A Novel Base-Pair Mutation of the CSPG2 Gene in a Family with Wagner Syndrome

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Purpose

Wagner syndrome (OMIM 143200) is an autosomal dominant vitreoretinopathy characterized by an optically empty vitreous cavity with fibrillary condensations, a preretinal avascular membrane, retinal perivascular sheathing, chorioretinal dystrophy, lattice degeneration, and high myopia, with a predisposition to retinal detachment and cataracts. Wagner syndrome has significant phenotypic overlap with other conditions, such as ocular Stickler syndrome type 1 (OMIM 609508). Stickler syndrome type 1 maps to chromosome 12q13.11-13.2, with associated COL2A1 gene mutations. Wagner syndrome maps to chromosome 5q13-q14 (WGN1 locus), with previously reported mutations in the CSPG2 gene confirming that this is a distinct syndrome. We report a three-generation Caucasian family with 6 affected individuals clinically diagnosed with Wagner syndrome, and screening for sequence variants in the COL2A1 and CSPG2 genes.

Methods

Genomic DNA samples derived from venous blood were collected from 9 total family members. Complete sequencing of COL2A1 was performed on the proband. Direct sequencing of CSPG2 was performed on all family member samples. Primers for PCR and sequencing were designed to cover all exons and intron-exon boundaries.

Results

No detectable COL2A1 mutations were noted, making the diagnosis of ocular Stickler syndrome highly unlikely for this family. A unique base-pair substitution (G>T) in intron 8 cosegregating with disease status was identified. This mutation occurs in a highly conserved previously reported splice site with a similar base-pair substitution (G>A). Direct sequencing of this splice site mutation in 107 unrelated external controls revealed no variants, supporting the rarity of this base-pair change and its causation in Wagner syndrome.

Conclusions

CSPG2 encodes versican, a proteoglycan and component of human vitreous. This novel base-pair substitution is thought to cause deletion of exon 8 and formation of a truncated protein product as previously reported. Further mutation screening of CSPG2 in additional Wagner syndrome families is important for functional characterization.