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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

MS Pathogenesis: Understanding the Genetic & Environmental Triggers

Narrator:
Welcome to ReachMD. This is *On the Frontlines of Multiple Sclerosis*, brought to you by an independent educational grant from Merck KGaA, Darmstadt, Germany.

Dr. Birnholz:
This is ReachMD. I'm Dr. Matt Birnholz. Joining me today is Dr. Gavin Giovannoni, Professor of Neurology at Queen Mary University of London. On today's episode, we'll explore the challenges and opportunities for utilizing medical genetics in multiple sclerosis diagnosis and treatment. Dr. Giovannoni, welcome to you.

Dr. Giovannoni:
Thank you.

Dr. Birnholz:
So, to start, I'm fascinated in hearing more about this interplay between the genetic contributors and the environmental triggers for MS, because there've been some new understandings there, and I'd love to get a sense, if you can overview for us, what are the genetic contributors; what are the environmental triggers that we know about, at this point?

Dr. Giovannoni:
So, we know that there is a genetic risk to MS. Some people will argue that it contributes 30 or 60% of the susceptibility to the disease, and we've known about it since the 1970s. So, in the major histocompatibility complex, there was an antigen called DR2 and it's now DR1501 with the new nomenclature, and if you carry one of those alleles or one of those genes, it ups your risk by about 3 of getting the disease, and if you carry 2 of them it's about 6.5 higher than the background population. And then, in addition to that, using the whole genome-wide association studies, there's now about 150 to 160 variants in the genome that increase your risk, but their contribution is very, very small. The relative risks there are 1.1 to 1.3 say, nowhere near. So, it's dominated by the major histocompatibility complex which has also been seen in other autoimmune disease. In addition to that one, there are some MHC alleles that protect you from getting the disease. And so, if you've got the protective factors they often trump the at-risk factor. So, it is quite complicated. They call it the genetic architecture. But that's not sufficient to predict who's going to get the disease, because most people who carry the at-risk genes don't get MS. And so, you can't really go to the population and find out who's got these genes and say, "You're at high risk," because actually, it's not very predictable who's going to develop the disease. What's much more interesting is the environmental factors. And we now identify 3 main ones, and the others are probably linked. The main one is where you're born, latitude. And so, we think the risk is linked to probably sunlight and vitamin D metabolism, because people with low vitamin D levels are at higher risk. The other one is Epstein-Barr virus and that may be actually causal, because people who don't have Epstein-Barr virus don't get MS. And we think it may be latent infection, because people who get symptomatic EBV infection, that's infectious mono, have about a 2.4 times risk of getting it and the other risk factor is smoking. People who smoke are at 50% higher risk. Why, I think, the environment's more important, because migration studies show that if you're born in an area of the world where there's very low levels of multiple sclerosis, and you live there to an adult, then you migrate to a high-risk area, you're risk stays low. If you migrate as a child, you take on an intermediate risk. If you're born of parents that come from a low-risk area, your risk is usually similar to the new country where you're born. So, the environment, I think, is critical for this trigger.

Dr. Birnholz:
That's fascinating, because in the U.S. we talk often about the MS belt that's related to latitude. Just to help clear up any

misconstructions on my end, is that simply a latitude question that carries through that age-old concept of the belt, or is it actually something else?

Dr. Giovannoni:
No, I think it's both genetics, because different population groups are at higher risk than others. But it's also the latitude, and that actually is disappearing. The ratio from the north to the south United States is disappearing. But at the same time, the ratio of melanoma, which is a sunlight-linked, sun exposure-linked tumor, is disappearing. You used to be at a much higher risk of getting melanoma in the south versus the north, and it's disappearing. And we think it's because of behavioral change. People are using tons of sunblock and they're beginning to look after themselves in terms of sun exposure. And that's probably what's happening now, is by using sunblock and avoiding sunlight, we're getting increased incidences of vitamin D deficiency across the country, and that's probably what's driving this latitude gradient disappearing. And it's also disappearing in quite a few other countries that are monitoring it. So, I think that's how we're adapting to our environment, by using sunblock and avoiding sunshine.

Dr. Birnholz:
So, if we get back to the genetic side, clearly we can assess greater risk, but that's not enough to be able to say someone is going to predictively get MS. So, does genetic screening have any place in MS therapy right now?

Dr. Giovannoni:
I don't think, in terms of picking up asymptomatic patients, I don't think. Because we actually, in quite a few groups, have done what we call risk profiling using genetics. That may improve in the future, as more variants come out, but there's a thing called the receiver operating curve, and you look for area under the curve. And the area under the curve is about 70 to 80%, and for prediction you really need that to be in the 90s, to be honest with you, to have any clinical utility. So, I don't think we're going to be sending off our genes and coming back and you've got a risk. A much better predictor is simply family history. If you happen to be a first or second-degree relative of somebody with MS, particularly if you're on the female lineage, because it's common in females, that's a much better predictor of being high risk. But again, if your mother had MS, and you're a daughter, your chance is 1 in 40. And the background risk is about 1 in 500. So, it's not that predictive. So I personally don't think we should be using genetics to predict who's going to get the disease. What the genetics do tell us though; it tells us about the pathways involved in the pathogenesis of multiple sclerosis. And by studying those pathways, we get insights about potential treatments, and how we should be developing new therapies for multiple sclerosis. I think the genetics is very, very important from a research perspective.

Dr. Birnholz:
But even in the absence of a family history, if a patient, for another autoimmune disease, happens to have picked up smoking, has lived in a low-sunlight area, and did, indeed, have Epstein-Barr virus in the past, is that somebody who automatically gets put on the board as, "We should be following this person, or maybe even getting ahead of it?"

Dr. Giovannoni:
So, until we've got therapies that have been shown to prevent the disease. I do think, based on the evidence, the vitamin D hypothesis is so compelling, and vitamin D supplementation is so safe. We always tell all our patients to make sure that their first and second-degree relatives are aware of the link between vitamin D and multiple sclerosis. And we advise them to go onto vitamin D supplementation life long, based on a much higher level of supplementation that's currently in the recommended daily allowance, because the RDA, the recommended daily allowance, is based on bone health, preventing ricketts; it's from 60 to 80 years ago, the recommendation. And it's far too low for immune functions. So, we recommend a much higher dose of vitamin D. I use the Vitamin D Council recommendations which for an adult is 5000 units per day.

Dr. Birnholz:
And I imagine smoking cessation is a pretty common area for you to counsel as well?

Dr. Giovannoni:
Well, the thing about smoking cessation is that it's a public health issue, and the reason why people smoke are very complex. It's got to do with peer pressure, image, and the tragedy in the UK, where I work, is that for the first time now, it's more common for women to smoke than men. In teenage girls now, the incidence of smoking's going up, versus boys that it's going down. And that's driven by role models; it's driven by marketing. The fashion industry, all the models smoke; there's this perception that it keeps you thin. There're a lot of social drivers of smoking behavior which is difficult to counteract as an MS clinician. You have to rely on the public health doctors and the politicians to put in place legislation and public health programs to stop that from happening, but they seem to be ineffective at stopping young girls from smoking.

Dr. Birnholz:
It's an American problem as well, of course. So, just looking ahead, as my last question to you, what do you see needed to get us to a

point where the term personalized medicine, and everything that comes with it, from pharmacogenomics to doing combination therapies that are targeted per patient, will be a reality for MS?

Dr. Giovannoni:
I think it'll come around individual disease-modifying treatments. We'll probably find that certain people with a genetic profile are a bit more likely to respond to drug X versus drug Y, and that's classic pharmacogenomics. We've been using an enzyme called thiopurine methyltransferase activity, TPMT, to select who is more likely to respond to azathioprine, who can tolerate azathioprine, versus not. And that's a typical example of us using genetics to exclude people who are going to have adverse events, and I think that will come with MS therapies as well. Particularly with monitoring long-term response, we'll be able to do gene chip at baseline and say, "Actually, this particular individual is unlikely to respond to this drug. More likely respond to that drug." And then, we'll probably use biomarkers to predict when to retreat, for example. So, I think we are on the cusp of biomarker/genetics, which is another biomarker affecting clinical decision making, based on response or non-response to treatments, rather than predicting who's going to get the disease.

Dr. Birnholz:
Well, with that look forward, I really want to thank you for your time. This has been an excellent conversation. Thanks again, Dr. Giovannoni.

Dr. Giovannoni:
Pleasure.

Narrator:
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