Strategies to Find Candidate Genes for Bipolar Disorder

Sir,

Linkage studies have been revealing many new linkage loci not supporting previous regions of interest in the development of bipolar disorder. In addition, a number of association studies failed to get continuous replications as well as family based association studies in bipolar disorders.¹ Moreover, 5-HTTLPR and brain-derived neurotrophic factor (BDNF) promoter polymorphisms are now found to be more complex than previously thought, and thus previous papers on these polymorphisms should be treated with caution, although some researchers picked these genes as relatively most promising candidates for bipolar disorder.^{1,2}

As proposed before, we could have more well-organized and robust information by interactive approaches combining multiple candidate genes, contributing psychosocial factors and establishment of potential endophenotypes for bipolar disorder. However, these new approaches would be liable to a repetition of trial and error as did past studies since such individual approach has its inherent pitfalls (i.e., complexity of polymorphisms, for example, 5-HTTLPR was found to have novel alleles showing different functional significance; syndromal diagnosis of bipolar disorder; presence of small effect genes).^{2,3}

Hence we need more clearly-defined new pathway to find candidate genes, for example, setup of worldwide co-operation, consensus and protocols for genetic studies which may be lessoned from practical clinical trials, i.e., CATIE⁴ and EUFEST⁵ studies. In fact we may focus on more highly selective diseased family data with this approach, i.e., focusing on single large family excluding geographic and genetic heterogeneity.

We may also need to quantify the role of candidate genes after complete interactive analyses for their contribution to the disorder and then weighted values should be given as their rates of contribution, which eventually might give us a statistically stringent model incorporating proven potential genes (i.e., namely targeted candidate gene cluster level I, II and III etc.).

Other option might be a combination of phylogenetic and endophenotypic approach to bipolar disorder since

the disorder has different clinical and biological faces, although currently bipolar disorders are simply categorized as same phenomenological classification and genetic studies are also based on simple diagnostic criteria. Finally well-organized and systematized pathway-based candidate gene analysis not searching individual gene analysis based on specific pathophysiology will also help us to shorten finding high risk genes.

Definitely today is just preparing the first puzzle but not finding the final one. I believe that the efficient strategies and tactics to find precise implications through stepwise integration of currently available findings are more important than finding a new candidate gene today.

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