THE NISONGER CENTER
IDD/RESEARCH FORUM PRESENTS:

JULIA PINSONNEAULT, PHD

Dopamine Transporter Gene Variant That Affects Expression in Human Brain Is Associated With Bipolar Disorder: Implications for ADHD Subtypes and Drug Response in Autism

About the Presenter:

Julia Pinsonneault is a research scientist in The Ohio State University College of Medicine School of Biomedical Science’s Department of Pharmacology. Dr. Pinsonneault received her PhD from Yale University, from the Department of Molecular Biophysics and Biochemistry, working with William McGinnis on the genetic regulation of pattern formation in Drosophila embryos. After two postdoctoral stints with Drosophila, she made the switch from flies to humans, joining the laboratory of Wolfgang Sadee in 2002 to work on the pharmacogenomics and genetic regulation of complex disorders, becoming a research scientist in 2008. Her research addresses the question of how genetic factors contribute to disease susceptibility and drug response in complex disorders, particularly those that vary considerably between sexes. She is participating in several clinical collaborations involving CNS disorders, including a genetic study of postpartum depression (Collaborator: M. Steiner, McMaster University) and a pilot study, currently funded by the Center for Clinical and Translational Science (CCTS), in which children with autism spectrum disorders with or without ADHD symptoms are being recruited for the genotyping of candidate polymorphisms (Collaborators: M. Aman, B. Hurt, & L.E. Arnold; OSU RUPP).

About the Forum:

The gene encoding the dopamine transporter (DAT) has been implicated in CNS disorders, but the responsible polymorphisms remain uncertain. To search for regulatory polymorphisms we measured allelic DAT mRNA expression in substantia nigra of human autopsy brain tissues, using two marker SNPs (rs6347 in exon 9 and rs27072 in the 3′-UTR). Allelic mRNA expression imbalance (AEI), an indicator of cis-acting regulatory polymorphisms, was observed in all tissues heterozygous for either of the two marker SNPs. SNP scanning of the DAT locus and in vitro molecular genetics studies demonstrated that the minor allele of rs27072 affects mRNA expression and translation. Four polymorphisms
(rs6347, rs27072 and two repeat polymorphisms) were genotyped in clinical cohorts, representing schizophrenia, bipolar disorder, depression, cocaine abuse, and controls. Only rs27072 was significantly associated with bipolar disorder. This result was replicated in a second bipolar/control population, supporting a critical role for DAT regulation in bipolar disorder. Since DAT is also a candidate gene for ADHD, the next step is to examine our functional polymorphism in a clinical population with an exceptionally-high rate of ADHD. I will discuss an ongoing pilot study in which we are recruiting children with autism spectrum disorders with or without ADHD symptoms. Genetic evidence points to the dopaminergic, serotonergic and noradrenergic systems in the etiology of ADHD among typically-developing children. Variants that change the levels of expression of candidate proteins in biologically relevant tissues could lead to an imbalance causing an individual to be susceptible to psychiatric conditions – or perhaps protect individuals against these. In addition to DAT, we have identified functional polymorphisms and/or haplotypes in 3 other candidate genes for ADHD that affect mRNA expression in human brain: MAOA, TPH2, and DRD2. Our pilot study will enable us to test the hypothesis that SNPs in CNS disorder candidate genes that affect gene expression also contribute to ADHD symptoms or determine response to drug therapy.