The genetics of major depression remain elusive

by Eiko Fried, Sophie van der Sluis, and Angelique Cramer

A recent study published in *Nature* by the CONVERGE consortium[1] identified two Single Nucleotide Polymorphisms (SNPs) for Major Depressive Disorder (MDD) that replicated across two samples of Han-Chinese women with recurrent depression. The report was accompanied by an editorial[2] that hailed the findings as biologically and diagnostically relevant, suggesting that large-scale exploratory genome-wide studies offer enticing prospects towards aiding diagnosis and the development of new drugs.

We disagree with the editorial's interpretation (and most of the media coverage) of these CONVERGE results, which contrast with the careful phrasing of the authors themselves. Although the two SNPs discovered in the comparatively homogenous CONVERGE sample did replicate in a similarly ascertained group, the editorial fails to mention that they did not in the more heterogeneous Psychiatric Genomics Consortium (PGC) data also examined by the authors. Moreover, in polygenic risk score analysis, the genetic signal in the PGC sample explained less than 0.1% of disease risk in the CONVERGE data, implying a fundamental lack of overlap in genetic risk signal across samples.

The laudable effort of the CONVERGE consortium to ensure genetically and phenotypically homogenous samples confirms the elusiveness of the genetics of MDD. Hailing the results as robust insights into the biology of depression detracts from the true scientific relevance of the study: genetic effects for MDD are, even in large homogenous samples, small and do not generalize.

Given the hitherto negative results of genetic MDD studies[4,5], slogging along on this current road of ever-larger samples and discovering at best small effects is not an alluring prospect, especially so considering that these effects are likely not specific to MDD[6]. Instead, we suggest revising complex psychiatric phenotypes such as MDD that were transferred unquestioningly from psychiatry to genetics. Incorporating recently proposed network models[7], symptom- rather than syndrome-level analyses[8], and the development of new instruments that tap variation along the entire continuum[9,10] (i.e., in both "cases" and "controls") offer promising ways forward.

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