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Genetic Testing in PAH: Cascade Genetic Testing Approach

Announcer:
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Dr. Rajagopal:
So hello, my name is Sudarshan Rajagopal, and I'm Co-Director of the Pulmonary Vascular Disease Center at Duke University School of Medicine. And today I'll be talking to you about genetic testing in PAH the approach of Cascade genetic testing. So let's go through a case here. BC is a 56-year-old female. She has been recently diagnosed with presumed idiopathic PAH. Her parents have passed away, but she has two siblings and two children of her own, as well as grandchildren. She is concerned about the risk of PAH to her family members. Should we offer her genetic testing?

So heritable PAH is only approximately 2% of cases of PAH, as you can see on the chart to the right. However, 25 to 30% of patients with idiopathic PAH, when tested, are found to have an underlying genetic cause. The most common cause for this in around 70% of cases are mutations in the gene BMPR2. But this is complicated because of incomplete penetrance. That is, not all patients who have the mutation will actually go on to develop the disease. So for example, for BMPR2, only around 14% of male carriers will go on to develop PAH, while 42% of females will develop PAH if they have a known mutation in BMPR2 that could cause the disease. So this is a bit complicated.

So there are a number of genes that have been associated with PAH. As you can see here on this timeline, the first gene to be identified was BMPR2. And this was followed by the identification of ALK1 and endoglin. And what - and from this, it was very clear that these mutations all targeted TGF beta signaling in one way or another, these are all receptors for BMPs and TGFs. Later, other mutations were identified in the same pathway, now downstream of the receptor to the transcription factors that they control, such as SMAD9 and SMAD1. And then later, other mutations were identified, such as in caveolin-1, the potassium channel KCNK3, TBX4, and then EIF2AK4, which was observed in pulmonary veno-occlusive disease. And new genes have – are – continue to be identified using approaches such as whole exome and whole genome sequencing.

So what approach do we take to test patients and their families for these mutations? And the general approach that we use is cascade genetic testing. And this is highlighted in this figure here. So let's look at the bottom left, where we have a patient, this lady who's labeled as “Me” in red, and she has been identified to have the disease. She's been tested genetically and found to have a mutation. Well, we would then test her siblings because they would also be at risk, but they actually don't have that mutation. We go further up the genetic tree and test their parents. And we test her mom and her dad, and her dad has that mutation. So we now know that her mom's side of the family is not at risk for having this mutation and having disease develop. But the dad’s side of the family does have that risk. So now we would test out the dad siblings. And luckily for them, Aunt Sarah does not have this mutation. And then going back to his parents, to grandma and grandpa, we see that the mutation arose in grandma, and not in grandpa. So grandpa’s side of the family is not at risk either.

So using this approach, you can specifically identify which people are at risk for the mutation and developing the disease. We would not

just test every single family member, but you would go up and down the genetic cascade, as shown here. So to summarize, while most registries report that only 2% of PAH is heritable, studies have shown that 25 to 30% of idiopathic PAH patients have an underlying genetic cause. And indeed, if we look at the ESC/ERS guidelines, they do recommend genetic testing in these patients. Unfortunately, there are large barriers to this testing in the United States due to insurance.

Now, if a patient is found to have a genetic cause for PAH, genetic testing can be offered to family members through cascade testing. For unaffected family members negative for a mutation, the risk of PAH is the same as for the general population, and that's very low, 15 to 50 per million. But for those with the mutation, they are at risk for developing PAH. Now it doesn't mean they are going to develop PAH, because we know a lot of these mutations have incomplete penetrance. But these patients in general should be monitored annually or using another approach where their exercise tolerances tested or through echocardiography.

So thank you for joining me for this program today.

Announcer:
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