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Establishing Our Foundation of LGMD2I/R9: Unlocking the Genetics

Announcer:

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Dr. Weihl:

This is CME on ReachMD, and I'm Dr. Conrad Weihl. And today, I'm going to talk about the pathophysiology of limb-girdle muscular dystrophy 2I/R9. And so why don't we just get started?

So limb-gridle muscular dystrophy is a form of hereditary muscle disease, and it comes in several different subtypes. And the way that we categorize these subtypes is by adding numbers and letters to the end of them. And so the more historic way of calling this was limb-girdle muscular dystrophy type 2I, meaning 2, meaning that it's recessive, so it's inherited in a recessive manner. And the I, going through the alphabet, being the 9th letter of the alphabet. However, more recently, because of the increase in the number of limb-girdle muscular dystrophies identified, and the need to start using duplicate letters, it was decided that the nomenclature would change and be used as a number. And so it's now limb-girdle muscular dystrophy type R for recessive, and 9, being the 9th limb-girdle to have been just genetically discovered.

And so with that being said, those helpfully categorize it. It's helpful for us as clinicians to categorize the disease. It's helpful for patients to understand that they have a limb-girdle muscular dystrophy subtype. However, really what is important, is the genetic etiology of the disease. And the disease, in this case for limb-girdle 2I/R9, the genetic cause is due to mutations in a gene called FKRP, or fukutin-related protein. Fukutin-related protein is an enzyme. It's actually a glycosylase. It resides on chromosome 19. And in order to have disease, a patient has to have an inheritance of a pathogenic variant on both alleles. And when I say both alleles, I mean that we get one allele from our mother and we get one allele from our father, and there has to be a variation that's pathogenic on both of those in order for the patient to actually manifest with disease. And so just to kind of remind you, Mom and Dad would be carriers and the patient itself would be affected because they would have 2 mutations.

As you know in genetics, not all of the offspring would necessarily have the disease. Some of the offspring would be spared getting any mutations and some would be carriers themselves. And so my point is that in some families which are fairly small, it may appear that the disease mutation just arose out of nowhere. However, because of certain carrier frequencies and because of the small family structures we have in some places of the world, they may not have extended large families, and it may feel like this is something that is sporadic. And that's important when we think about the diagnosis of looking for a hereditary disease whenever there really doesn't appear to be any family history.

So what does FKRP do? So FKRP is a glycosylase, and so itself is not a structural protein. However, it's quite important in helping to



maintain muscle structure and function because of its ability to glycosylate a very key protein. And that key protein is alphadystroglycan. Alpha-dystroglycan is a protein that gets trafficked to the sarcolemma, or the plasma membrane of the muscle fiber. And once it's on the on the sarcolemma of the muscle fiber, it then can attach to an adjacent muscle fiber via the extracellular matrix. However, alpha-dystroglycan on its own is not very good at that, unless it has a bunch of sugar moieties attached to it. And so what I want you to think about is the protein is normally not very sticky unless it has sugars that are attached to it. And these sugars are decorated onto the end of alpha-dystroglycan and then allow it to be attached to laminin, which is at the extracellular matrix. And so FKRP is one of several different glycosylases that add sugars to alpha-dystroglycan, which then allow alpha-dystroglycan to be sticky and attach to laminin at the extracellular matrix, allowing forced transduction of a skeletal muscle to occur. If there is no sugar moieties or reduction in the number of sugar on it, that then leads to a decrease in muscle fiber integrity, can lead to muscle fiber necrosis, and muscle degeneration and regeneration.

Great. Well, hopefully you learned a lot. This has been a great kind of bite-sized chunk on the molecular pathophysiology of limb-girdle 2I/R9. Thank you.

Announcer:

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