HEREDITARY NEUROPATHY FOUNDATION

cmtupdate

Impact That Matters

Driving CMT Research with the Patient's Voice

FALL 2023

First Ever Biorepository Launched for CMT

Pg 4

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.

Book a CMT Genie Call
tinyurl.com/4d75xu45

"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
FALL 2023

Allison T. Moore
Founder and CEO
Hereditary Neuropathy Foundation

Happy Fall!

I hope everyone had a wonderful summer and made many memories with family and friends. The HNF team worked hard these past months to start the fall with exciting opportunities for the CMT community.

HNF launched the first-ever biorepository for Charcot-Marie-Tooth with COMBINEDBrain. HNF chose COMBINEDBrain as a partner for their state-of-the-art biorepository, dedicated team, and ability to quickly and efficiently fill a research gap to benefit the entire CMT research community. Patients will learn more about participating all over the United States in the coming weeks by providing blood samples with the "Roadshow."

We also launched new Pediatric CMT Natural History Studies at two Centers of Excellence at Lurie's Children's Hospital of Chicago and Arkansas Children's Hospital. Both are now open for enrollment! Patients will be asked to join GRIN and participate in the study by consenting to have their clinical data, including CMTPedS or CMTInfS scores, entered into GRIN.

HNF remains committed to helping patients access genetic testing with the CMT Genie program (https://tinyurl.com/4bj98ckh). Many negative CMT genetic test results are variants of unknown or uncertain significance—VUS. A VUS is a gene mutation in which scientists cannot yet confirm if the mutation is harmless or causes a disease. Therefore, more data is needed. HNF is committed to solving this dilemma and supporting families with answers and additional testing recommendations through our Genie's gene variant curation process.

The Global Registry for Inherited Neuropathies (GRIN) is expanding to three new languages, French, Italian, and Spanish, to support Natural History Studies. Expanding GRIN into additional languages will allow more CMT patients worldwide to participate in research!

We are also excited to share the latest update on Miralinc Pharma, Inc., which has recently completed a 6-month study of their HDAC6 inhibitor, MRL-A100, in a MFN2/CMT2A mouse model in collaboration with Prof. Dianna Willis from the Burke Neurological Institute. The team continues its process optimization, scale-up efforts, and additional testing to prepare the compound for an IND submission.

Last month, DTx Pharma announced the Novartis acquisition for an upfront payment of $500 million and additional payments of up to $500 million upon completion of pre-specified milestones. Patient registries, insights, and natural history studies are crucial for success from lab to market. You can help by joining GRIN (https://tinyurl.com/554kk2zh).

Lastly, be sure to watch our Making Sense & Science of CMT Symptoms webinar to connect with valuable resources and find out how to help further research for Charcot-Marie-Tooth.

I hope you will value the information in this *CMT Update*, and I look forward to hearing from you with any feedback, questions, or ideas. With all of the current advancements, there is no better time to support HNF! By donating today (https://tinyurl.com/4vfxb9hk), join the effort to find the treatments and cures for all Inherited Neuropathies. As always, I appreciate your support of the HNF mission and its programs.

Allison T. Moore

GLOBAL REGISTRY FOR INHERITED NEUROPATHIES

FIRST EVER BIOREPOSITORY FOR CHARCOT-MARIE-TOOTH: HNF LAUNCHES THE CMT BIOBANK

The Hereditary Neuropathy Foundation (HNF), announces enhancements to their Charcot-Marie-Tooth (CMT) and Inherited Neuropathies (IN) patient registry, Global Registry for Inherited Neuropathies (GRIN). GRIN is an IRB-approved, patient-consented registry. This research consortium consists of researchers and clinical experts, including various partnerships globally (CMT advocacy groups, data scientists, genetic experts and industry).

CMT is a group of inherited disorders with 128 genes responsible for all the CMT subtypes, CMT1A being the most common. GRIN acquires, records, and analyzes patient-reported data, associated genetic reports, and validated, clinical CMT scales (CMTPeds, CMTInfS) to identify the burden, diagnostic journey and prevalence of disease. CMT impacts the quality of life starting in childhood and is progressively debilitating. Currently, there are no treatments, but there are many potential therapies in the pipeline. There are still gaps in understanding the natural history of the disease correlation of genotype/phenotype, the availability of patient biospecimens for translational research, and validation of drug candidates and biomarkers for CMT.

COMBINEDBrain, a non-profit with a biorepository consortium, represents and partners with 65 rare-disease advocacy groups, including HNF. The CMT Biobank is an enhancement to the GRIN consortium and will offer GRIN patient registrants the opportunity to participate in innovative and translational research to accelerate CMT therapies. The new CMT Biobank will collect and store patient samples, including blood, tissue, skin fibroblasts, Induced Pluripotent Stem Cells (iPSCs), and more.

HNF chose COMBINEDBrain as a partner for their state-of-the-art bio repository, dedicated team, and their ability to quickly and efficiently fill a research gap and benefit the entire CMT research community.

"For clinical trials to be successful, targets for treatment and biomarkers must be identified. To date, there is no available biorepository of CMT samples for researchers or industry to pull from. Today, HNF has changed that and is excited to advance research and therapy development with the help of COMBINEDBrain," states Allison Moore, Founder/CEO HNF.

"We stick to our mission as an organization by collaborating with clinicians, scientists, and industry, and one thing they all agree on is the importance of biomarker discovery for each of these rare communities", said Dr. Bichell, Founder of COMBINEDBrain. ***"One easy way to start identifying biomarkers is to collect patient samples, often blood or other biofluid, for researchers, clinicians or industry to study and advance the field of CMT/IN research for your families,"*** said Dr. Bichell.

- **For patient participation:** Join GRIN!
  Visit: www.JoinGRIN.org
- **For GRIN questions or to volunteer to provide patient samples:**
  Contact: registrycoordinator@hnf-cure.org
- **To request patient samples and/or inquire about partnerships:**
  Contact: allison@hnf-cure.org

Breaking News

GRIN is Available in Three New Languages – French, Italian and Spanish – to Support Natural History Studies

Expanding GRIN into additional languages will allow more CMT patients worldwide to participate in research. Some CMT mutations are more relevant in specific regions and ethnicities, such as with GDAP1. Other mutations are rare and require global engagement to locate patients and their critical data, biospecimens, etc., for research and clinical trials, especially when targeting gene therapies.

With the exciting innovations of therapy developments emerging out of France and current and potential new clinical trials, HNF continues to support enrolling patients with surveys in French for vital natural history studies offered by GRIN.

We also chose Italian as a priority language due to the amazing research coming out of Italy, especially with the focus of evidence-based medicine studies in pediatrics to improve quality of life amongst CMT patients.

Many families affected by CMT expressed interest in sharing their patient journey. Patients and caregivers understand the importance of natural history research in improving the understanding of CMT, and HNF wanted to allow these patients to participate in HNF's research consortium. Every patient's voice matters!

JOIN GRIN

www.JoinGRIN.org

HNF ANNOUNCES **PEDIATRIC CMT NATURAL HISTORY STUDY ENROLLMENT** AT TWO CENTERS OF EXCELLENCE

The Hereditary Neuropathy Foundation (HNF), an advocacy and research 501c3 non-profit, today announces a Pediatric CMT Natural History Study enhancement to their Charcot-Marie-Tooth (CMT) and Inherited Neuropathies (IN) patient registry, Global Registry for Inherited Neuropathies (GRIN). GRIN is an IRB-approved, patient-consented registry. This research consortium consists of researchers and clinical experts, including various partnerships globally (CMT advocacy groups, data scientists, genetic experts and industry).

CMT is a group of inherited disorders with 128 genes responsible for all the CMT subtypes, CMT1A being the most common. GRIN acquires, records, and analyzes patient-reported data and associated genetic reports to identify the burden, diagnostic journey and prevalence of disease. CMT impacts the quality of life starting in childhood and is progressively debilitating. Currently, there are no treatments, but there are many potential therapies in the pipeline. There are still gaps in understanding the natural history of the disease and phenotype genotype correlation, especially in younger patients.

Together with Dr. Vamshi Rao, Lurie Children's Hospital in Chicago, IL; and Dr. Aravind Veerapandiyan, Arkansas Children's Hospital, Littlerock, AR; the HNF seeks to establish a Pediatric Natural History Study by collecting the validated, clinical CMT scales in the GRIN registry. Pediatric patients seen by Drs. Rao and Veerapandiyan will be asked to join GRIN and participate in the study by consenting to have their clinical data including CMTPedS or CMTInfS scores entered into GRIN. Staff at both sites have been certified to conduct the evaluations. If you would like to be considered for the study, or if you would like to nominate your pediatrician or pediatric neurologist to participate in the study, please complete this contact form. https://forms.gle/tBubB1Jpudo2zQUU9

Currently, data from GRIN shows pediatric patients ages 0-17 diagnosed with CMT are broadly affected with a wide spectrum of symptoms. CMT impacts quality of life starting in childhood. 22.3% of CMT patients experienced initial symptoms during early childhood, between ages 0 and 5 years. About half (50.5%) of CMT patients had symptoms onset before the age of 16 years. 55% of symptoms were noticed by family members before official diagnosis. This Pediatric CMT Natural History Study seeks to expand upon these findings which will have important implications for design of clinical trials and identification of meaningful endpoints. It's critical that pediatric physicians encourage enrollment of patients in GRIN.

CURRENT LOCATIONS RECRUITING ARE:

Arkansas Children's Hospital
Dr. Aravindhan Veerapandiyan
1 Children's Way, Little Rock, AR 72202-3591
To participate contact: aveerapandiyan@uams.edu

Ann and Robert H. Lurie Children's Hospital of Chicago
Dr. Vamshi Rao
225 East Chicago Avenue, Chicago, IL 60611
To participate contact: ptan@luriechildrens.org

Improving CMT Genetic Diagnosis

Despite gains made in CMT genetic discovery, and gains made in genetic testing technology and capabilities, genetic testing in CMT remains limited. Scientists have discovered more than 125 genes linked to CMT. Mutations in any of these genes cause more than 160 individual subtypes. With HNF support, scientists continue to make new discoveries every year. Although these numbers are monumental, more than half of all who have CMT are not able to obtain genetic confirmation of their disease.

A large part of negative CMT genetic test results are variants of unknown or uncertain significance—VUS. A VUS is a gene mutation in which scientists do not yet know if the mutation is harmless or if it causes a disease and more data is needed. Through our genetic test results gene variant curation, HNF is committed to solving this dilemma.

HNF's Global Registry for Inherited Neuropathies (GRIN) is a patient-led research platform consortium of CMT researchers and clinical experts, including various partnerships globally (CMT advocacy groups, data scientists, genetic experts) and industry. Through GRIN, CMT patients are able to securely upload their genetic test results. HNF then de-identifies and curates the gene mutations listed in the shared report. This data is curated in such a way that individual mutations are searchable and can be matched with phenotype profiles (symptoms reported by patients in their secure GRIN registration). Scientists are then able to study these correlations like never before.

Says Kenneth Raymond, HNF's GRIN Genetics Data Curator, "We believe we've designed and structured our gene variant curation in such a way that will allow scientists to have not only the capability to establish genotype-phenotype relationships, which is critical to understanding the disease burden of CMT on patients and to assess clinical trial outcomes, but to also resolve VUS's that could lead to many finally receiving a genetic confirmation of their CMT. Combined, GRIN provides CMT genomic science data unavailable elsewhere. These tools are available to CMT researchers at a scale not before seen in CMT, and through these efforts with GRIN, HNF's commitment to finding treatments and ultimately a cure remains as strong as ever."

For Researchers and Industry partnership opportunities, contact Allison Moore

allison@hnf-cure.org office: 212-860-5405

Join GRIN:

www.JoinGRIN.org

Need a genetic diagnosis? Make an appointment with the CMT Genie:

www.CMTGenie.org

JOIN GRIN

Turn CMT Symptoms into Science

60
Countries Represented

3929
Participants

41
Types of CMT Represented

62%
Willingness to Donate Bio Specimens

TRIAD

MIRALINC

Miralinc Pharma, Inc., has recently completed a 6-month study of their HDAC6 inhibitor, MRL-A100, in a MFN2/CMT2A mouse model in collaboration with Prof. Dianna Willis from the Burke Neurological Institute. MRL-A102 showed statistically significant and dose-dependent neuroprotective effects, preventing motor and sensory deficits as evaluated by von Frey, Hargreaves and Rotarod. They are continuing their process optimization and scale up efforts and additional testing to prepare the compound for an IND submission.

DTx Pharma Announced the Novartis Acquisition

Last month, DTx Pharma announced the Novartis acquisition for an upfront payment of $500 million and additional payments of up to $500 million upon completion of pre-specified milestones. DTx Pharma is a young company that has developed a platform for RNA therapeutics called Fatty Acid Ligand Conjugated Oligonucleotide or (FALCON™). This is a very exciting next step as Novartis brings substantial resources and drug development experience to help accelerate the process of getting DTx-1252 through clinical trials and into the marketplace to benefit an estimated 150,000 patients living with CMT1A in the U.S. and Europe.

The increasing attention to CMT and the notable strides in research and drug development highlights the significance of non-profits in the medical landscape. As these organizations continue to drive venture philanthropy and collaborate with industry leaders, we can anticipate even more breakthroughs in CMT treatment options.

Venture philanthropy through non-profit organizations has proven instrumental in attracting major pharmaceutical industry players' attention.

So what's next?

Patient registries, insights, and natural history studies are crucial for success from lab to market. By better understanding the disease progression and patient needs, researchers and pharmaceutical companies can design more effective clinical trials, increasing the likelihood of success in bringing life-changing medicines to CMT patients.

Clinical research is inherently complex and unpredictable. Addressing these issues requires rigorous study design with sensitive clinical measures and/or biomarkers, careful patient selection, efficient trial management, and continuous evaluation and adaptation throughout the trial process.

"We encourage the CMT patient community to join GRIN and upload their genetic report. The clearer picture we paint of CMT, the higher chance we have for clinical trial success"
– Allison Moore

HNF continues to expand GRIN as a state-of-the-art CMT clinical trial preparation tool. This Global Patient Registry, currently includes 48 countries in multiple languages and enables biotech and pharma to address clinical trial failure risks. By capturing complex genotype and phenotype data from the most common types of CMT, such as CMT1A, as well as the rarest of CMT types, such as CMT4A (GDAP1), and everything in between, GRIN allows for meaningful curation that optimizes critical data.

HNF's GRIN is not only an IRB-compliant CMT natural history study, but is also a collaborative research platform that provides an unrivaled opportunity for scientists and research foundations from across the globe to study how CMT affects patients in their day-to-day lives.

The data models from GRIN have already revealed new potential symptom correlations, facilitated the identification of potential biomarkers, and have shown that innovative technology integrations such as digital wearables and real-time video capture are strong candidates for assessing outcome measures.

WEBINAR:

Making Sense & Science of CMT Symptoms

"Is this symptom related to CMT?"

This is a frequent question asked by many individuals living with CMT and their loved ones. Most of us are familiar with the most common symptoms of CMT, such as foot drop & hand weakness. However, many less-recognized symptoms can be just as disruptive to our lives but have not yet been studied or linked to CMT; the rarer the symptom, the more uncertain and isolated we may feel.

What participants are saying:

This webinar was fantastic. I have felt alone in this land of CMT. I am going to look into testing. I am grateful.

– Judith

Thank you so much…I am looking forward to hearing back from you and appreciate such a wonderful night full of information!!!

– Staci

Just wanna say thank you all for doing this for us! Appreciate this!

– Traci

I LOVE these zoom CMT meetings and I thank you for all you do for us!

– Leanne

Great job on the webinar last night! Very informative, I am sure it was valuable for all participants!

– Peter

How do we know if our symptoms are CMT-related, and how can we drive research to better answer this question?

Watch HNF's "Making Sense & Science of CMT Symptoms" webinar to find how to help further research for Charcot-Marie-Tooth. **Join GRIN:** https://tinyurl.com/554kk2zh

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- 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:
As part of TRIAD, the Global Registry for Inherited Neuropathies (GRIN) was established as a patient registry and research consortium to advance knowledge of patient records, analyze patient-reported data, collect genetic reports and clinical CMT validated scales (CMTPeds, CMTInfS). The data has been instrumental in identifying the burden, diagnostic journey and prevalence of CMT.

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.