HEREDITARY NEUROPATHY FOUNDATION

cmtupdate

Impact That Matters

Driving CMT Research with the Patient's Voice

SPRING 2023

The Flynt family

Jaxson is 10 years old and a patient with MTRFR/C12orf65.

CMT Genie

Despite the best efforts of our CMT community providing resources to obtain genetic testing, there are still barriers that remain challenging in obtaining a definitive diagnosis. HNF has changed that by developing the CMT Genie program. We are here to support and facilitate genetic counseling and provide immediate access to information and support for in-home testing and the translation of genetic reports to patients. Whether you need to learn more about variants identified in your DNA or seek further explanation of inheritance patterns, the CMT Genie is available to all patients and families affected by CMT, and for those that suspect CMT is the cause of their symptoms.

"The process was very easy. I met with Genome Medical and received the genetic test kit within a few days. The kit was well packaged in a small box and had everything I needed. Shortly after I shipped the kit back, I received an email to register online. Less than two weeks later, I received my test results – CMT1A, just as I suspected. Genome Medical notified me via text and email about scheduling a follow-up appointment to go over the results."

— Carrie H.

"I got the results which were negative. I am glad I did the testing, so I now know more than I did before about genetic variants I do not have. Kind of like Thomas Edison and his search for a filament for a light bulb."

— Jeff M.

CMT UPDATE
SPRING 2023

Allison T. Moore
Founder and CEO
Hereditary Neuropathy Foundation

Dear CMT Community,

I am so excited to be able to share this latest *CMT Update* with you! It is packed full of research updates (in fact, we had to save a few for next time because we ran out of space!). This edition focuses on a group of CMTs we are calling "Mitos" (mitochondrial diseases). I would like to personally thank the Flynt family for their generous support and endless work to champion this cause. The poor growth, developmental delays and muscle weakness caused by these types of CMT are the result of the inability of the mitochondria to completely burn food and oxygen to generate energy, which is essential for normal cell function. There is a lot of industry investment (see the chart on page 5) and interesting research (see Dr. Horvath's project on page 6) into Mito CMTs. HNF is committed to bringing treatments and cures for ALL types of CMT, not just the most common types. You can learn more about Mito CMTs in our Feature Article.

The HNF team is working on many other important projects - drug repurposing with Rarebase, clinical trial readiness with the CMT Genie and our IRB-approved GRIN patient registry. A BIG thank you goes out to Estela Lugo for her work to win HNF a grant award from Global Genes fund the "No Camines Solo/Don't Walk Alone" campaign, a Spanish CMT PSA Awareness Campaign with Diagnosis & Patient Care Toolkit. With this grant we hope to add more diversity to our GRIN patient registry which is required by the FDA in a clinical trial population for drug approval.

As always, we could not do this work without participation and support from YOU! If you have not received a genetic confirmation of your CMT diagnosis, please don't wait! Make an appointment to speak with one of the HNF team members on a CMT Genie call TODAY. www.cmtgenie.org. And when you receive your genetic report in 4-6 weeks, or if you already have one, please participate in CMT research by joining GRIN and uploading your genetic report into the IRB-approved, secure GRIN documents section. If you are able to donate - either financially or eventually, biospecimens – you'll find the contact info at the top of the chart on page 5.

Finally, I would like to offer a HUGE welcome to the newest member of the HNF team, Kenneth "Kenny" Raymond. He is already proving to be invaluable to the curation of genetic reports in GRIN - and adding humor and diversity to our small, but mighty, HNF team. Welcome, Kenny!

I am heading off to share important GRIN data and HNF research with the hundreds of investigators and clinicians at this year's Peripheral Nerve Society meeting, the European CMT Federation and Euromit 2023. I'll look forward to sharing insights with you when I return in the next edition of the *CMT Update*. Until then, enjoy your summer and…join GRIN!

Best,

Allison T. Moore

Allison T. Moore

TRIAD
THERAPEUTIC RESEARCH IN ACCELERATED DISCOVERY

HNF SHEDS LIGHT & RESEARCH FUNDING ON MITOCHONDRIAL DISEASES LINKED TO CMT

Mitochondria are the powerhouses of our cells. Think of them as our body's batteries. Mitochondrial disease causes these batteries to run low. Some CMTs fall under the umbrella of mitochondrial diseases, which account for approximately 1 in 4000 people worldwide. Like CMT, each "Mito" disease is unique and can be present at birth or later in life. They are typically progressive, causing motor and sensory dysfunction, and may include developmental or cognitive disabilities.

How do mitochondria affect CMT?

Mitochondria are the organelles responsible for **producing energy within cells** through a process called oxidative phosphorylation. In Charcot-Marie-Tooth (CMT) disease, some subtypes can affect the function of mitochondria, leading to **decreased energy production and increased oxidative stress**. This can contribute to the **development of peripheral neuropathy**, which is the primary symptom of CMT.

In addition to producing energy, mitochondria also play a role in several other cellular processes that can be affected by CMT. For example, mitochondria are involved in **calcium homeostasis**, which can be disrupted in some forms of CMT. Mitochondria also regulate apoptosis, or programmed cell death, which **may contribute to the loss of motor and sensory neurons in peripheral neuropathy**.

How is HNF funding mitochondrial CMT projects?

HNF is investing in natural history studies, and biomarker development to advance repurposed and novel drugs, gene therapies and to support HNF TRIAD industry partners for many subtypes of Mito CMT.

How can patients participate in research?

How alterations in mitochondrial motility impact mitochondrial function in CMT remains poorly understood. To help support answers, **join GRIN & complete ClinGen surveys!** After you **enroll in GRIN** (JoinGRIN.org) and complete the Natural History Study survey, you can provide mitochondrial info through the ClinGen surveys! The ClinGen surveys start with the Health & Development survey. Depending on your answers, you will have additional, more specific surveys such as Bones & Cartilage, Blood & Bleeding, Eyes & Vision, etc. If you have not yet done so, please complete all assigned ClinGen surveys.

Important:

If you are willing to provide a biological sample to advance biomarker research, **please email registrycoordinator@hnf-cure.org** with your contact information (name, date of birth, address (City/State), and phone number)

DONATE
Click here!

Research Partner	Description	Mito CMT
Rarebase	Leverages cutting-edge technology and biology using repurposed FDA-approved drugs to deliver accelerated, off-label treatments for various types of Mito CMT.	**MTRFR/C12orf65** **CMT2A (MFN2)** **CMT4A & 2K (GDAP1)** **CMT 6**
MIRALINC	Pioneering Next Generation HDAC6 inhibitors to advance life-changing disease cures for Mito CMT.	**CMT2A (MFN2)** **CMT4A & 2K (GDAP1)**
Undisclosed	Novel drug for Mito CMT.	**CMT2A (MFN2)**
Burke Neurological Institute	The Willis Lab has developed in vivo models and testing HDAC6 inhibitors and gene therapies to treat Mito CMT.	**CMT2A (MFN2)** **CMT4A (GDAP1)**
UHealth University of Miami Health System | University of Miami Miller School of Medicine	The Saporta CMT Stem Cell Laboratory has develop iPSCs to treat Mito CMT.	**MTRFR/C12orf65** **CMT4A (GDAP1)** **CMT 6**
University of Cambridge	Rita Horvath, MD, PhD is conducting a retrospective Natural History Study.	**MTRFR/C12orf65** **CMT 6**
The Jackson Laboratory	The Burgess Lab has developed in vivo model to test small molecules and gene therapies to treat Mito CMT.	**MTRFR/C12orf65** **CMT 6**
University of Helsinki	The Battersby Lab is working on small molecules and gene therapies with a focus on treating cytokine storms and optic neuropathy for Mito CMT.	**MTRFR/C12orf65** **CMT 6**

Cambridge-led Natural History Study identifies MTRFR/C12orf65 deficiency to improve diagnosis and therapy development

Cambridge-led retrospective natural history study funded by the Hereditary Neuropathy Foundation identifies MTRFR/C12orf65 deficiency with a method to improve diagnosis, patient care, and therapy development.

At the Department of Clinical Neurosciences, University of Cambridge, Rita Horvath, MD, PhD (Director of Research in Rare Neurogenetic Diseases) has opened a study collecting retrospective data on rare disease patients to assist the Hereditary Neuropathy Foundation (HNF), and its Therapeutic Research In Accelerated Discovery (TRIAD) research partners to advance a gene therapy to treat these patients with MTRFR/C12orf65 deficiency, a rare Mito CMT.

MTRFR/C12orf65 deficiency is a rare complex axonal hereditary motor neuropathy that presents with a series of diseases that cause blindness and cognitive impairment. MTRFR/C12orf65-related disease may result in CMT6, Leigh Syndrome, Spastic Paraplegia-55, Behr Syndrome and COXPD.

Dr. Horvath and her research team developed a retrospective Natural History Study to collect and review the symptoms of patients who have a genetic defect in the MTRFR/C12orf65 gene.

"We felt it was vital to identify as many patients as possible to learn as much as we can about this variant of CMT and to enable a better understanding of the disease. So far, Dr. Horvath's method has identified 33 patients who were previously reported with MTRFR/C12orf65 deficiency internationally",

HNF developed the **Therapeutic Research in Accelerated Discovery (TRIAD)** as a collaborative effort with academia, government and industry, to develop treatments for CMT. Currently, TRIAD involves many groups that span the drug discovery, drug development, and diagnostics continuum.

"By using Dr. Horvath's method, perhaps we can find additional patients in the US, UK and worldwide, which has been extremely difficult. Patients are most likely not getting diagnosed due to the vast genetic testing panels, which may or may not include these genes. Furthermore, neurologists and other medical practitioners would not typically know how to order the appropriate test" says Allison Moore, CEO, HNF.

It is our hope that our approach will enable a more robust characterization of the disease caused by MTRFR/C12orf65 mutations. We are looking forward to seeing as many patients as possible with this condition worldwide. The final aim of our study is to use the data to develop new treatments for this progressive neurodegenerative condition" says Rita Horvath, MD, PhD.

Patients will also be invited to enroll in the HNF patient registry, Global Registry for Inherited Neuropathies (GRIN). The registry's goal is to acquire, record, and analyze patient-reported data and associated genetic reports, Electronic Health Records (EHRs) and clinical notes to identify the burden, diagnostic journey, and prevalence of disease that will aid scientists in their work toward finding a cure.

The data collected has helped HNF and its partners in industry, academia, and government identify previously unknown genotype/phenotype correlations, uncover important comorbidities such as pain or respiratory issues, and target research spending based on actual patient need and likelihood of success. By including patients with MTRFR/C12orf65-related disease, additional data will be captured to gain more insight on direct patient and caregiver reported outcomes for research and clinical trials.

Since whole exome sequencing (WES) is more commonly becoming 'standard of care' in the first-line diagnosis of neurogenetic disease including mitochondrial disease and CMT, we predict that WES will identify more patients with MTRFR/C12orf65 deficiency, even with less characteristic phenotype.

To support patient diagnosis, HNF's CMT Genie was developed to assist patients and healthcare providers access to affordable options for genetic testing.

If you think you or a family member might have MTRFR/C12orf65 deficiency you can contact HNF for genetic testing (cmtgenie.org).

If you have MTRFR/C12orf65 deficiency and would like to participate in Dr. Horvath's research, please contact the study team directly.

Email: add-tr.mitoteam@nhs.net **Tel:** +44 (0)1223 33150

TRIAD

Rarebase

3,884 FDA-Approved and experimental drugs were screened for...

5 Types of CMT;

14 Genes

CMT1:

CMT1A
(PMP22 dup)

HNPP
(PMP22 del)

CMT2:

CMT2A
(MFN2 & MFN2 w/ optic atrophy)

CMT2K
(GDAP1 recessive)

SORD Deficiency

CMT4:

CMT4A
(GDAP1 dominant),

CMT4B
(MTMR2),

CMT4F
(PRX)

CMT4J
(FIG 4)

CMT6:

Mitochondrial Disease
(MTRFR, C12orf65), often clinically diagnosed as Leigh Syndrome, Spastic Parapheligia-55, Behr Syndrome, COXPD, and Ataxia.

OTHER INHERITED NEUROPATHIES:
CNTNAP, ADOA (OPA1)

MILESTONES

Drug Repurposing for CMT

2022
Stage I:

Discovery (identified drug repurposing candidates)

◆ **Completed**

2022-23
Stage II:

Testing top candidates in CRISPR-engineered cellular models of disease for potency and activity.

◆ **In Progress**

2023- 2024
Stage III:

(If applicable) Conduct clinical trials on top candidate(s)

HNF Awarded 2023 Health Equity in RARE **Impact Grant** For Spanish CMT PSA Awareness Campaign with Diagnosis & Patient Care Toolkit

The Hereditary Neuropathy Foundation is thrilled to announce that we are a recipient of the Global Genes **Health Equity in RARE Impact Grant** (Click here)!

The grant will fund the "No Camines Solo/Don't Walk Alone" campaign, a Spanish CMT PSA Awareness Campaign with Diagnosis & Patient Care Toolkit.

Why a Spanish Campaign?

Due to economic, language, and medical specialist barriers, Latino/a/x individuals are less likely to receive a CMT diagnosis and proper care. A **report by the Kaiser Family Foundation** (**Click here!**) found that Latino/a/x adults were more likely to report problems accessing healthcare compared to non-Latino/a/x white adults, with language and lack of health insurance cited as key barriers. In addition, Latinos/a/x are at the highest risk of being uninsured, with nonelderly adult Latino/a/x nearly two and half times as likely to be uninsured than nonelderly adult whites (22% vs. 9%). Uninsured children rates are lower than those for adults, but Latino/a/x children are still twice as likely as white children to be uninsured (8% vs. 4%).

About The Campaign

Our project will focus on disseminating a targeted bilingual awareness campaign starting with the top 20 Spanish-speaking zip codes in NYC, home of HNF and the city with one of the largest populations of our target demographic.

According to the U.S. Census Bureau 2019, approximately 2.4 million people in NYC speak Spanish at home, about 28.6% of the city's population.

Our focus is to support Spanish-speaking Latino/a/x individuals in self-identifying their CMT symptoms and providing vital CMT diagnostic resources, patient care, and research data.

Additionally, we will focus on educating newly identified patients on future clinical trials and provide bilingual genetic counseling services (already available) with genetic testing via **HNF's CMT Genie** (cmtgenie.org).

We anticipate increased diagnosis and awareness of CMT in the NYC area, including among children. According to HNF's **Global Registry for Inherited Neuropathies**, **GRIN** (JoinGRIN.org), 23.5% of CMT patients/caregivers reported experiencing symptoms in childhood (0-10 yo) yet waited ten or more years for a CMT diagnosis.

Nine of 102 Global Advocacy Alliance organizations submitted received the 2023 Health Equity in RARE Grants. These grants will allow patient advocacy organizations to improve outreach strategies, develop content, and address challenges that affect underserved and underrepresented people within the rare disease patient community.

ATTENTION!

HNF is currently seeking bilingual volunteers to join our mission.
If you are interested in donating translation services, please email Estela Lugo at estela@hnf-cure.org.

GLOBAL REGISTRY FOR INHERITED NEUROPATHIES

HNF & KENNETH RAYMOND JOIN FORCES TO CLARIFY CMT GENETIC REPORTS

Since the launch of HNF's CMT Genie last August, over 200 individuals have participated in hopes of receiving a genetic confirmation of their CMT symptoms. Although many have found a definitive diagnosis, many others have received their results as a variant of uncertain significance (VUS)."This is very common with a complex disease like CMT," says genetic expert Kenneth Raymond who has been studying and publishing CMT genetic data for over 20 years.

What are Variants of Uncertain Significance (VUS)?

They are changes in a gene's DNA sequence that have an unknown effect on a person's health. There is usually not enough information about a VUS to know whether it increases a person's risk of developing a disease.

Getting a VUS can be extremely frustrating for anyone already struggling through the difficult process of seeking answers about CMT and adequate medical care.

How does Kenneth Raymond review VUS reports?

Patients who already have a genetic report can upload them into their profile in HNF's Global Registry, GRIN (**JoinGRIN.org**). If they have not yet joined, they can create an account (**demo video: Click here!**) and upload their PDF or JPEG.

Those who have not yet had genetic testing they can book a CMT Genie call with the HNF team and get connected with a virtual genetic counselor and in home testing.

How do Genetic Reports Drive CMT Research?

Not only do genetic reports support patient care and diagnosis, but they also play a key role in CMT research by correlating a patient's genotype (genetics) with their phenotype (symptoms). This allows HNF to show real-world prevalence and occurrence rates, which are vital for biotech and industry, as presented in the recent webinar "Making Sense & Science of CMT Symptoms" **(Click here!)**.

From HNF CEO & Founder, Allison Moore

"Kenny will lead the development of the "right data" curation form to be added to the Matrix-GRIN platform for the curation of patient genetic report records. He will transcribe the pertinent data from each GRIN participant that provided a report. Kenny is an ideal candidate for this position as he has working knowledge and experience reading CMT genetic testing results, as well as the over 100 genes associated with CMT. We are thrilled to have him on board as a passionate, knowledgeable, and valuable member of the HNF team."

— Allison Moore

JOIN GRIN

Turn CMT Symptoms into Science

45
Countries Represented

3671
Participants

35
Types of CMT Represented

4.4%
Hispanic/Latino

182
Confirmed Mito CMT Patients

JOIN GRIN

Click here!

HNF
1641 3rd Avenue
#28K
New York, NY 10128
hnf-cure.org

DONATE!
CLICK HERE!

Learn more about HNF resources

Visit hnf-cure.org
to learn more about:

- Movement is Medicine™
- CMT-Connect Webinars
- HNF Centers of Excellence
- The CMT Genie
- Join Team CMT
- Patient Resources

Global Registry for Inherited Neuropathies (GRIN):

A Patient-Powered Registry Boosts the Study of Charcot-Marie-Tooth (CMT) Disease

CMT is a genetic, degenerative neuromuscular disease that affects 1:2500 in the US and 2.5 million worldwide—many are still undiagnosed—and currently, there is no cure. CMT is progressive, and over time, muscles in the feet, legs, and hands lose strength. Muscles waste away and cause atrophy leading to mobility issues. It can have a serious impact on vision, hearing, breathing, speech, and swallowing in extreme cases. Some patients experience hip dysplasia, scoliosis, and/or blindness.

MISSION:
Global Registry for Inherited Neuropathies (GRIN) was developed to conduct patient-focused research and for the development of treatments and cures for Charcot-Marie-Tooth (CMT). GRIN is the only comprehensive patient registry collecting patient-reported information about living with CMT in combination with genetic reports, electronic health records, and other critical data for research. The patient voice is at the forefront of all we do.

The Hereditary Neuropathy Foundation mission is to increase awareness and accurate diagnosis of Charcot-Marie-Tooth (CMT) and related inherited neuropathies, support people living with CMT and their families with critical information to improve quality of life, and fund research that will lead to treatments and cures.

www.hnf-cure.org

Publication of this newsletter was made possible with the financial support of Pharnext.