Familial Defective Apolipoprotein B-100 in Lancaster County and Beyond

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INTRODUCTION

Familial defective apolipoprotein B-100 (FDB) is an autosomal co-dominant genetic disorder of lipid metabolism characterized by increased serum concentration of low-density lipoprotein (LDL) and elevated risk for premature atherosclerosis.[1,2,3] FDB arises from a pathogenic mutation that alters the native conformational structure of apolipoprotein B-100, thereby decreasing its affinity for the LDL receptor.[4] The reduction in LDL to LDL receptor ligand-binding affinity observed in FDB leads to insufficient endocytosis and degradation of LDL particles through a well-described clathrin-pit mediated mechanism in hepatocytes.[1,5] In contrast to the more than 1300 mutations in LDLR that cause autosomal dominant hypercholesterolemia, the vast majority of FDB cases worldwide are caused by a low number of common mutations in a small region of APOB known as a "mutational hotspot."[6-11] By far the most frequent of these mutations is the missense substitution of glutamine for a wild-type arginine at codon 3527 of APOB, known as p.Arg3527Gln or R3500Q.[12,13]

PREVALENCE

Investigators have detected the R3500Q mutations in over thirty countries worldwide, with a high concentration of carriers in central and northern Europe.[14-21] Switzerland, Germany, the Czech Republic, and Slovenia are thus areas with a high prevalence of R3500Q,[22-25] but the area that probably has the highest incidence worldwide is not in Europe, but in our own Lancaster County, Pennsylvania. In 2010, population screening of members of the Old Order Amish community revealed that approximately 12% of the general Amish population carries R3500Q. This rate is consistent with a genetic "founder effect," whereby a population bottleneck reduces genetic diversity and increases the frequency of otherwise rare alleles.[26] As the authors of the 2010 study observe, the mutation was likely carried to Lancaster County by one of three hundred German-speaking Swiss members of the Old Order Amish Church. The gene flow rate of R3500Q into the wider Lancaster County community and its incidence among Lancastrians of Mennonite or Germanic heritage is at the moment undetermined. Still, other recessive genetic disorders associated with the Amish have previously been found in non-Amish Lancastrians, and all newborns in the state are screened for diseases associated with the Amish such as glutaric aciduria and maple syrup urine disease.[27] As an analogous yet dominantly inherited disorder, the effect of FDB due to R3500Q on countywide health has considerable significance for the ongoing Lancaster General Health Familial Hypercholesterolemia Initiative.

CONSEQUENCES

In addition to the increased risk from elevated LDL-C, R3500Q has been independently associated with increased coronary artery calcification (CAC), and it appears at a higher rate among patients with ischemic heart disease than in the general population.[26,28] Carriers of R3500Q tend to display greater CAC even at lipid levels equivalent to those of their non-R3500Q peers. Population testing in Switzerland determined that carriers of R3500Q had rapid increases in LDL-C beginning early in life, leading to longer arterial exposure to hyperlipidemia.[23] Furthermore, the R3500Q genotype is associated with reduced LDL particle size and increased LDL circulation time, a marker for the oxidative state of LDL particles.[29,30] An atherogenic shift in lipid profile markers may also contribute to the independent association of R3500Q with CAC and ischemic heart disease.

Due to the similar clinical presentation of FDB and familial hypercholesterolemia (FH) associated with mutations in LDLR, the genetic locus encoding the low-density lipoprotein receptor protein (LDLR), standard diagnostic criteria for FH often include the molecular determination of a mutation

in APOB as diagnostic of FH. Phenotypic screening performed using the aforementioned standard criteria also utilizes identical criteria for the assessment of the probability of carrying a mutation in APOB and LDLR.[31] Despite this conflation of APOB and LDLR mutations as "familial hypercholesterolemia," population testing and family screening have frequently shown that FDB presents with milder and more variable hypercholesterolemia than that often observed in carriers of mutations in LDLR, an effect accentuated in younger patients.[32-35] Therefore, phenotypic criteria designed for the detection of FDB as opposed to LDLR-caused FH may be necessary to diagnose a greater share of FDB carriers.

CONCLUSIONS

R3500Q represents an opportunity for a paradigm shift in public health within and outside of Lancaster County. Wider-scale genetic testing, rather than reliance on fluctuating and imprecise phenotypic markers, will undoubtedly contribute to higher quality patient care and improved outcomes in R3500Q carriers. This opportunity follows the long-theorized yet infrequently realized trend towards genomic or individualized medicine. Lancaster General Health may now improve the health of the patients we serve and become a global leader in public health genomics by increasing awareness of, and screening for, R3500Q.

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