Department of Human Genetics
2015 Summer Research In Progress
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“Long-chain Acyl-CoA Dehydrogenase SNP K333Q: The Good, the Bad, and the Unexpected”

Abstract:

Long-chain Acyl-CoA Dehydrogenase (LCAD) is a fatty acid oxidation flavoenzyme involved in mitochondrial energy metabolism in the lung. LCAD knockout mice have reduced pulmonary compliance due to alterations in pulmonary surfactant. There are no known patients with genetic LCAD deficiency. However, there is a missense polymorphism of unknown consequence, rs2286963 (K333Q) that is present in 21.1% of the general population. The SNP has been assumed to be benign, but we identified two cases of sudden unexplained infant death that were homozygous for K333Q and had no detectable LCAD antigen in the lung. Therefore, we hypothesized that the common K333Q polymorphism inhibits LCAD function and is a risk factor for lung disease. Recombinant LCAD K333Q was found to have significantly reduced enzymatic activity due to partial loss of the essential FAD cofactor, which is non-covalently bound to the protein. We solved the crystal structure of human LCAD and observed that the residue K333 is within interacting distance of the FAD cofactor in the active site. Addition of exogenous FAD to LCAD K333Q protein rescues the loss of activity, confirming this to be the mechanism. In human lung, LCAD expression is restricted to alveolar type II (ATII) cells. Primary ATII cells from individuals homozygous for K333Q have five-fold less LCAD antigen than ATII cells from wild-type individuals, suggesting that the K333Q variant is less stable in vivo. In keeping with a loss of function, spent media from K333Q-bearing human ATII cells contain higher levels of C14:1-carnitine, a lipid species that we have shown to be diagnostic for LCAD deficiency in the mouse model. We then sought to correlate presence of the K333Q SNP with human lung disease across the lifespan. First, 112 infants with unexplained respiratory distress syndrome (RDS) were genotyped and the allele frequencies compared to those of the ExAC database. There was a non-significant trend (P=0.098) for increased K333Q homozygosity. Next, 775 older children hospitalized for pneumonia were analyzed. Among these children the K333Q SNP was significantly under-represented, suggesting that fewer children with the SNP develop pneumonia. Finally, data from an elderly cohort with a mean age of 65 was analyzed across 7 measures of lung function. Unexpectedly, it was found that those with the K333Q SNP had increased lung function compared to those without the SNP. We postulate that while K333Q may predispose to surfactant deficiency and RDS in the very young—as we have observed in young LCAD knockout mice—it then becomes protective in older individuals due to suppressed inflammation in the lung. In support of this we have observed fewer alveolar macrophages in LCAD/- mice, we have seen decreased surfactant protein A antigen, and in a preliminary experiment LCAD/- mice infected with influenza developed significantly less inflammation and tissue damage than wild-type mice. Further studies are underway to examine measures of the immune system in the elderly cohort, as well as to establish the prevalence of K333Q, and its association with measures of the immune system, among additional cohorts with lung phenotypes.