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Interpreting Genetic Testing Results for AMKD: How Do We Assess Disease-Causing Variants?

Announcer:
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Dr. Pollak:
Hi. I'm Martin Pollak from Harvard Medical School and Beth Israel Deaconess Medical Center. And I'm going to talk today about interpreting genetic testing results for APOL1-associated kidney disease. How do these two APOL1 alleles cause increased susceptibility to kidney disease? But more important to today's talk is, how do we recognize these variants? And how do we decide whether a person has a high-risk APOL1 genotype or not?

So, this slide shows the APOL1 genotype frequencies in people who are African American. What we call the G0/G0 genotype, the genotype, where a person does not have any copy of the risk variant APOL1 is about 50 to 55% among African Americans. If we look at the numbers, the percentages of people who are heterozygous for either G1 or G2, it's about 35%, again, among African Americans. About 13% of African Americans have two risk variants. So either a G1/G1 genotype, a G2/G2 genotype, or a G1/G2 genotype. These three genotypes that I've illustrated in red are the kidney disease, high-risk genotypes.

Now, it's important to point out these are really not tied to race per se. We think that the G1 and G2 variants in APOL1 had developed in western Sub-Saharan Africa, about 5,000 to 10,000 years ago. And so, these variants are more common in people have recent African ancestry than in other populations. And in the United States, there's considerable overlap between people of recent African ancestry, and the population that identifies as African American.

Now, it's important to point out that there's a lot of variation in APOL1 besides the variants that define G1 and G2, we really think of G1 and G2 as alleles, rather than variants, although we always talk about them as these risk variants or G1 and G2 variants. From left to right on this grid, you see the different amino acids that are somewhat variable among populations that define quite a number of different haplotypes. The point here is that the G1 and G2 forms of APOL1 exists on specific haplotype backgrounds. This is different from some of the commonly observed haplotypes lacking the risk allele to finding variants. So, while we can talk about G0, G1, and G2, and for most purposes, that's totally adequate, the variation in APOL1 is somewhat more complicated.

Now APOL1 variants increase the risk of several different forms of kidney disease. Of course, there are all sorts of ways we define kidney disease. We can define it histologically, we can define it mechanistically, we can define it by clinical syndrome. If you look at the left of this figure, the certain very well defined, very specific phenotypes are really highly associated with APOL1, these include interferon-associated FSGS. FSGS That develops after therapeutic treatments interferon, COVID-19-associated collapsing nephropathy, HIV-associated nephropathy.

These are all very highly associated with high-risk APOL1 genotypes with odds ratios of 29 or greater. Odds ratios for development of FSGS are also high are. So for FSGS, the odds ratios are about 17. For what we call hypertension-attributed end-stage renal disease. Odds ratios are more on the order of 7 to 11. And as we move farther to the right in this diagram and talking less well defined, more

clinically fuzzy phenotypes, these odds ratios are somewhat lower. So, for example, the odds ratio for development of nondiabetic chronic kidney disease in adults is about 1.5 to 2. For things like IGA nephropathy, it does not appear to be any increased risk of kidney disease in association with high-risk APOL1 genotypes.

So, typically, when a clinical laboratory reports the results of an APOL1 test, they report whether the individuals G0, G1, G2 genotypes and the combination. So here are three examples from one commercial tester. On the upper left, we see what's called a positive finding here. In gene APOL1, this lab reports the inheritance as being complex, reflecting the fact that not everyone who inherits a high-risk APOL1 genotype, in fact, gets disease. So, although it follows a recessive pattern
inheritance, it's not a Mendelian disease. And then this person is heterozygous for the G1 allele, as illustrated in the fourth column, and the G2 allele. So this person inherited G1 from one parent, and G2 from the other parent. So this person has two risk alleles, and they have a kidney risk-associated APOL1 genotype.

In the example in the middle, here again, is the result of APOL1 testing, a positive result. This individual in the fourth column variants, we see that this person has two copies of G2, this person is homozygous for G2. So he or she inherited a G2 allele from both parents. And again, this person has a high-risk APOL1 genotype.

Lastly, on the bottom right, we see a result that is not positive. Here we have an individual who is heterozygous for a G1 allele. Again, in the variants column, number four, you see that this person is heterozygous for both the serine 342 glycine, and isoleucine 384 methionine G1-defining pair of variants. So this person has one risk allele, so they could pass on a risk allele to their children. But this person, since they only have one copy of a risk variant, they do not have a high-risk genotype. They're a carrier, a high-risk allele, but they don't have a high-risk APOL1 genotype. I will end there. And thank you very much for your attention.

Announcer:
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