New analyses provide supportive evidence for specific genes related to bipolar disorder

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A recent article by Franklin and Dwyer[1] analyzes genes identified in two previous genome-wide association studies (GWAS) of bipolar disorder.[2, 3] They establish that the 230 genes identified in the two studies are evolutionarily conserved (in *C elegans* and zebrafish but not in drosophila) that they contain regions of homology and are highly interactive, and that some of them are clustered in syntenic groupings on chromosomes in humans and zebrafish. The findings are not dissimilar to previous findings with positional candidate genes in schizophrenia by Dwyer and colleagues.[4]

These findings are reassuring for those studying the genetics of psychiatric disorders and following the progress of GWAS in those disorders. It must be said that psychiatric genetics went through a long fallow period during which findings were not reliable or not specific enough to be biologically interesting. The technological revolution in molecular genetic methods changed that dramatically over the last 15 years, and the willingness of investigators to come together in large groups and share data provided the necessary clinical resources for that technology to produce results. Subsequent demonstrations of reproducible associations between psychiatric disease and gene variants have been increasing from the tens to the hundreds over the past decade. Individual variant effects have been small (at least among the GWAS – larger for copy number variants or rare variants identified by sequencing) and thus it is necessary to study interactions among these variants to seek functional significance.

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Such interactions in the present study are remarkable. The 230 genes implicated in bipolar disorder participated in an average of 22 interactions[1] compared with less than 5 for random gene sets studied for comparison. This is also much more than the interactions of genes implicated in schizophrenia (8 interactions) or genes implicated in rheumatoid arthritis (5.6 interactions). This suggests a particular biological coherence for bipolar disorder genes that implies a strong (yet to be identified) pathophysiologic mechanism. The counterparts of the bipolar disorder risk genes in C elegans were disproportionately likely to be essential for the life of the organism, and functional data suggested roles in development, locomotion, and in neurotransmitter activity.

It is notable that the two sources for positional candidate genes differed in their gene identification strategies. The first was a meta-analysis from the Psychiatric Genomics Consortium Bipolar Group[2] (starting with genes that included 2 or more single nucleotide polymorphisms (SNPs) with nominal $P < .05$ association with bipolar disorder in 3 of 4 independent GWAS datasets). The resulting genesets were validated with simulation studies that took gene size into account and the eventual list included 207 genes with an empirical p value of 0.05 or less. The second[3] was a standard GWAS using a combination of many datasets from the Psychiatric Genomics Consortium and the 29 genes included were those tagged by a SNP with $P < 10e\text{-}8$ significance (equivalent to a genome-wide P value of .05). The two sources provided similar results in terms of conservation and interaction. This would tend to support the view that there is substantial value in examining GWAS datasets using multiple methods and not confining efforts to the relatively small number of top hits. Studies of polygenic risk scores likewise show that gene variants at well under the p x 10e-8 threshold provide additional predictive power.

One of the more surprising findings of this study was the identification of syntenic regions on human and zebrafish chromosomes that contain multiple bipolar disorder-related genes. This suggests a functional relationship between these genes and also the likelihood that they may be transmitted together with reduced variance over generations. One similar phenomenon is the constellation of ADH alcohol dehydrogenase (ADH) genes on chromosome 4 in man, which share function and transmission

characteristics. The significance of this in bipolar disorder remains to be elucidated but there are functional clues noted in this study, principally the relationship to neuronal growth and development.

We should also note that while reliance on gene position (in relation to associated variants) produced good results in the present analysis, the coupling between position and function in the genome is only modest. Many times a gene variant acts most powerfully at a site distant from its position. Additional attention to more distant effects of gene variants will undoubtedly provide a more complete picture of functional genomic effects in bipolar disorder.[5]

Altogether this is a very helpful contribution to the literature on the genetics of bipolar disorder, and Franklin and Dwyer[1] are to be commended for their exhaustive work with the genetic databases required to produce these fascinating results.

References

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