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Talking Rare: Epidemiology and Pathogenesis of APOL1-Mediated Kidney Disease

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Talking Rare: Epidemiology and Pathogenesis of APOL1-Mediated Kidney Disease” is provided by Prova Education.

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Dr. Pollak:
The mechanisms by which APOL1 variants cause kidney disease is still under very active exploration as is the related question of why only a subset of those people with high-risk APOL1 genotypes develop overt kidney disease.

This is CME on ReachMD. I'm Dr. Martin Pollak.

Dr. Nicholas:
Hi, and I'm Dr. Susanne Nicholas. And you're right, Martin, we also need to better identify individuals who are carriers of APOL1 risk alleles. Having that type of information could help us administer targeted therapies specific for APOL1 and prevent the progression of APOL1-mediated kidney disease.

Dr. Pollak:
So, Susanne, let’s first talk about the evolving story of APOL1-associated kidney diseases by first talking about some of the interesting aspects of the genetics of these diseases along with populations at risk.

What should we know about APOL1 risk alleles and the population at risk?

Dr. Nicholas:
Well, I'd like to start by saying that APOL1, or apolipoprotein L1, is a genetic signal on chromosome 22 that codes for a protein identified in 2010 that was earlier linked to hypertension-related kidney failure and FSGS-related kidney disease in patients of African ancestry. As such, APOL1-mediated kidney disease, or AMKD, contributes to significant disparities in CKD [chronic kidney disease], particularly in patients with non-diabetic kidney disease.

When we look at the global burden of CKD, 1 in every 10 individuals, or approximately 844 million people, may have chronic kidney disease. And while in the US, Black or African American individuals make up 13% of the overall population, they constitute up to 35% of cases of kidney failure. In fact, Black and African American individuals tend to have more risk factors for CKD, higher incidence of CKD, more rapid progression, as well as an earlier age of onset of CKD compared to whites.

And while the most common causes of CKD are diabetes followed by hypertension, up to about 9% of CKD may be due to genetic causes. The APOL1 risk genetic variants, termed G1 and G2, are actually found worldwide. And they evolved in Sub-Saharan Africa as protection against African trypanosomiasis, or African sleeping sickness. And it was really the transatlantic slave trade and the more recent great migration that led to the global distribution of APOL1 risk variants.

Therefore, it's really individuals of African ancestry – in other words, individuals in whom their country of origin is Sub-Saharan Africa – and not just those who self-identify as Black based on their skin color may be eligible for genetic testing for APOL1-mediated kidney disease. As such, people from the Caribbean, Central America, and South America may also be eligible for APOL1 genetic testing.

In the US, more than 30% of African Americans have at least 1 APOL1 risk variant, while up to 13% of African Americans have 2 of the risk variants. In the Caribbean and South America, the population frequency may be about 1% to 10%. Interestingly, though, individuals with 2 APOL1 risk variants are at higher risk of developing APOL1-mediated kidney disease and may have a more rapid progression of kidney disease compared to individuals with either 1 or 0 APOL1 risk variants. But not everyone with 2 APOL1 risk variants will develop AMKD. The reason is because of the second-hit theory, which requires another environmental factor, such as infection or inflammation, to trigger the disease.

In general, the disease affects probably about 40,000 people in the US and 100,000 people in both the US and Europe. But I think these numbers may be an underestimate.

Dr. Pollak:
So, of course, APOL1 and these high-risk APOL1 genotypes are associated with a variety of kidney phenotypes as traditionally defined – really well-defined entities like COVID-19-associated kidney disease and HIV-associated nephropathy are highly associated with these high-risk genotypes. Essentially, it's barely an exaggeration to say that people without these genotypes do not get HIV-associated nephropathy and COVID-19-associated nephropathy; it's not quite true, but it's almost true. The effect of these variants is so overwhelming.

For more common forms of kidney disease, these odds ratios are not as high. But nevertheless, these variants seem to play a big role in the susceptibility of people of Western Sub-Saharan African ancestry to kidney disease.

It's also clear that the majority of people with these high-risk genotypes don't, in fact, get overt kidney disease. So as you said, there's something – other factors must be involved. And these may be genetic, environmental, infectious. I mean, it's pretty clear that one sort of modifier or second hit, if you like that phrase, is a high-inflammatory state. High-inflammatory states, high-interferon states stimulate the expression of APOL1 and can lead to overt disease.

Dr. Nicholas:
So, Martin, could you tell us more about the underlying cause of AMKD and how we can identify it in patients?

Dr. Pollak:
So we think these variants in APOL1 that are associated with disease cause disease by a toxic effect, a gain-of-function effect of the encoded protein. So, you know, it's people with 2 of these risk alleles that are at high risk of disease. So it's inherited as essentially as a recessive trait. We believe that these G1 and G2 variants are toxic to cells in which this protein is present. Perhaps the best mechanistic hypothesis is the notion that APOL1 encodes the membrane channel and ion channel, and activity of this channel is altered by the presence of these variants. But there's also data suggesting that the mRNA encoded by the gene is the function of the RNA and its impact on some downstream signaling pathways are altered. There's been some suggestion that variant APOL1 affects the endoplasmic reticulum stress response, that it affects mitochondrial activity. So this is still an evolving area of investigation.

As I mentioned earlier, there's a huge spectrum of clinical presentations of disease associated with high-risk APOL1 genotypes. Things that are very highly associated are things like focal segmental glomerulosclerosis, HIV-associated nephropathy, COVID-19-associated nephropathy. These odds ratios are less overwhelming for things like hypertension-associated end-stage kidney disease, but they're still strong.

In terms of identifying high-risk alleles and high-risk genotypes, you know, APOL1, there are really 2 alleles that are common and that we care about for making this kind of genetic diagnosis, what we call G1 and G2. So we can do targeted testing; we don't need to sequence an entire genome or sequence an entire gene. At a technical level, it's about as simple as you can get looking for the presence or absence of these variants.

As to whether, when, and who should look for this genetic diagnosis and when it should be made, you know, that's controversial. I think there is going to be increasing data and evidence about how we treat the subset of kidney diseases and how we might treat it differently from other diseases that are not driven by APOL1. And so I think it's going to be increasingly important that we identify high-risk APOL1 genotypes, the presence or absence of these genotypes in people with kidney disease. I think a lot of the data will emerge on this topic in the next few years.

Dr. Nicholas:
Well, as you know, genetic screening for AMKD is not considered standard of care and requires a high degree of suspicion in those with

chronic kidney disease. Therefore, APOL1-mediated kidney disease screening really begins with testing for CKD with a spot – preferably early morning – urine albumin for albumin-to-creatinine ratio, and a blood test for EGFR determination based on either the serum creatinine or a cystatin C. And since testing for CKD is already suboptimal, it's not surprising that genetic testing for AMKD is underutilized. The types of individuals who really should be tested include those with hypertension-associated chronic kidney disease or those who develop CKD at a younger age, or essentially anyone of African ancestry with CKD, with or without significant proteinuria.

So for those tuning in, you're listening to CME on ReachMD. I'm Dr. Susanne Nicholas, and I'm here today with Dr. Martin Pollak. We're discussing the epidemiology and pathogenesis of APOL1-mediated kidney disease and potential new therapies on the horizon.

Dr. Pollak:
So now that we've discussed the genetics of APOL1 and the clinical manifestations of these genetic variants and specific high-risk genotypes, Susanne, maybe you can tell us about some of the possible therapies being studied.

Dr. Nicholas:
Of course. Well, as you can imagine, in order to better understand the manifestations of APOL1-mediated kidney disease, there are a number of clinical trials focused on genetic testing for APOL1 in vulnerable patients, such as those with sickle cell anemia and in kidney donors. Only a minority of studies, though, are focused on testing new therapies for AMKD.

And one of the studies I'd like to tell you more about is a phase 2/phase 3 clinical trial of an investigational drug called inaxaplin, or VX-147. This study is an international double-blind, placebo-controlled clinical trial designed to evaluate the efficacy, safety, tolerability, and the pharmacokinetics of VX-147 in participants who are between the ages of 18 and 60 years with AMKD, an elevated urine protein-to-creatinine ratio between 0.7 and less than 10 g of protein/g of creatinine, and EGFR is between 25 and lower than 75 mL/min for 1.73 m^2, who are already receiving stable standard of care therapies.

This study began earlier this year, and it will end in June 2026. And it's estimated to recruit 466 subjects. In the phase 2 part of the study, 66 participants will have received 1 of 2 doses of VX-147 or placebo for about 12 weeks. And following those results, subjects will receive a single dose of VX-147 or placebo in the phase 3 part of the study, which will last until the study ends.

The primary efficacy endpoint is the percentage change in urine protein-to-creatinine ratio and the EGFR slope from baseline to 48 weeks, which constitutes a planned interim analysis. But in addition, the primary endpoint will look at the percentage change in the EGFR slope between the baseline and the end of the study.

There are other secondary endpoints that include the time to achieving a composite endpoint of a sustained decline of at least a 30% reduction in EGFR from baseline, the onset of kidney failure, or death. And in addition, this study will also assess the safety, tolerability, and pharmacokinetics.

The way that the drug actually works is to block the function of the APOL1 protein, which, as you know, is responsible for the type of kidney injury and/or cell death that leads to glomerular damage that's associated with APOL1-mediated kidney disease.

Dr. Pollak:
So, you know, there are a lot of challenges here; APOL1-associated kidney disease is quite heterogeneous. It's kind of a unique gene in that these variants are quite common. And the risk associated with these genotypes is very large. That's not typical for inherited kidney diseases. You know, I think there's a lot of information that we will learn in the coming years about the impact of early diagnosis, pre-symptomatic diagnosis, genetically how this affects the optimal treatment in the setting of patients who come to see us in clinic, patients who are getting kidney transplants, and a variety of other clinical scenarios.

So this has been fun. But before we finish, Dr. Nicholas, can you maybe share one take-home message with our audience?

Dr. Nicholas:
So I have at least two take-home points. One, that individuals of African ancestry, not just those who self-identify as Black based on their skin color, with non-diabetic chronic kidney disease, those with a family history of CKD, and those who may have family members diagnosed with AMKD, should be considered for genetic testing.

And the second take-home point is that providers should have a high suspicion for CKD testing for genetic APOL1 risk variants in eligible individuals.

Dr. Pollak:
I think we're increasingly recognizing the importance of the high-risk APOL1 genotype in the development of kidney disease, particularly in people of recent West Sub-Saharan African ancestry. I think we're going to learn a lot in the coming years about how best to take care of patients with these diseases.

Unfortunately, that's all the time we have, so I want to thank our audience for listening in and thank you, Dr. Susanne Nicholas, for joining me and sharing your insights. It was fun to talk today.

Dr. Nicholas:
Well, thank you, Dr. Pollak, for the opportunity to engage in this very enlightening and informative discussion.

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