Characterization of a novel recessive ataxia gene

Randi M. Burns[1], Weiping Peng[2], Jishu Xu[2], Jun Z. Li[2, 3], and Margit Burmeister [2, 3, 4, 5]

(1) Cellular and Molecular Biology Graduate Program, (2) Department of Human Genetics, (3) Department of Computational Medicine and Bioinformatics, (4) Molecular and Behavioral Neuroscience Institute, and (5) Department of Psychiatry, University of Michigan, Ann Arbor, MI

Cerebellar ataxias are a heterogeneous group of neurological disorders with onset of symptoms occurring between early childhood and late adulthood. While the genetic causes of many forms of ataxia have already been identified, many more are still unknown, especially rare recessive forms. Heterogeneity – the large number of genes that can cause recessive ataxias – is the major reason why many genes for recessive forms are still unknown - individual families with essentially private mutations are too small to positively identify a chromosomal region by genetic linkage. By combining linkage, linkage disequilibrium, homozygosity mapping and next generation sequencing, we have identified a variant in an obligatory splice sequence (the first base of an intron is changed from GT to AT) in a consanguineous Turkish family affected with non-progressive, congenital ataxia. The gene is expressed in brain and blood-derived lymphoblastoid cell lines, but its function is not well established. This mutation is absent in 400 Turkish and American controls and >10,000 control DNAs (Exome Variant Server: http://evs.gs.washington.edu/EVS/). We have determined that this splice mutation causes skipping of an exon that is present in all isoforms and expression of the gene is lower in patients than controls, probably due to nonsense-mediated decay. Our results suggest that we have identified a novel gene causing recessive ataxia. We are currently analyzing this gene in other unexplained ataxia cases, and determining the effects of this mutation on mRNA expression and protein translation. Additionally, we are developing a zebrafish animal model to study this disorder.