Identification and Characterization of Genetic Factors Responsible for Cavitary Optic Disk Anomalies

Glaucoma is the second leading cause of blindness in America and its chief feature is progressive degeneration of the optic nerve. A major risk factor for glaucoma is elevated intraocular pressure (IOP), but glaucoma can occur at any IOP; glaucoma at normal IOP is called normal tension glaucoma (NTG). One way to study NTG is to investigate similar forms of optic nerve disease that also occur in the absence of elevated IOP. Cavitary optic disk anomalies (CODA) are associated with congenital excavation of the optic nerve that in some patients progressively deteriorate resembling the cupping seen in glaucoma. Based on the similarities between NTG and CODA patients, we are searching for the gene that causes CODA in a large family. Prior linkage studies mapped the CODA gene to a 13.5Mbp segment of chromosome 12q14. We have examined the linked region for the gene that causes CODA using comparative genome hybridization (CGH) and identified a 6kb heterozygous triplication of DNA found to be co-inherited with CODA in this pedigree and absent in normal controls. Subsequent analysis revealed a two-fold increase in expression when the 6kb segment transfected into HEK293T cells. We report a CNV within the previously linked region that is co-inherited with CODA in our family. We hypothesize that this CNV leads to dysregulation of gene expression and ultimately to the development of CODA.