

Genetics Is Redefining the CMT Field

When Charcot-Marie-Tooth disease (CMT) was first described in 1886, the cause wasn't known. Today, we know that mutations in more than 100 genes can lead to the peripheral neuropathy symptoms that characterize CMT. This knowledge is becoming increasingly important in the CMT treatment landscape.

"Supportive care is still the backbone of treatment, but CMT care is becoming much more genetically informed," says Matias Lopez Chacon, MD, a pediatric neurologist at Johns Hopkins All Children's Hospital in St. Petersburg, Florida.

When a patient presents with signs of CMT, genetic testing combined with family history, a neurological examination, and nerve conduction studies give healthcare providers and families a more complete picture. "Nowadays, genetic testing can end years of diagnostic uncertainty. It can clarify inheritance and recurrence risk and will guide family counseling and sometimes change what associated features we monitor for," Dr. Lopez Chacon says.

For all types of CMT, care focuses on maintaining mobility, preventing falls, treating pain and fatigue, optimizing hand function, utilizing orthotics, and treating musculoskeletal deformities of the feet and spine. However, "the standard of care is still multidisciplinary, but counseling is increasingly subtype-specific," Dr. Lopez Chacon says.

He explains: "For example, in CMT1A due to PMP22 duplication, it's often slowly progressive, so counseling focuses on long-term function, orthotics, family counseling for themselves, and future research around PMP22. On the other hand, CMT2A, caused by MFN2, can be more severe, have earlier onset, and some patients can have associated features, such as optic atrophy, so we have to be more preventive than reactive."

In addition, knowing the genetic cause and subtype of CMT is increasingly important for determining a patient's eligibility for certain clinical trials or future targeted therapies.

Dr. Lopez Chacon points to several promising genotype-specific therapy approaches being explored, such as using antisense oligonucleotides (ASOs) or small interfering RNA (siRNA) to lower the expression of PMP22 in CMT1A.

“The most promising thing is not one medication but the fact that the field is becoming more precise, more genetically defined, and we’re getting more ready for targeted trials,” he says.

Resources

- Washington University, St. Louis, [Neuromuscular Disease Center website](#) glossary of neuropathies
- Charcot-Marie-Tooth Association [Types of CMT](#)
- Studies on lowering PMP22 in CMT1A:
 - jci.org/articles/view/96499
 - jci.org/articles/view/159814
 - nature.com/articles/s42003-021-01839-2
 - nature.com/articles/s43856-023-00400-y
- INSPIRE phase 2/3 trial of Govorestat in CMT-SORD:
 - clinicaltrials.gov/study/NCT05397665