Variation in \textit{APOL1} Gene May Contribute to High Rates of Kidney Disease in African Americans

Nicole L. Glazer, PhD


Study Hypothesis

African Americans have much higher rates of kidney failure than those of European ancestry. Previous genetic studies found variation at or near the \textit{MYH9} gene to be associated with increased risk of focal segmental glomerulosclerosis (FSGS) and hypertension-attributed end-stage kidney disease (H-ESKD), but the causal mutations in \textit{MYH9} were not identified. The authors hypothesized that the kidney disease risk alleles might be located in a genomic region larger than previously thought, due to a strong signal of natural selection in the region containing the \textit{MYH9} and \textit{APOL1} genes.1

How Was the Hypothesis Tested?

Sequence data from the 1000 Genomes Project was used to identify polymorphisms with large frequency differences between Africans and Europeans. These variants, together with some additional single-nucleotide polymorphisms of biological relevance, were genotyped using Sequenom technology. Initial association analyses were done comparing 205 African Americans with biopsy-proven FSGS but no family history of FSGS with 180 African American control subjects. Thirty-six variants were chosen for association testing the association in the larger cohort of H-ESKD cases and control subjects, with G1 and G2 emerging as the strongest association signals. After controlling for both G1 and control subjects; allele G2 had a frequency of 23% in cases and G1 and G2, no residual association with \textit{MYH9} single-nucleotide polymorphisms remained. The mode of inheritance of kidney disease was determined to be recessive. Comparing participants with no risk allele to participants with 1 risk allele (G1 or G2) conferred an odds ratio of 1.04 (95% confidence interval, 0.63 to 2.13) for FSGS and 1.26 (95% confidence interval, 1.01 to 1.56) for H-ESKD. Comparing participants with zero or 1 risk allele with participants with 2 risk alleles conferred an odds ratio of 10.5 (95% confidence interval, 6.0 to 18.4) for FSGS and 7.3 (95% confidence interval, 5.6 to 9.5) for H-ESKD. Comparisons of allele frequencies across HapMap populations revealed that G1 was present in 38% of Yoruba chromosomes but not in any from European, Japanese, or Chinese individuals. Likewise, G2 was detected in 8% of Yoruban individuals but not in any of the other groups. These
data, along with data from tests that detects selection, suggested that the prevalence of G1 has risen quickly in the past 10,000 years as the result of natural selection, with the variant loci exhibiting longer patterns of LD. The APOL1 gene codes for the blood protein ApoL1, which is a serum trypanolytic factor that confers resistance to the subspecies of T. brucei (“sleeping sickness”), T. b. brucei. Plasma samples with various combinations of G1 and G2 genotypes efficiently lysed T. b. brucei, but none of them lysed T. b. gambiense. However, both APOL1 variants lysed T. b. rhodesiense, a subspecies that is normally completely resistant to ApoL1 lytic activity. These results were confirmed with recombinant ApoL1 proteins.

Implications
The authors provide strong evidence that sequence variation in APOL1 gene is highly associated with kidney disease risk in African Americans that was previously attributed to MYH9. Given the lytic activity of the kidney disease variant proteins against Trypanosoma, the authors speculate that these variants may have arisen as the result of recent selection pressures. Similar to sickle cell disease, this may be an example of genetic variants causing common disease while playing a role in the protection against infectious disease. It is not yet known, however, through what mechanism this genetic variation contributes to kidney disease, and unraveling the biological pathways will be of great importance in the prevention and treatment of renal disease in African Americans.

Disclosures
None.
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