Thrombospondin 1 missense alleles induce extracellular matrix protein aggregation and TM dysfunction in congenital glaucoma

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Glaucoma is a highly heritable disease that is a leading cause of blindness worldwide. Here, we identified heterozygous thrombospondin 1 (THBS1) missense alleles altering p.Arg1034, a highly evolutionarily conserved amino acid, in 3 unrelated and ethnically diverse families affected by congenital glaucoma, a severe form of glaucoma affecting children. Thbs1R1034C-mutant mice had elevated intraocular pressure (IOP) , reduced ocular fluid outflow, and retinal ganglion cell loss. Histology revealed an abundant, abnormal extracellular accumulation of THBS1 with abnormal morphology of juxtacanalicular trabecular meshwork (TM) , an ocular tissue critical for aqueous fluid outflow. Functional characterization showed that the THBS1 missense alleles found in affected individuals destabilized the THBS1 C-terminus, causing protein misfolding and extracellular aggregation. Analysis using a range of amino acid substitutions at position R1034 showed that the extent of aggregation was correlated with the change in protein-folding free energy caused by variations in amino acid structure. Extracellular matrix (ECM) proteins, especially fibronectin, which bind to THBS1, also accumulated within THBS1 deposits. These results show that missense variants altering THBS1 p.Arg1034 can cause elevated IOP through a mechanism involving impaired TM fluid outflow in association with accumulation of aggregated THBS1 in the ECM of juxtacanalicular meshwork with altered morphology.

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