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A rare mutation of *CACNA1C* in a patient with bipolar disorder, and decreased gene expression in brain associated with a bipolar-associated common SNP of *CACNA1C*

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Recently discovered associations of SNPs in common diseases from GWAS have had very weak statistical effects on risk. Furthermore, the markers are not chosen for genomic functionality, although as it happens there is over-representation of functional SNPs in the GWAS associations. It has been proposed that rare mutations in linkage disequilibrium with the common associated SNPs may reveal more about disease mechanisms. Timothy Syndrome (TS) is caused by very rare exonic mutations of the *CACNA1C* gene that produce delayed inactivation of Cav1.2 voltage-gated calcium channels during cellular action potentials, with greatly increased influx of calcium into the activated cells. The major clinical feature of this syndrome is a long QT interval that results in cardiac arrhythmias. However, TS also includes cognitive impairment, autism, and major developmental delays in many of the patients. We observed the appearance of Bipolar Disorder (BD) in a patient with a previously reported case of TS, who is one of the very few patients to survive childhood. This is most interesting because the common SNP most highly associated with BD is rs1006737, which we show here is a cis-expression quantitative trait locus (eQTL) for *CACNA1C* in human cerebellum, and the risk allele (A) is associated with decreased expression. To combine the *CACNA1C* perturbations in the presence of BD in this patient and in patients with the common *CACNA1C* SNP risk allele, we would propose that either increase or decrease in calcium influx in excitable cells can be associated with BD. In treatment of BD with calcium channel blocking drugs (CCBs), we would predict better response in patients without the risk allele, because they have increased *CACNA1C* expression.

Biography

Elliot S. Gershon is Foundations Fund Professor of Psychiatry and Human Genetics at the University of Chicago, and a Fellow of the American College of Neuropsychopharmacology. His major research interests are in genetics of psychiatric disorders and in the past few years in structural changes in the human genome (large deletions, insertions, and other rearrangements). The goal of this proposal is to systematically evaluate somatic structural genomic mutations in brain, and to determine if they are associated with Alzheimer's disease. He has been collaborating with the other PIs in this MPI grant proposal for several years, including funded studies of human autopsy brain specimens, and study of germline structural genomic variants (also known as copy number variants) associated with bipolar disorder and schizophrenia.

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