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The Genetics of Migraine: Advancing Diagnosis and Personalizing Treatment

Mr. Quigley:
Welcome to *On the Frontlines of Migraine* on ReachMD. I'm Ryan Quigley with ReachMD, and joining me to discuss the future of genetic research and applications in migraine is Dr. Lyn Griffiths. She's a Distinguished Professor and the Director of the Centre for Genomics and Personalised Health at Queensland University of Technology.

Dr. Griffiths, thanks for being here today.

Dr. Griffiths:
Oh, you're most welcome, Ryan. I'm happy to be here.

Mr. Quigley:
So to start us off, Dr. Griffiths, how has our understanding of the genetic basis of migraine evolved in recent years?

Dr. Griffiths:
So when there was the first work undertaken on migraine genetics, a lot of people thought there might be one or two genes that might be involved in the disorder, and there hadn't been a lot of studies a few decades ago. But over the last couple of decades, there's been a lot of studies on the genetics of migraine. We now know that there are multiple genes involved in the disorder. We also know that migraine has a strong genetic basis.

So if you think about families, 90 percent of migraine sufferers have a close relative who suffers from the disorder—usually a first or second-degree relative. And if you look at twin studies and family data, even across various populations across the planet, you can see that probably about 60 percent of the disorder is due to heritable factors. So we do know that there are environmental triggers and other factors and that play a role, but it's believed that those triggers and environmental factors play a role across a genetic basis of migraine.

Mr. Quigley:
Now, polygenic risk scores are getting a lot of attention lately. What do they offer when it comes to migraine risk assessment and prediction?

Dr. Griffiths:
I think the first thing to think about when you're thinking about things like polygenic risk scores is, what type of migraine are you thinking about? There are, in fact, two specific types of migraine. There are monogenic forms of migraine, and these are due to single genes. These are the rarer, more severe types of migraine, like familial hemiplegic migraine.

We know that there are specific genes in specific families with specific causal mutations that result in these disorders, and we know the genes that are involved—not all of the genes, but we've got several of those that are now used routinely in diagnostics—and so you can define familial hemiplegic type 1 as due to mutations in a calcium channel gene—the CACNA1A gene. Type 2 is due to mutations in an ATPase gene—ATP1A2. And Type 3 is due to mutations in a sodium channel gene. We're also looking for other mutations because there are many families where there are no mutations in those three genes or even the fourth one, so there must be more genes.\

These are monogenic forms. If you have the mutation, then you have the disorder, and it runs in clear patterns through the family. However, the more common types of migraine are polygenic, and this means that there are multiple genes that are playing a role. They tend to interact together, and each of these genes has small effects. So it's called polygenic because it's not just a single gene; it's not monogenic.

And polygenic risk scores, which you mentioned before, have now been developed for these common types of migraine. We are not 100 percent sure whether we've got all those polygenic risk markers yet. There's over 120 loci that are involved at this stage. And we're also not really sure how clinically useful those polygenic risk scores are going to be at this stage, but I think over the next few years, that will evolve even more, and it will become much more clinically useful in defining some types of migraine too.

Mr. Quigley:
That's a really great overview and a very good preview as to just how complex this disorder really is.

For those just joining us, this is *On the Frontlines of Migraine* on ReachMD. I'm Ryan Quigley with ReachMD, and I'm speaking with Dr. Lyn Griffiths about the future of genetics in migraine care.

So if we zero in on personalized medicine, how might genetic profiles help us provide truly individualized care for migraine management?

Dr. Griffiths:
Well, again, if we look at the monogenic forms of migraine, they are absolutely essential for the diagnosis of that type of migraine. They're also really important for differentiating other sorts of related neurological disorders that may have migraine as one of the symptoms. So to differentiate those disorders, it's important to have a genetic diagnosis through things like DNA sequencing, and that genetic diagnosis will say, actually, is it familiar hemiplegic migraine, or is it a hereditary stroke disorder, like CADISAL, as an example. But it will also tell you what particular type of hemiplegic migraine it is, and that can give really good indications on what's the most appropriate treatment.

For the monogenic forms, we are currently using personalized approaches to migraine diagnosis and treatment now, and those tests are available for differentiation, but also for diagnosing the type of migraine and for guiding the clinical treatment. For the polygenic and more common types of migraine, I don't think we're quite there yet, but I think we will be. Once we define the polygenic risk scores that relate to specific subtypes of migraine and then use that information to that genetic profiling information to try and identify the appropriate treatment on that individual profile, I think we'll have more personalized approaches to medication for more common types of migraine. So that's certainly the growth area of the future.

Mr. Quigley:
And that's certainly very encouraging. So as we approach the end of our program, Dr. Griffiths, what are you most excited about as our approach to migraine care continues to evolve?

Dr. Griffiths:
Well, I'm quite excited about making sure that we get predictive medicine into the more common types of migraine. As I've mentioned, with the rarer types, I think it's there. Maybe it's not rolled out everywhere, but I think it's certainly started. But for the more common types of migraine, we haven't really started to do that. We really need to start taking genetic information into account in terms of diagnosis but also in terms of treatment, and I think that's really what's going to happen in the future—using genetic profile information to define the most appropriate treatment with the least adverse side effects rather than the current and often hit-and-miss approach to defining the appropriate treatment per migraine sufferer.

Mr. Quigley:
And that's a great comment for us to think on as we come to the end of today's program. I want to thank my guest, Dr. Lyn Griffiths, for joining me to discuss how understanding the genetics of migraine can help us better care for our patients.

Dr. Griffiths, it was excellent having you on the program today.

Dr. Griffiths:
You're most welcome, Ryan. Thank you.

Mr. Quigley:
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