GENETICS OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Maximilian Muenke, M.D.

Chief, Medical Genetics Branch, Director, Medical Genetics and Genomic Medicine Residency and Fellowship Programs, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, U.S.A.

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental behavioral disorder, affecting about 10% of children and adolescents worldwide. It frequently persists into adulthood and can have serious life-long health consequences. Affected individuals are at increased risk for poor educational achievement, low income, underemployment, legal difficulties, and impaired social relationships. The annual societal burden of ADHD was conservatively estimated to reach $42.5 billion in the U.S. In addition, ADHD increases the risk of substance use disorder (SUD) and disruptive (externalizing) disorders such as oppositional defiant disorder (ODD), conduct disorder (CD). SUD is characterized by compulsive drug seeking behavior and drug use in the face of severe adverse consequences. The World Health Organization estimates that there are worldwide at least two billion alcohol users, one billion tobacco users and almost 185 million illicit drug users. Genetic factors are strongly implicated in ADHD.

We initiated a clinical, neuropsychological, and molecular genetic study of ADHD. Our initial approach emphasized detailed phenotypic and linkage studies in large families from a genetic isolate. This led to the identification of ADHD and comorbid disorder (e.g. substance use disorders) susceptibility loci, namely 4q13.2, 5q33.3, 8p23.1, 11q22, and 17p11). (Arcos-Burgos et al. Am J Hum Genet 2004; Jain et al. Biol Psych 2007). We found and replicated the association between ADHD, including treatment response, and LPHN3 variants (Arcos-Burgos et al. Mol Psych 2010). We then demonstrated that an interaction between LPHN3 and a region on chromosome 11 (NCAM1, TTC12, ANKK1, and DRD2) doubles the risk for ADHD and predicts severity and long-term outcome (Jain et al. Mol Psych 2011; Acosta et al. Transl Psych 2011). We are now generating genotypes on samples already available in the lab as well as from samples from a cohort of individuals who have been followed for 16 years as a part of the NIH MTA (Multicenter Treatment Assessment) study in order to define a genetics-symptoms-function-treatment predictive framework as a step towards personalized medicine for children and adults who have ADHD.