Science at the Edge Seminar Series

Quantitative Biology Graduate Program/ Gene Expression in Development and Disease

Dr. Maja Bucan, Ph.D.

Department of Genetics, Perelman School of Medicine
University of Pennsylvania

Family-Based Analysis of Bipolar Disorder in a Genetic Isolate

Genetic dissection of complex disease such as bipolar disorder (BP) can often be complicated by the presence of other medical co-morbidities. In such cases, family-based studies reduce confounding effects resulting from non-genetic components, however teasing out genetic associations to BP risk is still challenging. Recent studies suggest that variants in Mendelian disease genes can contribute to complex disease risk. Our previous work in the expanded multigenerational Old Order Amish pedigree (ASMAD) revealed multiple linkage regions (in different subpedigrees) with BP risk-alleles, supporting a high degree of locus and allele heterogeneity. This may in part be due to the co-morbid disease loci within this family that segregate in different subpedigrees. To address the genetic heterogeneity of bipolar risk factors through the investigation of medical comorbidities, we utilize a combination of whole genome sequence (WGS) for 80 subjects (30 parent-child trios) with dense SNP genotype data for 394 family members to provide an accurately imputed and phased whole genome sequence. Long-range phased haplotypes allow us to explore the possible pleiotropy of Mendelian disease genes in relation to BP and the co-segregation between bipolar risk factors and Mendelian loci. We conducted carrier screening for all disease causing mutations in the Human Genome Mutation Database (HGMD-DM), and identified known and novel alleles in 3017 disease genes in both the heterozygous and homozygous state, many that are private to the ASMAD population. We created a complete catalog of all variants (both CNVs and SNPs) in disease genes, and compared allele frequencies between 1000 Genomes, an Amish control population, and the ASMAD sample. We can capture the distribution of these variants and follow them across multiple generations by utilizing the rich pedigree data. Strikingly, we find that burden of all variants in HGMD-DM genes is nominally elevated in individuals with BP, both in SNP and CNV analysis. Moreover, RNA-seq data for a subset of family members demonstrates the expression changes associated with these variants. These results reinforce the hypothesis of a complex genetic architecture underlying BP, and suggest that studies will benefit from investigating the role of variants in disease genes in BP and co-morbid conditions.

Friday, December 4, 2015 at 11:30a.m.
Room 1400 BPS