Michael L Nickerson, J Mol Genet Med 2017, 11:2 (Suppl)
DOI: 10.4172/1747-0862-C1-014

Michael L Nickerson

National Cancer Institute, USA

Altered *UBIAD1* prenyltransferase function in Schnyder corneal dystrophy affects cholesterol metabolism and mitochondrial function

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 *UBIAD1* variants introduce missense mutations 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* results in reduced MK-4 synthesis and molecular models indicate mutations disrupt active site residues and transmembrane helices. Yeast two-hybrid screening, co-immunoprecipitation, and confocal microscopy show a physical interaction between *UBIAD1* and the cholesterol synthesis and storage enzymes HMGCR and SOAT1. Molecular models indicate cholesterol and geranylgeranyl diphosphate, a substrate for MK-4 synthesis, binding 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 vitamin K resulting in hemorrhages and uncontrolled bleeding. Our data suggests a first physiologic role for endogenously produced vitamin K in maintaining cornea health and visual acuity, in addition to its role in blood clotting. The data indicates that the synthesis of vitamin K, CoQ10 and cholesterol may be tightly linked with implications for vision, mitochondria function, cardiovascular health and cancer.

Biography

Michael L Nickerson has completed his PhD in Molecular Medicine at George Washington University. He has made significant contributions to disease gene identification using positional cloning, including an altered Birt-Hogg-Dubé gene in chromophobe RCC, fumarate hydratase in papillary RCC, the dead-end gene in testicular cancer, and the *UBIAD1* gene in Schnyder corneal dystrophy. More recently, he has sequenced urologic tumor genomes and identified alterations in TET2 in prostate cancer and the BRCA pathway in bladder and kidney cancer, which have been translated to a clinical trial starting in 2016. He is an active participant in Precision Medicine, ClinVar and the TCGA project.

nickersonml@mail.nih.gov

Notes: