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Genetic analysis of families with Schnyder corneal dystrophy identifies UBIAD1, an enzyme producing endogenous vitamin K, which interacts with enzymes regulating cholesterol synthesis and storage

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Schnyder corneal dystrophy (SCD) is an autosomal dominant disease characterized by deposition of cholesterol in the cornea, progressive opacification, and loss of visual acuity. Germline variants in UBIAD1 introducing missense alterations have been characterized in over 50 SCD families, including four large families from Finland who share a likely founder mutation. UBIAD1 was recently shown to catalyze synthesis of two mitochondrial electron carriers, menaquinone-4 (MK-4) and coenzyme Q10/ubiquinone (CoQ10). MK-4 is the predominant active form of vitamin K and an important cofactor in bone metabolism and blood clotting. We show SCD-altered UBIAD1 resulted in reduced MK-4 synthesis and molecular models indicated mutations disrupted active site residues and transmembrane helices. Yeast two-hybrid screening, co-immunoprecipitation, and confocal microscopy indicated interactions between UBIAD1 and HMGCR and SOAT1, enzymes catalyzing cholesterol synthesis and storage. Molecular modeling indicated cholesterol and geranylgeranyl diphosphate, a substrate for MK-4 synthesis, bind the same substrate binding cleft and likely compete for occupancy of UBIAD1. Vitamin K was originally identified by depletion of dietary cholesterol in chickens, which co-depleted dietary vitamin K, and resulted in hemorrhages and uncontrolled bleeding. In addition to a role for vitamin K in blood clotting, our data suggests a first physiologic role for endogenously produced vitamin K in maintaining cornea health and visual acuity. The data indicates synthesis of vitamin K, CoQ10, and cholesterol are tightly linked and may have significant impact on oxidative stress, vision, cardiovascular health, and cancer.

Biography

Michael L. Nickerson obtained a Ph.D. in Molecular Medicine from the George Washington University and has made significant contributions to the identification of disease genes, including the Birt-Hogg-Dubé gene in chromophobe kidney cancer, the dead-end gene in testicular cancer, the fumarate hydratase gene in leiomyomatosis and papillary kidney cancer, and the UBIAD1 gene in Schnyder Corneal Dystrophy (SCD). He has applied exome sequencing of tumor genomes to identify TET2 alterations in prostate cancer and BAP1 and CHD1 mutations in bladder cancer. UBIAD1 mutations in over 50 SCD families, and enzyme structure, function, and binding partners have been published.

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