



Episode 254: Actionable Genetic Pathways in the Treatment-Resistant Migraine

Lindsay Weitzel, PhD:

Hello, everyone, and welcome to HeadWise, the videocast and podcast of the National Headache Foundation. I'm Dr. Lindsay Weitzel. I have a history of chronic and daily migraine that began at the age of four. I have brought you today one of my favorite people, headache specialist Dr. Amelia Barrett. Hello, Dr. Barrett, how are you?

Amelia Barrett, MD:

Hello there. I am well, thank you.

Lindsay Weitzel, PhD:

Dr. Barrett is a board-certified neurologist and the creator of the Migraine Relief Code. Today we are going to talk about actionable genetic pathways in the treatment-resistant migraine. Now, that's a mouthful, but what that means is genes that you can actually target with behavior. So, these are genes that Dr. Barrett found in some of her subjects in a study. And then you can use your behavior to target these pathways and alter your migraine. So, this is data from an abstract Dr. Barrett recently submitted to a scientific meeting and we're going to discuss it today because it is really, really interesting. Dr. Barrett, let's begin with you. Can you just tell us some background as to why this research is so helpful?

Amelia Barrett, MD:

Absolutely. I think the key insight is that these genes regulate biological systems in your body. I think a lot of us, when we hear the genetics of migraine, we kind of shut down because like we don't need a DNA test to tell us that we have migraine. We already know that. It's not that kind of genetics. This is data that is extracted from what are called genome-wide association studies. It's very, very precise data about what's going on under the surface for people with migraine. What are those biological systems that are impacted. And most of all, what can we do about them. So, I really want to emphasize that the relevance here is more about the biology.

Lindsay Weitzel, PhD:

I'm going to go in order. There were a few genes you found. We're not going to discuss them all in detail, but we're going to talk about the most important ones and some of the things that people can do, since they were pretty common in the people that you studied. We're not all going to know if we have abnormalities in these pathways, but we're going to be able to maybe take on some of the behaviors that you're going to discuss. So, I'm going to go sort of in order from some of the most important ones that you mentioned in your study. And one of these is the MTR gene. Now I want to

make a note that many people in the migraine world are familiar with something called the MTHFR gene. And this is not that, correct? This is different. This is the MTR gene. Can you talk to us about that?

Amelia Barrett, MD:

Correct. It is not MTHFR, but it is still involved in the methylation pathway. I like to think of methylation honestly as kind of like recycling. You're taking something in your body, homocysteine in this case, and you're turning it into something useful. And that is methyl groups which are involved in nearly everything in your body. This is a lot like actually recycling your plastic. This homocysteine you can think of that as like the plastic that you have in your recycling bin and you're turning it into something useful. And it's springtime when I'm doing this interview and there are all these recycled plastic Adirondack chairs at the stores these days. I love those things. I think they're so cool. I think of it as turning your recycling into one of these beautiful chairs. That's basically what methylation is.

Now here's the difference between the MTHFR and the MTR. So MTHFR is what starts the whole thing. It is like you taking your recycling out to the curb if the truck comes to your street or taking it to the recycling center, whatever you have to do. MTHFR is that very first step. It initiates the whole process of turning something, some waste products, into something that's actually useful and beautiful in your body. Now, MTR is completely different. MTR is more like what happens when your plastic gets taken to the recycling factory. So, the truck comes by and picks it up and they take it to the plastic recycling place. And there are all these other genes that are involved in methylation, but it's all at the factory. So that's where MTR comes in. MTR is kind of like the recycling factory itself. And then there are all these other pathways that come into play.

So, the reason this matters is twofold. Number one, this homocysteine, your old plastic containers basically, when it builds up to a high level in your body, it is directly linked with worsening of migraine, especially with aura. And not only that, it is also an independent risk factor for heart attack and stroke, definitely things we want to avoid. So, there are many, many reasons to take care of this homocysteine and make sure that it gets processed and turned into these methyl groups in your body. So that's really the big distinction between MTHFR and MTR.

Lindsay Weitzel, PhD:

So first, can you tell us why homocysteine can increase our migraine?

Amelia Barrett, MD:

You know, I don't know that we understand the mechanism of that. You can think of it as the accumulation, the abnormal accumulation of something in your body. Your brain is like the canary in the coal mine. It's so sensitive, especially a migraine brain. And so, it's going to detect these abnormalities and say something's wrong here, we need to fix this. And we've known for a long time that abnormalities of MTHFR are linked with migraine. Some studies, not all, but some studies show as many as 40% of us have abnormal versions of MTHFR. So, this is very consistent with other migraine literature.

Lindsay Weitzel, PhD:

So back to the MTR gene which you found in your study. Obviously just a random person walking down the street doesn't know if they have an abnormality in this gene. But many of the people in your study that have treatment-resistant migraine did. What was it? Was this an actionable gene? Was this something that there was something these people could do to alter this outcome, or was this just something that you were able to tell them, hey, you have this?

Amelia Barrett, MD:

Oh, no, this is absolutely actionable. In fact, those are the only kind of genes I think are interesting. I think the rest of them I don't really want to know, to be honest if I have a gene I can't do anything about, especially if it's a bad gene. I'd rather just not know.

The methylation cycle actually can be improved in two ways. One ingredient of the methylation cycle comes from plants. The other ingredient comes from animals. So, the relevant one for the plant phase is folate. And you can take that either in pill form or even better in food form. And the strongest place you can get that is leafy greens. I mean, all greens in general have some folate in them, but the leafy greens in particular are super high in the kind of folate that your body needs.

And then for the animal portion of the pathway, that is mostly where we get B12 from. If you're taking this in pill form, you want to emphasize things like methylcobalamin as opposed to cyanocobalamin. You just check the label on your B vitamins and make sure you've got the right kind of you can just eat it in actual protein form. This does come from animal sources. That includes things like eggs and dairy, but it's higher in meat sources, fish, etc. So, these are two very easy things to prioritize in your diet that are going to help improve your body's ability to methylate and you can start them right now. I'm not saying it's going to reduce your headache tomorrow. But if you can implement habits in your life that improve your biology, then you are not going to have as many headache days because of those habits that you have put in place in your life.

Lindsay Weitzel, PhD:

The next one that was really common, now there were only 21 subjects in your study, but these genes that you found to have common abnormalities in them all had an actionable thing that we could do to improve migraine. And that's why this is interesting. It was the CYP3A4 gene, which I think many people have heard of. Can you talk to us about that and why it's important?

Amelia Barrett, MD:

Yeah, absolutely. The CYP3A4 gene is one of the ways that your liver processes all of the medications that you take. And I think what's so important about this finding that 90% of people had an abnormality of CYP3A4 and these are all people who have treatment-resistant migraine. But I think the reason that it's important that so many of them had abnormalities of this gene is that it means you are not going to tolerate medications as well as other people do. So could that be part of the reason that people become treatment resistant? Because they try a medication, they get a side effect, they stop it. And then there's only so many medications. You blaze through the whole list of them fairly quickly.

Lindsay Weitzel, PhD:

I love that you just said that, because I think the ears of so many people in our audience just perked up.

Amelia Barrett, MD:

Yeah. You've gone through all the medications because it gave me side effects. It gave me side effects, then of course you're going to feel like, oh my gosh, there's nothing left for me to do, when actually, the truth is it was just a dosing issue. And if we had started it lower, then you might have tolerated it. So, I think this is a really good reason to know this about yourself genetically.

And so, for this CYP3A4 gene, what happens is it means that that enzyme in your liver works slower. That's the direction that this genetic variant goes. It makes it so when you take a medication it doesn't get processed as fast. The levels go up higher in your bloodstream, and you feel side effects even when nobody else does, or when your doctor says no, you shouldn't be getting side effects on that dose or whatever, but you know you are.

And I think one of the places this is impacting people the most right now is with the gepants. This class of drugs is heavily metabolized by CYP3A4. And if you happen to be one of those sensitive people, you're going to get a lot more nausea, you're going to get a lot more fatigue. And I see this a lot, and it makes people give up on the drugs. They're like I would rather have pain than feel like a zombie all day long. So, I think that that's one place that people are really seeing it.

It also happens that eletriptan, one of the triptans drugs, is heavily metabolized by CYP3A4, so you're going to get more side effects there. Verapamil and zonisamide, which are two preventives, we don't use them very often anymore, not so much as first line, but they are often used as migraine preventive. And they're both effective for a subset of people. But those are heavily metabolized by CYP3A4 as well. So, if people are on those, again they're going to get side effects at the starting dose, whereas other people don't. So, I think that's what's really the most important thing to know about this gene.

Lindsay Weitzel, PhD:

That's so interesting. Migraine is thought to be a brain disease. Were any of the genes that you found in this study that you did related to brain pathways?

Amelia Barrett, MD:

Absolutely. In fact, the majority of the genetic abnormalities that we see in the treatment-resistant population do have to do with neurotransmitters, in one way or another. So, for example, I like to think of the way neurons talk to each other of neurotransmission, I think it's kind of like playing ball with your kid. So, if you and your kid are two neurons, you throw them a ball, they catch it. That's really what neurons do. You throw the neurotransmitter across the synaptic cleft, and the other neuron catches it. That's kind of the scientific lingo, but it's basically just one neuron tossing a ball to another.

The reason I'm mentioning this is because one of the more common genes that's really important for people to know about is involved in this pathway. So, let's go back to our example of your throwing the ball with your kid. Let's say it's a little kid. They're just learning. They're not catching the ball very often, so you have to go run after and chase them and get them and pick them up and throw them again. You are basically kind of recycling those balls. Your neurons do the same thing with your neurotransmitters.

They recycle that neurotransmitter back inside the neuron so they can toss it across the synaptic cleft again. It's just like you tossing the ball again to your kid when they drop it.

And the reason this matters is because the gene that affects this recycling problem in the neurons, for serotonin in particular, is very strongly linked with migraine. All of the studies for the past 20 years have consistently found problems with this gene. And it's 5-HTTLPR. But what matters even more is that people who have variants of this gene, genes where you're recycling doesn't work too great, they tend not to respond well to the selective serotonin reuptake inhibitor class of medications. What does reuptake mean? It means recycling. This is your serotonin recycling system. So, people who already have a problem with that system, you're trying to make a drug work on a system that's already broken. It's not going to work.

And I think this is so important because we know that things like anxiety travel with migraine is part of the same neurotransmitter problems. And a lot of doctors will prescribe SSRIs for anxiety. This is things like Paxil, Prozac, Celexa, Lexapro. And our studies we're showing that upwards of 75% of people with treatment-resistant migraine aren't going to experience any benefit from that class of medication. So, I think it's important for people to just have that real validation that there could be a biological reason that they are not responding to these drugs, or that they're not responding as well to them as they would to one that worked differently, which is always a difficult judgment call to make. But in my mind, it just means go get the information, like go figure out your data so that you have a roadmap to maximum wellness given your biology.

So that's really the take home about the way these neurotransmitter genes work, that there can be abnormalities in how you're wired that make it so you over respond to medications in terms of side effects or you under respond in terms of the benefit that you get. And without that clear guidance of knowing exactly how you're wired, I think it's really hard to know, like, am I as good as I can be? Could I be better? Could I be having fewer migraines if I just tweaked things up a bit and got like the dozen things in place that I need to have in place? So, I think that's really the power of that information. And for those of you out there who are kind of going, oh, maybe that's why I don't respond that well to this medication, just go back in and have a conversation with your doctor and maybe think about something else.

Lindsay Weitzel, PhD:

Dr. Barrett, now that we know some of these genes that can be abnormal in treatment resistant migraine, I'm wondering if some of these at home tests like 23andMe that people do, do they test for some of these genes?

Amelia Barrett, MD:

Yes, they do. So, this information is becoming accessible to people everywhere. There are a lot of commercially available at-home DNA test companies that will give you this information. Now, of course, it's a little overwhelming if you just try to Google, like, what do I do? But that's why I think it's important to get guidance about what you do with this information once you've got it. Because honestly, this is new for doctors too and they may not know either.

Lindsay Weitzel, PhD:

Thank you so much for this. This was great information. I think a lot of us we don't know if we have these abnormalities in these genes but knowing that 75 or even 90% of people with treatment-resistant migraine have them. If some of the things you said ring true, it can be very validating and interesting, and we can be on the lookout for future studies that hopefully look further into this sort of information.

Thank you so much for being here. This was really fun to chat about, and I bet everyone got something out of this. So, everyone please join us again on the next episode of HeadWise. Bye bye.

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