Audio file

The Cryptid Sloth Show Episode 1_It's All in The Genes

Transcript

Genes Genes Genes Genes Genes Genes Genes Genes, they're good!

Oh, those pesky little CMT genetic tests. The tests are Hella Complex. The tests are Hella, confusing and the meanings behind the results seem to be some sort of closely guarded national secret. I've got G-14 top level double secret probation. Security clearance and I'm going to spill the beans and que you in on all the little secrets hidden in CMT genetic test results.

Sssssshhhhh! It's a secret...
[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, the podcast where CMT and life meet. I'm your host, Kenneth Raymond, and I have CMT.
Today we're here to talk about the genetics of Charcot Marie Tooth disease and the genetic test results for CMT.

I'm going to be saying CMT a lot. However, CMT is morphing into a term that the scientific community is coming to use as an umbrella term to refer to all inherited nephropathies. I know. You're, like, what? Hold up! Wait just a minute there, Mister. Don't worry. I'm going to fully explain this notion in the next episode. But, for today, with CMT as an umbrella term in mind, everything I'm going to cover can also apply to any inherited neuropathy. How? Well, because, it's all about the disease-causing mutations in genes. More importantly, it's all about the mutation types that cause inheritable neuropathies.

Rather than mentioning every inheritable neuropathy by name and acronym, I'm going to stick to CMT for ease of discussion. Now let's dive in shall we?

Clinical symptoms and nerve conduction characteristics when considered together can provide enough information for the doctor to diagnose CMT. The Doctor can determine if CMT is likely demyelinating, or what is a CMT1. Likely axonal, or what is a CMT Type 2. Or, to a lesser degree, sometimes, Intermediate CMT, and all via nerve conduction studies. The CMT scientific community agrees with this. However, the doctor cannot determine the specific subtype by clinical symptoms or through the electrodiagnostics, that is, nerve conduction studies.

There are cases where the Doctor can make an informed probable subtype diagnosis based on symptoms and nerve conduction characteristics. But, the subtype diagnosis still wouldn't necessarily be definitive. However, like all things CMT, there is an exception to this rule, when there's an established family history of genetically confirmed CMT. And I'll give you an example.

John has CMT 2A. He received genetic confirmation of a dominant MITOFUSIN2 gene mutation that causes 2A. His 10-year-old daughter, Sarah, is showing symptoms that are consistent with CMT. John having genetic confirmation for the mutation that causes 2A gives the doctor valuable information for evaluating Sarah. The doctor, after evaluating Sarah, determined that Sarah symptoms are consistent with CMT. The Doctor then determine that Sarah 's nerve conduction characteristics are consistent with a CMT Type 2.

The doctor knowing that Sarah 's dad. John has genetic confirmation for 2 a diagnosis era with 2 A and did so without obtaining genetic confirmation. The Doctor can make this diagnosis with a fair degree of certainty because of the inheritance pattern of Johns causative gene mutation.
This isn't why we're here today, though. Well...
Ish...

We're here today to talk about CMT genetics and genetic tests. So… I guess the little story is why we're here. So, yeah, anyways...

The genetic test results report for CMT don't give a yes/no, pass/fail, or even a positive/negative. Instead, the tests either identify a CMT causing gene mutation that the lab included in their

panel, or the test does not. If the test identifies a mutation known to cause CMT, it's easy, CMT is confirmed, and the specific subtype is identified. Piece of cake.

When the test identifies the CMT causing mutation, several things are learned beyond the specific subtype. Certain subtypes are known to cause things that others are not known to include. Deafness is often associated with CMT4D. Optic nerve atrophy can be associated with 2A. A certain kidney disease called Focal Segmental Glomerulosclerosis, or FSGS, try to say that 10 times real fast, is associated with Dominant Intermediate CMT-E. And, just, by the way, the acronym for Dominant Intermediate CMT-E? CMT D-I-E… Seriously, not amused. CMT DIE? What were they thinking? 'Cause, nawh, it ain't right, man. They could have easily skipped over E. They need to rename it, 'cause it just doesn't work for me. [Sound Effect; “Bruh!”]

Whichever the underlying mutation causing CMT though, once it's identified, its inheritance is identified. Ah-ha! Now we're getting somewhere.

There are 4 ways to inherit CMT. The keyword here is, "inherit." CMT is inheritable, yes, but somebody does not have to have inherited CMT to have it. When CMT is not inherited, it's called a, "de novo," or a new case. A de novo case is one that occurs spontaneously at conception, meaning that neither parent had the mutation that's causing the CMT.

When somebody does have CMT, whether it was inherited from a parent or whether it's a de novo case, the CMT can be passed on. How it's passed on, how it's inherited, depends on the specific underlying gene mutation that's responsible for causing the CMT.
Each of the 4 ways that CMT can be passed on are referred to as the inheritance patterns.
Life really is about parents go figure. These four inheritance patterns are autosomal dominant, autosomal recessive, X-Linked dominant, and X-Linked recessive. I know, that's a lot of tech talks and fancy speak. There's not much to these though once we break them down.

First, throw out what you know about the use of the words "dominant" and "recessive." In genetics, and in inheritance patterns, the two words are used differently than what most of us are used to. Hang with me, this will make sense, I promise. When we're done, you'll be, like, well, then, bruh, that was easy.

Alright, so, autosomal dominant, autosomal recessive, X-Linked dominant, X-Linked recessive. Autosomal refers to a gene that lives on any of the non-sex-chromosomes: the autosomes.

Dominant refers to needing a mutation in only one copy of the gene to have the disease. Recessive refers to needing a mutation in both copies of the gene, with an exception for X-Linked. X-Linked refers to a mutation in a gene that lives on the X chromosome. Easy, right? So, what's all this business with gene copies? It's not as complicated as it seems.

Genes live on chromosomes. Chromosomes live in our DNA. People have 23 pairs of chromosomes. This is where 23andMe got their name. Who knew? Pairs. Why pairs?

Our DNA is like a zipper. On one side of the zipper is the DNA we inherited from our mom, and the other half we inherited from our dad. We are the zipper key that joins the two halves into one, just as a zipper is joined into one when you zip up your jacket. The half of the zipper inherited it from our mom contains all her chromosomes, and the genes that live on those chromosomes; and the half of the zipper we inherited from our dad, likewise, contains all of his chromosomes and the genes that live on those chromosomes. When zipped up, those two halves come together and join to form our chromosomes, and each chromosome, therefore, contains two copies of each gene, with one copy inherited from each parent.

The 22 pairs of non-sex-chromosomes, the autosomes, are known as chromosomes 1 through 22. The 23rd pair, known as the sex-chromosomes, are the X and the Y. Females have two X chromosomes, inheriting one X chromosome from each parent. Males have one X chromosome and one Y chromosome. Males inherited their X chromosome from their mother, and their Y chromosome from their father. Easy peasy.

Let's recap right quick though, so that I don't lose you. We have 2 copies of each gene because we inherit one copy from each parent. Autosomal: gene lives on an autosome, which is any of the chromosomes numbered 1 through 22. X-Linked: gene lives on an X chromosome. Dominant: only one gene copy needs a mutation. Recessive: both copies of the gene need a mutation. See? Piece of cake.

How does all this business apply though? We're getting there. Trust me. In a minute, you're going to be, like, whoa. It's, it's, uh, it's easy.

So. there are no CMT genes, per se. Rather, CMT is about gene mutations. Everybody has every gene that has a CMT causing mutation. It's the mutation that makes the CMT, and not the gene.

Now, an argument can be made that if a gene has a mutation that causes CMT, that mutated gene is then a CMT gene. But for ease of discussing, I'm going to stick to the premise that mutations cause CMT.

Now, every type of CMT can be passed on. The chances of passing on our CMT to our children, or the chances of our children inheriting our CMT is fully dependent on the exact gene mutation. Enter the inheritance patterns.

Autosomal dominant. With autosomal dominant types of CMT, the responsible mutation is with a gene that lives on an autosome. Only one of the genes two copies has the CMT causing mutation, and there's a 50/50 chance of passing on that CMT causing mutation to each child, regardless of gender. The CMT1's, most of the CMT2's, and the Dominant Intermediate CMT's fit this inheritance pattern.

\When you have a type of CMT that is in any of these categories, regardless of your gender, there's a 50/50 chance that it will be passed on to each of your children, regardless of their gender. If they do not inherit the mutation, they will not have the CMT and they cannot and will not pass it on to any of their children. You still with me? Yeah? Ok. Good!

So, autosomal dominant, regardless of gender, 50/50 chance of passing it on to each child, regardless of the children 's gender. Piece of cake. Autosomal recessive on the other hand, is a little more complicated to explain. Hopefully, I don't lose you.

Autosomal recessive. With autosomal recessive subtypes of CMT, the responsible mutation is with the gene that lives on one of the autosomes, go figure, and both copies of the gene have to have the CMT causing mutation in order for there to be CMT. When only one copy of the gene has the recessive mutation, there isn't CMT. But, when both copies do, then there is the specific type of autosomal recessive CMT. This is the easy part. Now, for the fun stuff.

When somebody has an autosomal recessive type of CMT, both copies of the associated gene have the mutation. One copy was inherited it from mom, and the other from dad. So as to not over-complicate an already complicated explanation. I'm going to use CMT4J, and myself, as an example.

CMT4J is caused by recessive mutations in the FIG4 gene. Hypothetically, I have 4J. Neither of my parents had CMT. However, I did inherit both copies of my FIG4 gene. One copy came from my mom, the other copy came from my dad. Turns out that one copy of my mom's FIG4 has a mutation that nobody knew about, and one copy of my dad 's FIG4 also had a mutation that nobody knew about. On their own, individually, in two separate people, the mutations don't do anything. However, when you put both of them together in the same person, you get CMT4J.

Now, the FIG4 gene lives on chromosome 6. At conception, and remembering that chromosomes are paired, and that each half of each chromosome contains one copy of every gene that lives on that chromosome, mom randomly passed on one-half of her chromosome 6, and dad randomly passed on one-half of his chromosome 6. These two halves came together to form my chromosome 6, with half the genes that live on my chromosome 6 coming from my mom, and the other half coming from my dad.
In this hypothetical case, I just so happened to have inherited my mom's copy of her FIG4 that had a mutation, and I just so happened to have inherited my dad's copy of his FIG4 gene that had the mutation. Because I have both mutations in my FIG4 gene, I have CMT 4J.
In this scenario, the chance of having inherited both copies of that mutation was one in four, or 25%.

When somebody has only one copy of an autosomal recessive mutation, they're considered to be a carrier of the mutation. They won't have the associated autosomal recessive CMT. With respect to the CMT types that are autosomal recessive, one mutation equals carrier two mutations equals CMT.

In this hypothetical example, both my mom and my dad were carriers of the mutation.
Still cool? Still with me? Yeah? Alright. Cool!

So, when each parent is a carrier of an autosomal recessive CMT causing gene mutation, each child has a 25% chance of inheriting both mutations, regardless of gender. If just one copy is inherited, they are then a carrier of that mutation just like mom and dad, and do not have the associated CMT. When they inherit both copies, they have the associated autosomal recessive CMT. You still with me? Yeah? Alright, let's rock this joint some more.

So, I still have CMT4J. Both copies of my FIG4 gene have a mutation that caused my 4J.

Each one of my children, regardless of gender, will inherit one copy of my FIG4 gene. The copy they inherit from me will have the same mutation. But, they will not have my CMT unless their mom has the corresponding mutation in FIG4 and happens to pass it on, or unless each of my children develop the required second mutation spontaneously.

When somebody has autosomal recessive CMT, their children also having autosomal recessive CMT is exceedingly rare, but the chances are never zero. Never.

Alright, recapping one more time because this stuff is hella confusing. So, autosomal dominant, regardless of gender, 50/50 chance of passing it on to each child regardless of the children 's gender. Autosomal recessive, regardless of gender, when both parents each have just one mutation, there's a 25% chance that each child, regardless of gender, will inherit both mutations and will then have the associated CMT.

When there is only one copy of a recessive mutation, the person is a carrier of the mutation. When a person has both copies of the recessive mutation, they have the associated CMT.
The CMT4's and the Recessive Intermediate CMT's are all autosomal recessive in inheritance, and a few of the CMT2's are also autosomal recessive. And now for the fun stuff: X-Linked CMT.

In X-Linked CMT, the responsible mutation is with a gene that lives on the X chromosome. X-Linked CMT is different amongst the types of CMT. Why is X-Linked different?
Well, X-Linked CMT involves gender where no other type of CMT does. X-Linked CMT involves gender because of how the X chromosome is passed on, or how it's inherited.
Not only does gender matter with X-Linked inheritance patterns, but there's no male-to-male inheritance with X-Linked CMT. I know, trippy, right? But, like the autosomal inheritance patterns, X-Linked inheritance can be dominant or recessive. These are known as X-Linked dominant and X -Linked recessive.

X-Linked dominant. Females have two X chromosomes. Females randomly inherit one X chromosome from their mom, and they inherit their dad's only X chromosome. Because females have two X chromosomes, they will randomly pass on one of their X chromosomes to each of their children, regardless of gender. For females, this is exactly like autosomal dominant except that the gene with the responsible mutation lives on the X chromosome.

When a female has X-Linked dominant CMT, one of her two X chromosomes has a mutation in one copy of the associated gene, and the other copy is normal, again, just like autosomal dominant. Therefore, a female who has X-Linked dominant CMT, has a 50/50 chance of passing on their CMT causing mutation to each of their children, regardless of gender. And, again, just like autosomal dominant, but the gene here, lives on the X chromosome. When a male has an X-Linked dominant type of CMT, however, the inheritance works way different. Seriously different. How different? Completely different.

Males have one X chromosome and one Y chromosome. Males randomly inherit one of their moms two X chromosomes, and they inherit their Y chromosome from their dad. So, when a male has X-Linked CMT, he cannot pass it on to any of his sons because he does not pass on his X chromosome to his sons, He will, however, pass on his X-Linked CMT to every daughter because he passes on his only X chromosome to every daughter. Therefore, when a male inherits X-Linked CMT, he could only have inherited it from his mom. It's impossible for a male to inherit X-Linked CMT from his dad. Fun stuff, right? Well, hang on, because the party is just getting started, man.

X-Linked recessive. A female who has X-Linked recessive CMT will pass on one of her two mutations to each of her children, regardless of gender, just as in autosomal recessive.
When the child is a girl, inheriting this one copy of the X-Linked recessive mutation does not cause the associated CMT. Instead, the daughter is a carrier of one copy of the X-Linked recessive CMT causing mutation.

When the child 's a male, despite the term "recessive" inferring that there must be two mutations within a gene in order to have the associated CMT, inheriting only one copy of the X-Linked recessive mutation is sufficient to cause the CMT. Say what? Yeah, I know. Mind blown, right?

When a male has X-Linked recessive CMT, he cannot pass it on to any of his sons because he passes on his Y chromosome to his sons and not his X chromosome. However, he will pass on his X-Linked recessive CMT causing mutation to every daughter. Each daughter having only one copy of the X-Linked recessive CMT causing mutation will not have the associated CMT. Instead, each daughter will be a carrier of one copy of the mutation. Although a male having only one copy of an X-Linked recessive CMT causing mutation is sufficient to cause the associated CMT, a female must have both copies of the mutation in order for her to have the associated X-Linked recessive CMT.

When a female has only one copy of the X-Linked recessive CMT causing mutation, thereby making her a carrier of the mutation each of her children have a 50/50 chance of inheriting the mutation from her. If the child 's a female, she, too, would be a carrier of the mutation, but will not have the associated CMT. But, if the child 's a male and he inherits the X chromosome that has the X-Linked recessive CMT causing mutation, having only the one copy of the mutation is sufficient for him to have the associated X-Linked recessive CMT even though his mother did not and was only a carrier of the X-Linked recessive CMT causing mutation.

Isn't X-Linked inheritance fun! [Sound Effect: “Bruh!]

To recap, X-Linked, for females, the rules are the same as autosomal dominant and autosomal recessive. When a female has X-Linked dominant CMT, 50/50 chance of passing it on to each of her children, regardless of the children's gender. A female who has X linked recessive CMT will pass on one of her two mutations to each of her children. Her daughter will be a carrier of the X-Linked recessive mutation, but won't have CMT. Her sons inheriting the one copy of the X-Linked recessive mutation, because they have only one X chromosome, will have X-Linked recessive CMT.

When males have X-Linked CMT, whether X-Linked dominant or X-Linked recessive, they will pass it on to every daughter, but it is impossible to pass it on to any of their sons. A female who is an X-Linked recessive carrier has a 50/50 chance of passing on her one mutation copy to each of her children. Her daughters who inherit the mutation will also be a carrier. But, her sons who inherit the mutation will have the associated X-Linked recessive CMT.

Females can inherit X-Linked from either parent, but males can only inherit X-Linked CMT from their moms, and never from their dads. CMTX1 and CMTX6 are dominant in inheritance, and CMTX2, X3, X4, and X5 are recessive in inheritance. X-Linked subtypes used to be called, simply, CMT1X. That was when there was only a single X-Linked subtype, and it was categorized with the CMT type 1's because it's a demyelinating subtype. However, with the discoveries of new X-Linked gene mutations, X-Linked became its own category. What a blast!

Before moving on to the good stuff, there's three more terms that we have to cover.
Don't worry, these are easy, though.

So, the inheritance patterns tell us how CMT is inherited, how it's passed on. But, each inheritance pattern is also a type of genetic mutation. I know, right? Nice! More confusion! This is way easier though than everything we just went through. I promise.
Three words: heterozygous, homozygous, compound heterozygous. OK, four words. But, for this example to work, there's just three: heterozygous, homozygous, compound heterozygous.

Heterozygous refers to a gene having only one mutation. Homozygous refers to a gene that has two identical mutations. Compound heterozygous refers to a gene that has two different mutations. All dominant inheritance mutations, both autosomal and X-Linked are heterozygous mutations. Recessive mutations, because both copies of the gene have a mutation, are either homozygous or compound heterozygous. The exception to this is when a male has an X-Linked recessive CMT. Because he has only one X chromosome, his X-Linked recessive mutation could be termed heterozygous, meaning one copy. See? No problem. That was easy. Now, for the fun stuff: the test.

Why did we go through all of that? Well, there's a method to my madness. You see, we're really here today to celebrate the opening of a new box, and the closing of an old box. No. wait, no no, that's not right. CMT genetics and genetic tests. That's why we're here today. We're here today to talk about the genetic test for CMT. That's right! OK.

So, we're here today to talk about CMT genetics and genetic tests. But, more importantly, we're here to talk about what all of the confusing language is in the test reports. First and foremost, I'm not a doctor and I cannot diagnose anybody with anything, and I would never try. However, what I can do is explain word use in the test reports so that you can know what your doctor is referring to when they give you their interpretation of the results.

The genetic test reports for CMT don't give a yes/no, pass/fail, positive/negative, right? Instead, they give a bunch of technical data and they give a lab written narrative that's hella confusing. If you've ever seen one of these reports, you know what I mean. The narratives use the terms that we just covered, the inheritance patterns, and the mutation types. They use these terms to explain what was found. Ah-ha! You see? There is a method to my madness!

I know, you're all, like, fair enough, but I need an example. Alright, then, fair enough, fair enough. I've got examples for you.

Here's an example of how a genetic test report for CMT might read, and this is from a real, legit genetic test report for a CMT genetic test.

A pathogenic variant [insert genetic code transcription here] was identified in TRIM2. The TRIM2 gene is associated with early onset compound heterozygous autosomal recessive axonal peripheral polyneuropathy that is consistent with a diagnosis of Charcot Marie Tooth Disease Type 2R. This individual is a carrier for the TRIM2 compound heterozygous autosomal recessive condition noted, but the result is insufficient to cause compound heterozygous autosomal recessive TRIM2 associated CMT2R However, carrier status does impact reproductive risk, and genetic counseling for this individual is recommended.

Bruh! Holy crap! See? I told you! Hella confusing! As crazy as all of that is, it's actually not too bad once we break it all down. We already know what most of it means because we went over some important keywords already.

Right at the very beginning, pathogenic simply means a mutation that causes something. Variant is the medical term for gene mutation. Rather than being an unremarkable gene, as medical terminology might describe a normal gene, a mutated gene is a gene variant.
Next up, compound heterozygous tells us the type of mutation that causes the CMT associated with the identified mutation.

Next, autosomal, of course, tells us that the gene lives on a non-sex-chromosome - an autosome, and recessive tells us that both copies of the gene must have a mutation. Hence, compound heterozygous.
Next, axonal peripheral polyneuropathy tells us CMT2 because CMT2 is axonal, and because CMT is a peripheral nervous system disease that involves many nerves - peripheral polyneuropathy.

The test report tells us that the identified mutation is associated with 2R. Groovy, right?
You see what I mean, though, when I said that these test reports don't give a pass/fail, yes/no, positive/negative, right? And, this particular report has a crucial detail. Let's go over the report again so I don't lose you.

A pathogenic variant was identified in TRIM2. The TRIM2 gene is associated with early onset compound heterozygous autosomal recessive axonal peripheral polyneuropathy that is consistent

with a diagnosis of Charcot Marie Tooth Disease Type 2R. This individual is a carrier for the TRIM2 compound heterozygous autosomal recessive condition noted, but the result is insufficient to cause compound heterozygous autosomal recessive TRIM2 associated CMT2R. However, the carrier status does impact reproductive risk, and genetic counseling for this individual is recommended.

I want to focus on one sentence: This individual is a carrier for the TRIM2 compound heterozygous autosomal recessive condition noted, but the result is insufficient to cause compound heterozygous autosomal recessive TRIM2 associated CMT2R. Basically, this sentence is the most diagnostically relevant one in the report. Why is that? The sentence says that 2R is caused by a recessive mutation, but the CMTer has only one mutation in the gene where two copies are needed to cause 2R.

If this particular report confirmed the CMT, the report would not include, "but the result is insufficient to cause CMT2R." So, what exactly does the test report tell us?

Well, the TRIM2 gene lives on chromosome 4. So, you then know that the mutations in the TRIM2 gene are autosomal. Check. We know that CMT2R is caused by a recessive mutation in TRIM2 - compound heterozygous. Check. We know that this CMTer has a CMT causing mutation in the TRIM2 gene - pathogenic variant. Check. The test report then concludes that this CMTer has only one of the needed two mutations in the TRIM2 gene for causing 2R. The result is insufficient to cause 2R.

So, this particular test report does not confirm CMT. This does not mean that the person does not have CMT though. This means only that this person's particular test did not identify any mutation in the genes that the test looked at. Nothing more than that.

Now, the CMTer's doctor could very well determine that the mutation identified, while it's only one copy of the needed two within the gene for causing CMT2R, is actually causing this CMTer's CMT. Something like that is well within a doctor's purview and discretion.
A doctor can very well say, "You know what? This little mutation here, despite what the report says. I know enough to say that it's actually causing your CMT. We're just not going to call it 2R because your mutation is not 2R." It's all up to the doctor, man.

So, now that we have a seriously confusing and complicated one out of the way, what does a test report that confirms CMT look like? Well, I'm glad you asked.

Here's another legit report for a CMT genetic test. I mean, totally legit real. Unlike the first one, this one straightforward confirms CMT though. You ready? Alright, here we go.

A duplication of the peripheral myelin protein 22 gene, or PMP22, was identified. A duplication of the PMP22 gene is associated with a demyelinating autosomal dominant peripheral polyneuropathy that is consistent with a diagnosis of Charcot Marie tooth disease Type 1A. This individual is likely to be affected by or predisposed to CMT1A. CMT1A is an autosomal dominant disorder, and, therefore, family members of this individual are at risk for possessing or inheriting this disorder. Genetic counseling is recommended for this individual and his or her family.

Yes, that is another confusing mouthful. Like a math story problem from grade school though, if we break it down and separate out the important stuff, then throw away the rest, we're left with a straightforward explanation.
Duplicated PMP22 gene was identified. A duplicated PMP22 gene equals CMT1A - three gene copies instead of the normal two. The report says that the mutation is autosomal dominant. PMP22 lives on chromosome 17 - an autosome. And, only one mutation copy is needed to cause the CMT - dominant. CMT1A is autosomal dominant in inheritance. This report confirms CMT and identifies 1A. Straight and to the point. As easy as pie. So...

What if the test report lists a VUS as the only finding? Well, that's the interesting part.

Often, the genetic test for CMT returns a result that lists a variant of unknown significance (or uncertain significance, depending on author), or VUS for short, as it's only finding, An example of how that report might be written is: “a heterozygous variant of unknown significance in MITOFUSIN2 gene, or MFN2 gene, was identified. The MFN2 gene is associated with autosomal dominant and autosomal recessive axonal forms of Charcot Marie Tooth Disease Type 2. This VUS finding is non-pathogenic.” What does this mean?

If we, again, separate out the important stuff, then throw away the rest, we can easily get to the bottom of it. You ready? Let's do this.

A mutation in just one copy of the MFN2 gene was identified - heterozygous.
MFN2 lives on chromosome 1 - autosomal. Both dominant and recessive mutations in the MFN2 gene are known to cause CMT2 subtypes. But this particular identified mutation is not known to cause any type of CMT - this VUS finding is non-pathogenic. See? So, now what? What does this mean? How does it apply?

Well, on one hand, the test result does not confirm the CMTer's CMT. The test identified only a VUS. A VUS finding, especially in CMT genetic tests, is common. A VUS means only that scientists have not yet linked the particular mutation to any condition or disease. A VUS finding doesn't necessarily rule out anything, nor does it rule in anything. It's just a finding. Remember a few minutes ago, though, when I mentioned that a doctor has discretion with interpreting these test results? Well, there's a thing about that because on the other hand, a doctor has the discretion to determine that a VUS finding in a CMT genetic test is actually responsible for the CMTer's CMT, that the VUS is actually pathogenic. Many of the known causes of CMT started out as a VUS, and then some really smart people have been able to link the VUS to causing CMT, flipping the mutation status from VUS to pathogenic.

The most important thing to remember with the VUS finding in a CMT genetic test, and I can't stress this enough is that a VUS does not mean it's not CMT. Again, I cannot stress that part enough. But what if the test doesn't show anything? Well, there's a thing about that.

So, my doc thinks I have CMT. They sent me to a neurologist buddy of theirs. That neurologist thinks, too, that I have CMT. They Zap the hell out of me with a nerve conduction study. The dude diagnoses me with CMT, and orders a genetic test. That test comes back with nothing. Now what? I mean, the doctor was sure. I mean, the genetic test should have found something, right? The test found nothing, though, so I don't have CMT, right? Well, that's not really what the test showed.

Diagnosing CMT is difficult. There isn't any one thing that a doctor can rely on for diagnosing CMT, or for ruling out CMT. A doctor has to consider the sum total of all diagnostic findings. While a genetic test can confirm CMT and can identify the specific subtype by identifying the genetic cause of the CMT, the genetic test cannot be used as a standalone diagnostic test for CMT, nor for ruling out CMT. The keyword here is "can." The test can, but it's not a guarantee.

A CMT genetic test result that identifies nothing means only that the test did not identify the CMTer's underlying genetic cause, and the result means nothing else. A result like this does not mean that the CMTer does not have CMT. A test result that turns up nothing is more common than you might think. And, why is that?

Well, in June of 2020 Dr. Shy, who is quite literally the CMT God, gave a presentation during the MDA's Engage CMT Symposium. I'll put a link to the video of the event in the show notes in case you want to check it out.
In this presentation, Dr. Shy explained that “about 95% of CMTers with a demyelinating CMT are able to obtain a genetic confirmation. In sharp contrast, only about 30% of CMTers with an axonal CMT are able to obtain a genetic confirmation.” In 2000, there were only 3 known genetic causes of CMT. Today, there are over 100. Dr. Shy explained that “researchers expect that, by the time they're done finding all the genetic causes for CMT, there will be over 200.” This means that scientists are only about halfway there. Adding to the disparage of CMT genetic tests that come up empty handed are what labs include in their tests.

You see, there isn't anyone commercial lab that can test for all known mutations that cause. CMT. Lab A might check for 72 in their "Complete CMT Panel." Lab "B" might look at 54. Neither will test for everything that the other does. There isn't a standard that labs have to adhere to for deciding what to include or exclude. Often, in their panels, labs are testing for mutations in genes that cause things other than CMT. So, if Lab C has 40 genes include in their "Comprehensive Neuromuscular Panel” 12 of those 40 might be associated with CMT.
So, when the test comes up empty, it's more important to know the genes that were looked at rather than the test name and its results. See, isn't this stuff a riot?

With CMT, nothing is simple. [Sound Effect: “Bruh!”]

But, recapping now, because, holy crap, did we cover a lot of ground today. So, autosomal dominant - gene lives on an autosome: chromosome 1 through 22, one mutation in one gene copy is enough to cause the CMT type, and then regardless of gender, there's a 50/50 chance of passing it on to each child, regardless of the children's gender. The Type 1's, most of the Type 2's, and the Dominant Intermediate types are autosomal dominant in inheritance.

Autosomal recessive - gene lives on an autosome, a mutation in both copies of the gene is needed for there to be CMT, regardless of gender. When both parents each have just one mutation,

there's a 25% chance that each child, regardless of gender, will inherit both mutations and will then have the associated CMT. When there's only one copy of a recessive mutation, the person is a carrier of the mutation. When a person has both copies of the recessive mutation, they have the associated CMT. The CMT4's and the Recessive Intermediate CMT's are all autosomal recessive, and a few of the CMT2's are autosomal recessive in inheritance.
X-Linked - for females, the rules are the same as autosomal dominant and autosomal recessive. When a female has X-Linked dominant CMT, she has a 50/50 chance of passing it on to each of her children, regardless of the children 's gender. When a female has X-Linked recessive CMT, she will pass on one of her two mutations to each of her children. Her daughters will be a carrier of the X-Linked recessive mutation, but won't have the associated CMT. Her sons, however, inheriting the one copy of the X-Linked recessive mutation, because they have only one X chromosome will have X-Linked recessive CMT.

When males have X-Linked CMT, whether it's X-Linked dominant or X-Linked recessive, they will pass it on to every daughter, but it is impossible to pass it on to any of their sons. A female who is an X-Linked recessive carrier has a 50/50 chance of passing on her one mutation to each of her children. Her daughters who inherit this one mutation will be a carrier, but her sons who inherit the mutation will have the associated X-Linked recessive CMT.

Females can inherit X-Linked CMT from either parent, but males can only inherit X-Linked CMT from their moms, and never from their dads. CMTX1 and CMTX6 are dominant in inheritance; and CMTX2, X3, X4, and X5 are recessive in inheritance. X-Linked subtypes used to be called simply, "CMT1X." That was when there was only one single X-Linked subtype. With new X-Linked gene mutations, X-Linked became its own category.

Genetic tests for CMT cannot be relied upon as a standalone diagnostic tool. The test reports don't give a pass/fail, yes/no, positive/negative. Instead, they give a bunch of tech data that doctors have to interpret to mean something. A VUS finding does not mean that the CMTer does not have CMT, and I can't stress that enough. A doctor can determine that a VUS finding is actually pathogenic, that the VUS is actually responsible for the CMT.

A genetic test result that identifies no mutation does not mean that the CMTer does not have CMT. And, again, I can't stress that one enough either. The result means only that the CMTer's underlying genetic cause was not identified by the particular test that was performed. There isn't a single commercial lab that can test for all known CMT causing mutations in a single test. 95%

of CMTers with a demyelinating CMT are able to obtain genetic confirmation while only about 30% of CMTers with an axonal CMT are able to obtain genetic confirmation. Finally, there are over 100 known causes of CMT, and scientists estimate that there will be over 200 by the time they're done identifying all causes.

CMT is so clutch, man.

So, I want to share a couple genetic testing resources with you.
The National Society of Genetic Counselors can be an invaluable resource for a CMTer. They can help you find genetic counselors near you, and a genetic counselor can help you sort out if testing is right for you. And, a genetic counselor can even arrange for the testing itself. You can check them out on their website at nsgc.org and I'll put a link to their website in the show notes.

Invitae, if that's even how you even pronounce their name, I'm not sure, it's spelled, like, way weird. But Invitae has an awesome free program that will test for mutations in 72 genes that are associated with inherited neuropathies. CMT is nothing more really than a collection of inherited neuropathies and, again, there will be much more on this in the next episode. But, it's the Invitae test number 3200. This test is free to people who live in the USA and Canada, and the test is part of a much larger program that the lab has. And, really, Invitae is the current Worldwide Heavyweight Champ in CMT genetic testing, too. But, I'll put a link to their program in the show notes for you. And, with that, I bid you farewell until the 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.