UNIVERSITY of WASHINGTON
PSYCHIATRY & BEHAVIORAL SCIENCES
School of Medicine

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Faculty Profile

Summary of Research Program:

I am a geneticist and Internist/Medical Geneticist and for the past 20 years a major focus of my research has been the genetic basis of neurologic and developmental disorders. In a long-term collaboration with Dr. T. Bird, a clinical neurogeneticist, we have used many molecular and statistical genetic approaches to map and identify genes for multiple disorders. This process now mainly utilizes exome sequencing. Currently we are studying four disorders whose causative genes we discovered. 1). Mutations in adenylate cyclase 5 cause a broad range of movement disorders (ADCY5-related Dyskinesias). We are investigating the relationship between genotype and phenotype by in vitro functional studies and clinical assessments. We have shown that two of the mutations cause increased cAMP accumulation in stimulated conditions in transfected cells. We are planning studies to explore the upstream effectors with the hope to identify therapeutic targets. We are generating a molecular inversion probe panel to screen patients with movement disorders to identify additional cases. 2) SCA14 is caused by mutations in protein kinase C gamma. We have generated 3 lines of human-BAC transgenic mice, wild-type and two mutants, in which to study the pathogenesis of the disorder. Although the mutant mice develop brain abnormalities at an early age, they manifest only mild neurologic problems. By breeding, we manipulated the dosage of human PRKCG and mouse prkcg and are now studying lines that have two copies of the human gene and only one functional copy of the mouse gene. Ongoing studies involve neurobehavioral testing and brain pathology. 3) Ataxia-pancytopenia syndrome. We very recently discovered the gene for this disorder and plan to investigate the effects of the two mutations we have found to date. 4) X-linked parkinsonism with spasticity (XPDS) is caused by a splicing defect in ATP6AP2, a gene that also causes a syndrome of intellectual disability and spasticity. We have generated iPSCs from 3 affected men for studies in neuronal cells. This project is headed by Dr. Korvatska. We are continuing the gene-finding endeavors for Charcot-Marie-Tooth disease type 2A, spastic paraplegia, hereditary neuralgic amyotrophy and spinocerebellar ataxias.

A second focus of the lab is to identify genes for component phenotypes of dyslexia. We have mapped locations for various phenotypes, including phonological decoding, spelling and rapid automated naming, modeled as QTLs. We have agreement from four other dyslexia research groups to form a consortium to share samples for a project to deep sequence the coding and regulatory elements within the linkage regions we have identified and in already proposed dyslexia candidate genes. We will use a statistical method that combines both common and rare variants in gene burden testing. The consortium will be actualized if the competitive renewal of the NIH R01 that supports the research is successful.