of many factors that need to be explored in the analysis of complex phenotypes. Even though the complexity of omnigenic interactions is mind-boggling, it is not sufficient to give a coherent analysis of the biology of complex phenotypes.



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