Audio file

The Cryptid Sloth Show Episode 3: Change Changing Places

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Transcript

Tony has genetically confirmed CMT1A. Tony has one son, Andy. Andy, at an early age shows obvious signs of CMT. Genetic testing reveals that Andy does indeed have CMT, but he has CMT4H rather than 1A. Andy obviously inherited his dad's CMT, it's just a different type. Or did he inherit his dad's CMT? Can somebody inherit a different type of CMT than what their mom or dad has? Can CMT change types when passed on? The answers are easy, but getting to them requires diving into how CMT is inherited.

[Theme Music]

Stop standing there! Attention, everyone!

The Cryptid Sloth Show: Where CMT and Life Meet.

With your host...

Kenneth Raymond

[Theme Music Ends]

Hi everybody, and welcome to the Cryptid Sloth Show, here CMT and life meet. I'm your host, Kenneth Raymond, and I have CMT.

CMT isn't so much about CMT genes, per se, as it is about the underlying responsible mutation in a gene. I say this a lot, but why? CMT is caused not by a gene but, rather, by a mutation in a gene. Every person has every gene that can have a mutation that causes CMT, right? However,

the mutation causes CMT and not the mere presence of a gene. An argument can be made that a gene with the CMT causing mutation is in and of itself a CMT gene, but I prefer the former over the latter. Because we inherit our genes from our parents, we inherit any mutations our parents might have in their genes. Hence, CMT is inheritable. The chances of inheriting our parents' CMT are fully dependent the underlying responsible gene mutation.

CMT, that is, the gene mutations that cause CMT, are inherited in one of four ways. These four ways are autosomal dominant, autosomal recessive, X-Linked dominant and X-Linked recessive. And, I go into great detail with these in episode 1 if you'd like to learn more. But these inheritance patterns also described a type of mutation that cause the associated type of CMT. What do these mean?

In a nutshell, autosomal refers to a gene that is found on any of the chromosomes numbered 1 through 22. Dominant, in genetics, means that only one copy of a gene has a mutation. Recessive means both copies have a mutation. Copies? What do I mean by copies of a gene?

We normally have two copies of every gene, except for genes that are found on the X chromosome. For genes that are found on the X chromosome, females have two copies and males have only one. For ease of discussion, whether autosomal or X-Linked, dominant types of CMT: one copy of the associated gene has a mutation and the other copy is normal; and, with recessive, both copies of the gene have a mutation.

Getting back to Tony, Tony has genetically confirmed CMT1A. 1A is caused by an autosomal dominant mutation of the P-M-P-22 gene. Specifically, CMTers with 1A have an extra copy of the gene—a third copy of the P-M-P-22 gene. Because this mutation is autosomal dominant, every CMTer who has 1A, regardless of gender, has a 50/50 chance of passing on their mutation to their children, regardless of the children's gender. When the children inherit this mutation, they'll have CMT1A. If they don't inherit this mutation, they won't have 1A.

Andy, Tony's son, has CMT. He started showing signs at an early age. Clinical symptoms point to CMT, and nerve conduction characteristics are consistent with a demyelinating CMT. Andy's dad, Tony, has 1A, of course, and 1A is a demyelinating CMT. Although Andy's nerve conduction characteristics are worse than his dad's, as are his symptoms, the doctor confidently diagnoses Andy with 1A, the same as his dad. Given the inheritance pattern of 1A, and Andy clearly having a demyelinating type of CMT, the diagnosis makes perfect sense. Just to be sure, the doctor ordered the genetic test for 1A. With Tony having genetically confirmed 1A, it didn't make much sense to test for other mutations. Andy's test result, however, showed the normal 2 copies of the PMP22 gene. Andy, unequivocally, does not have 1A. The doctor believes that

Andy definitely has CMT though. The signs are obvious. The nerve conduction characteristics are obvious. His dad has CMT. For all intent and purpose, Andy has CMT.

Floored, the doctor ordered genetic tests for every CMT causing mutation that can be tested for, and this includes retesting for the 1A causing mutation, just in case. The genetic test results come in and revealed that Andy actually has an autosomal recessive mutation in his FGD4 gene that is associated with causing CMT4H, a demyelinating and recessive type of CMT. With this information, the doctor diagnoses Andy with 4H. This genetic diagnosis explains the symptom severity and the nerve conduction characteristics that are more severe than Tony's, who has 1A, because 4H tends to have a more severe presentation than 1A.

Everything is starting to make clinical and diagnostic sense. Tony has 1A, but his son, Andy, seemingly inherited a different type of CMT. The begging questions? How and why did CMT change types? I mean, Andy clearly inherited CMT from his dad, who has genetically confirmed CMT, but he has a different type. Why? The CMT in Tony's family did not change types when Andy inherited his dad's CMT. The keyword is, “inherited.”

Yes, there are two different types of CMT. Andy, however, unequivocally, did not inherit Tony's 1A causing PMP22 duplication. Genetic testing clearly showed this. Andy has only two copies of normal unmutated PMP22. Andy absolutely did not inherit his dad's CMT. Andy's mom does not have CMT. Therefore, Andy did not inherit his CMT. If Andy did not inherit his CMT, how does he have it?

CMT4H is caused by an autosomal recessive homozygous mutation in the FGD4 gene. What does this mean? Homozygous is a type of mutation in which both copies of the associated gene have the same mutation. When only one of the two gene copies has this mutation, there isn't CMT. When both copies of the FGD4 gene have the same specific mutation, the person has CMT4H. Tony had a 50/50 chance of passing on his CMT1A causing mutation to Andy. Andy did not inherit it. Andy, instead, has a recessive mutation in a different gene.

We inherit our genes from our parents. For ease of discussion, with our genes, each having 2 copies, one copy is inherited from our mom, and the other from our dad. Tony might have one of Andy's two FGD4 mutations. We don't know. Tony's dad also had genetically confirmed 1A. Because of this, and like Andy's first genetic test, Tony was tested only for the 1A responsible gene mutation. Tony's test showed that he has the 1A causing mutation like his dad, so no other genetic testing was needed. If Tony has one copy of Andy's 4H causing mutation in his FGD4 gene, Tony still only has CMT1A, because having only one copy of the 4H causing mutation is

not enough to cause CMT. This is not a case where Tony would have two different types of CMT. Why? Because of the mutations.

Hypothetically, let's presume that Tony, in addition to having his 1A causing PMP22 duplication, also has one copy of the mutation that, when there are two copies in the same person, causes 4H. For Tony though, this one mutation is just sitting there not doing or causing anything. On its own, it doesn't do anything, and is otherwise harmless.

Now, the FGD4 gene is found on chromosome 12. This means that it is autosomal in inheritance. Being autosomal, Tony had a 50/50 chance of passing on to Andy his one copy of his FGD4 gene that has the mutation. The PMP22 gene is found on chromosome 17. This means that it, too, is autosomal, and Tony had a 50/50 chance of passing on to Andy his copy of the gene with the mutation—the copy that is duplicated. What's the difference? A CMT gene is a CMT gene, and CMT is CMT, right? Well, not exactly.

[♪ Bruh! ♪]

CMT1A is caused by a mutation in just one copy of the associated gene. In the case of 1A, one of the PMP22 copies is duplicated. Having just one copy of the gene with the mutation is enough to have CMT. CMT4H, however, is caused by a mutation in both copies of the associated gene. In the case of 4H, the associated gene is the FGD4 gene. When only one copy has the mutation, it's not enough to cause CMT. Although Tony has mutations in two genes that are associated with having mutations that cause CMT, the two are uniquely separate from one another and they do not affect one another. In Tony's case, he has CMT1A, and only CMT1A.

There was a 50/50 chance that Andy would inherit Tony's PMP22 mutation, and he did not; and, therefore, did not inherit Tony's CMT. Parallel to this, there was a 50/50 chance that Andy would inherit Tony's FGD4 mutation, and he subsequently did. This one copy of the FGD4 mutation is not enough to cause anything. Where did Andy's other FGD4 mutation come from? Well, there are two possibilities.

After Andy was genetically confirmed to have 4H, Andy's mom was tested. Her test revealed, and unbeknownst to anybody, that she, too, like Tony, has one of the two 4H causing mutations in her FGD4 gene. Having this one copy, she does not have CMT and having this one copy means that, she, too, had a 50/50 chance of passing it on to Andy. As it turns out, Andy had inherited one copy of his CMT4H causing mutation from each of his parents. With each parent

having just one copy of this mutation, there was a 25% chance that Andy would inherit both copies.

The second possibility: if Andy's mom did not have one copy of the FGD4 mutation, was that Andy developed his second copy spontaneously, at conception, or what is called, de novo. For ease of discussion, CMT is inheritable, yes, but one does not have to have inherited CMT in order to have CMT. I know, plot twist, right?

[♪ Brun! ♪]

CMT is inheritable because the gene mutations that cause every type of CMT are inheritable. However, the mutations that cause CMT can occur on their own, spontaneously, at conception. When this happens, it is called a de novo, or "new" case. A de novo CMT case is one that was not inherited from either parent. When a CMTer's CMT is a de novo case it is then bound to the rules that govern the inheritance pattern of the underlying responsible gene mutation, just as though the CMT had been inherited.

Now, let's consider that neither Tony nor Andy's mom had a copy of the CMT4H causing mutation in their respective FGD4 genes. Surely, then, CMT changed types when Andy inherited it from Tony, right? Not exactly.

CMT is inheritable only because the mutations that cause CMT are inheritable. If somebody does not have a CMT causing mutation they cannot pass it on. Their children cannot inherit it. Hypothetically, we'll now presume that neither of Andy's parents have a copy of the two FGD4 mutations that are needed in the same person to cause CMT4H. Therefore, Andy did not inherit his CMT causing mutation, and, subsequently, his CMT4H was not inherited. In this situation, Tony's PPMP22 mutation did not correct itself in Andy, and nor did the mutation cause the mutations in Andy's FGD4 gene. The two are completely unrelated. In this case, Andy's CMT4H is a de novo case completely distinct and separate from Tony's CMT 1A. The CMT in this family did not change types through inheritance, and Andy did not inherit the mutations that are causing his CMT. He did not inherit his CMT.

Does CMT change types through inheritance? No. Can CMT change types through inheritance? Also, no. On the surface, it might appear that CMT can or does sometimes change types from parent to children. Careful analysis of the genetics and inheritance patterns, however, reveal that CMT does not and cannot change types through inheritance. The old understandings were that this could happen, but advances in DNA analysis and advancements in being able to isolate and

analyze individual genes along with the genetic understandings developed since the advent of the human genomic project have proven unequivocally that CMT cannot change types through inheritance.

Are there families who have more than one type of CMT? There absolutely are. Albeit rare, it can and does happen. In cases where somebody has a different type of CMT than their parent, the responsible gene mutations were not inherited. Their CMT was not inherited and the CMT did not change types through inheritance, nor from it.

The mathematical chance of somebody having a different type of CMT than their parent is exceedingly rare, but it is never zero. Whenever there is an appearance that CMT has changed type through inheritance though, genetic analysis will always show otherwise.

[♪ Bruh! ♪]

That'll do it for today, thanks for stopping by, and I'll catch you again next time.

As we close, no matter who you are, no matter where you're listening from, although so very few people have ever heard of CMT, I want you to know that you are not alone, and that we're in this fight together. Thanks for tuning in. Make sure to visit the website at thecryptidsloth.com, a website dedicated to all things CMT, where you'll find our show notes, the episode library and The Cryptid Sloth Blog. Follow us on your favorite social media, and you can find me, your host, Kenneth Raymond, in many of the Facebook CMT groups. Thanks again, and I look forward to talking to you really soon.

This has been The Cryptid Sloth Show Podcast: Where CMT and Life Meet.