Abstract/Session Information for Program Number 2305T

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Session Information

Session Title: Complex Traits and Polygenic Disorders **Session Type:** Poster

Session Location: Exhibit Hall, Lower Level South, Moscone Center **Session Time:** Thu 7:00AM-4:30PM

Abstract Information

Program Number: 2305T **Presentation Time:** Thu, Nov 8, 2012, 2:15PM-3:15PM

Keywords: Complex Traits and Polygenic Disorders, KW011 - brain/nervous system, KW015 - candidate gene, KW087 - immune system

Abstract Content

Whole-exome sequencing study of four families with bipolar disorder. *E. Elhaik[1,2], M. Pirooznia[1], F. S. Goes[1], J. Parla[5], R. Karchin[3], A. Chakravarti[2], P. P. Zandi[1], R. W. McCombie[5], J. B. Potash[4]* 1) Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; 2) McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; 3) Medical Research Center, University of Iowa, Iowa City, IA; 4) Department of Biomedical Engineering and Institute for Computational Medicine, Johns Hopkins University, Baltimore, MD; 5) Cold Spring Harbor Laboratory, Woodbury, NY.

Background: Bipolar disorder (BP) is a common mental disorder often associated with lifelong disability and premature mortality. We are conducting a whole-exome study of BP using next generation sequencing to examine the whole exomes of up to 100 multiplex BP families (with at least 6 individuals from 2-3 generations of each family), 1,800 BP cases, and 1,800 controls with the goal of identifying rare and common genetic variants associated with the disease. **Methods**: Exome sequencing was performed in a pilot sample of 22 individuals from four multiplex BP families using solution-based capture and paired-end sequencing on the Illumina GA II. Alignment and variant calling were performed with BWA, SAM tools, and GATK. SNVs were annotated with the SIFT and PolyPhen tools. Families were analyzed separately for the segregation of functionally relevant variants with disease. **Results**: We identified a single common (MAF=0.2) deleterious splice site variant (rs8373) in a zinc-finger protein gene (ZFP91) that segregated with all affected relatives and none of the unaffected married-in relatives in all four families. A family-based test indicated the variant was significantly associated with BP in these families (p=0.0026). ZFP91 is involved in the non-canonical nuclear factor kB (NF-kB) signaling pathway, which regulates the canonical NF-kB pathway. The non-canonical pathway is associated with adaptive immunity and protection against inflammation and apoptosis. **Conclusions**: Our initial analysis of four multiplex families with bipolar disorder revealed a common splice-site polymorphism in ZFP91 that segregates with disease in all pedigrees. Mutations inhibiting the non-canonical NF-kB, such as the one identified here, have been shown to induce apoptosis and inflammation due to the continuous activation of the complementary pathway. This variant was imputed in the Psychiatric GWAS Consortium (PGC) mega-analysis of Bipolar Disorder, but it was not significantly associated with illness. However, if the current finding can be replicated in other sequenced families, it may provide evidence of a potential inflammatory etiology in bipolar disorder. Such replication efforts are ongoing.

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