Variation in APOL1 Gene May Contribute to High Rates of Kidney Disease in African Americans

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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 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 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 MYH9 and 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. After determining that the strongest genetic association with FSGS was clustered in the APOL1 gene region, multiple logistic regressions were performed controlling for the strongest signals to identify the 2 independent sequence variants, termed G1 and G2. Next, the association of APOL1 variants and renal disease was tested in a larger cohort of 1030 African American H-ESKD cases and 1025 geographically matched control subjects. Thirty-six variants were chosen for association testing, based on strongest signals of positive selection in the region, along with nearby coding variants including G1, G2, and putative MYH9 risk single-nucleotide polymorphisms. Association analyses were performed using the Fisher exact test and logistic regression. To test for their potential contribution to selection, G1 and G2 were genotyped in 180 Yoruba samples from HapMap3, and selection was detected using statistical tests that evaluate differential degrees of linkage disequilibrium (LD) surrounding the assumed selected allele compared with the LD around the alternate allele. Finally, because APOL1 encodes apolipoprotein L-1 (Apol1), a trypanolytic factor that confers resistance to Trypanosoma brucei, 75 human plasma samples with different combinations of G1 and G2 genotypes were analyzed for their in vitro lytic potential on 3 subspecies of Trypanosoma: T b brucei, T b rhodiense, and T b gambiense. Results were confirmed using recombinant Apol1 proteins.

Principal Findings
The most significant associations with FSGS were clustered in a 10-kb region in the last exon of APOL1. The strongest signal ($P = 1.07 \times 10^{-23}$) was obtained for a 2-locus allele, G1, consisting of 2 nonsynonymous coding variants, rs73885139 and rs60910145, that were in perfect LD. Another strong independent signal, G2, was also identified close to G1 in APOL1, a 6-bp deletion (rs71785313) ($P = 4.38 \times 10^{-7}$). Allele G1 had a frequency of 52% in FSGS cases and 18% in control subjects; allele G2 had a frequency of 23% in cases and 15% in control subjects. Results were similar when 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 G2, no residual association with 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. rhodiense*, 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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