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Research discovers gene mutation causing rare eye disease

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Research conducted by Dr. Jayne S. Weiss, Professor and Chair of Ophthalmology at LSU Health Sciences Center New Orleans, and colleagues has discovered a new mutation in a gene that causes Schnyder corneal dystrophy (SCD.) The gene was found to be involved in vitamin K metabolism suggesting the possibility that vitamin K may eventually be found useful in its treatment. The findings are published in the February 2013 issue of the peer-reviewed journal, *Human Mutation*.

Schnyder corneal dystrophy is a rare hereditary eye disease that results in progressive loss of vision as abnormal deposits of cholesterol and other fats cloud the cornea. Affecting both eyes, it often requires corneal transplantation surgery.

Dr. Weiss is one of the world's leading authorities on the disease. She identified the largest group of people with SCD in the world and corrected misconceptions about the disease facilitating its diagnosis. Dr. Weiss and her colleagues discovered UBIAD1, the gene that causes SCD, in 2007 – a gene that is also involved in cholesterol metabolism. Their research continues to try to identify exactly how the disease develops.

Researchers suspected that the function of UBIAD1 might be related to the production of endogenous vitamin K. UBIAD1 was recently shown to trigger the production of menaquinone-4, or MK-4, the predominant form of hormonally active vitamin K in humans. Vitamin K is an important cofactor in blood clotting and bone metabolism. Cholesterol

heavily influences the proteins that work with vitamin K.

This study identified a new DNA mutation in UBIAD1 that substituted one amino acid with another in 51 members of six SCD families. The mutation, which alters enzyme function, is likely involved in causing the disease as it was found in 47 of 47 people with clinically diagnosed SCD and was not observed in 300 control individuals.

The research team also showed significantly reduced production of MK-4 due to SCD alteration of UBIAD1, and the association of UBIAD1 with enzymes involved in cholesterol production and storage, providing direct links between UBIAD1 and cholesterol metabolism that are likely involved in the development of SCD. These findings indicate that decreased MK-4 production by SCD-mutant UBIAD1 is a consistent biochemical defect associated with the accumulation of cholesterol observed in the corneas of SCD patients.

The current study indicates endogenous, intracellular MK-4 produced by UBIAD1 has a physiologic role in maintaining corneal health and visual acuity that is distinct from the role of dietary vitamin K in blood clotting. The finding of decreased MK-4 production by SCD mutant UBIAD1 suggests MK-4 supplements, potentially delivered by topical administration to the eyes, might be useful as a therapy to treat clouded corneas, or at least prevent the continued accumulation of cholesterol and lipids that are seen in SCD.

"Research like this helps us target new treatment or prevention approaches that may benefit not only people with Schnyder corneal dystrophy," notes Dr. Jayne Weiss, who also holds the Herbert E. Kaufman, MD Endowed Chair in Ophthalmology at LSU Health Sciences Center New Orleans and is Director of the LSU Eye Center. "Discovering a new component of the dynamic cellular cholesterol regulatory network gives us information that can be applied to every

disease arising from a defect in it. Besides Schnyder's corneal dystrophy, this includes many types of cancer."

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