Cardiovascular Twist to the Rapidly Evolving Apolipoprotein L1 Story

Martin Farrall

Blacks form the largest (13%) ethnic minority group in the United States with predominant ancestry from subsaharan Africa. This group experiences multiple health disparities, for example, they have relatively high death rates for chronic kidney disease, cardiovascular disease (CVD), and stroke with hypertension as a particularly prevalent risk factor. An appreciable proportion of the disparity can be explained by inequalities in social and environmental factors, but there remains plenty of room for population-level differences in genetic susceptibility to make an important contribution. To test this hypothesis, Ito and colleagues1 have undertaken DNA sequence analysis of a candidate apolipoprotein gene (APOL1) in black cohorts and report ancestry-specific genetic associations with CVD. The decision to examine APOL1 in this context is in itself an intriguing tale that merits reflection.

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The apolipoprotein L gene family comprises 6 genes clustered on human chromosome 22q.2 Apolipoprotein L1 is the only member that includes a signal peptide, and with apolipoprotein A1, is secreted into a particularly dense subspecies (HDL) of high-density lipoprotein (HDL) particles.3 APOL1, along with its immediate genomic neighbors APOL2, APOL3, and APOL4, has only been found in primate genomes.4 All 6 apolipoprotein L genes contain characteristic protein domains that imply important intracellular physiological roles possibly involving ion transport and apoptosis.5 Primates benefit from the innate immune ability of apolipoprotein L1 to lyse the Trypanosoma brucei brucei protozoa that cause African trypanosomiasis (sleeping sickness).6 This lysis property is derived from the affinity of apolipoprotein L1 for lysosomal membranes where it forms ion-transporting pores after circulating HDL, has been engulfed by the parasite.6 However, relationships between hosts and parasites are subject to strong evolutionary forces, and the subspecies T. b. rhodesiense and T. b. gambiense have adapted to become resistant to apolipoprotein L1 and infect humans. In a further twist, genetic variants that encode nonsynonymous (p.S342G and p.I384M) or in-frame deletions (p.NYK388K) alleles in human APOL1 have arisen but can lyse T. b. rhodesiense.7 These variants are frequent in Africans but absent in populations of European or Asian ancestry (http://browser.1000genomes.org). Curiously, the APOL1 variants confer susceptibility to chronic kidney disease (CKD) with a 7-fold increase in risk for hypertension-attributed end-stage kidney disease in blacks.7 Together with evidence for positive (evolutionary) selection across the APOL1 genomic region, Genovese and colleagues7 propose that the high prevalence of CKD in blacks is an unfortunate consequence of a rapidly evolving innate immunity mechanism.

On this background, Ito and colleagues1 sought links between genetic variation in APOL1 and coronary artery disease and stroke. The authors first studied a couple of thousand DNA samples collected through the Jackson Heart Study (JHS), a community-based cohort of blacks living in the southern United States. The JHS is a longitudinal epidemiological study with detailed clinical, biochemical, hematological, and imaging data apposite to cardiovascular and renal disease. High-throughput (so-called next-generation) sequencing was an efficient and contemporary technique to scan the 1.2 Kb exonic (ie, protein-encoding) portion of APOL1, an approach that can thoroughly survey genetic variation both in terms of type of variant (eg, nucleotide substitution, insertions, or deletions) as well as the full spectrum of allele frequency from unique mutations to common polymorphisms. Thirty-two sequence variants were identified, two thirds of these were rare (frequency<0.1%) comprising mostly nonsynonymous and the occasional nonsense or frame-shift mutation but there was insufficient data to generate conclusive results for the low-frequency variants. There was more mileage in the analysis of the common variants, the nonsynonymous APOL1 variants (p.S342G and p.I384M), and the 6 bp deletion allele (p.NYK388K) showed a strong association with CKD with a recessive-pattern consistent with the previous study.7 The authors then analyzed their CVD data and found that a double dose of the common variants roughly doubled an individual’s risk of coronary disease or stroke, revealing a new pleiotropic dimension to APOL1. For example, in a survival analysis of major adverse cardiac events, the hazard ratio for JHS individuals carrying 2 risk alleles was 1.8 in an analysis that was adjusted for classic cardiovascular risk factors as well as CKD. This finding was confirmed in a replication study of 749 blacks collected through the Women Heath Initiative (WHI) clinical trial (hazard ratio=3.2).

The genomes of blacks are well known to be admixed with 15% European contribution; much of which has haunting associations with slavery. There is substantial variability in the level of admixture across the United States, those living in Southern states have been found to carry 24% autosomal admixture.9 The 3 common APOL1 variants have strikingly different allele frequencies in the ancestral subsaharan African
(up to 40%) and European populations (0%), so there is an obvious opportunity for population stratification to confound genetic association studies in blacks. The impact of the confounding will be proportional to the increased prevalence of disease contrasting blacks with Europeans (ie, 2- to 3-fold for CVD and 5-fold for CKD). Recognizing this issue, the authors used genome-wide single-nucleotide polymorphism data to undertake a global ancestry analysis of each individual. This shows that there is considerable ancestry heterogeneity within the JHS and WHI participants, some of which could reflect variable autosomal admixture (see Online Figure I). Global ancestry metrics, when included as covariates in the statistical models, reduce the confounding effects of admixture in association analyses and control the type I error rate.10 Remembering that every individual’s genome is a unique mosaic of different ancestries, there are however plausible scenarios where such a global ancestry adjustment can actually reduce power to detect a true disease association. This might (at least partially) explain why the magnitude of the APOL1–CVD association in JHS (odds ratio=2.6) was substantially lower than previous estimates7 although systematic phenotype differences provide another potential explanation.

In terms of potential explanations of the APOL1-encoded susceptibility to CVD, the authors found no evidence for mechanisms involving classic risk factors. This is perhaps surprising given the striking APOL1 association with hypertension-attributed kidney disease, and the presence of apolipoprotein L1 in HDL particles. But the APOL1–CVD association was statistically independent of hypertension status or HDL-cholesterol levels. That said, a recent Mendelian randomization study of heritable HDL-cholesterol levels did not support a direct (causative) mechanism to explain the association.8 This might (at least partially) explain why the magnitude of the APOL1–CVD association in JHS (odds ratio=2.6) was substantially lower than previous estimates7 although systematic phenotype differences provide another potential explanation.

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