NEUROMUSCULAR
DISEASE FOUNDATION

# We are committed to delivering more than a cure.

## The Neuromuscular Disease Foundation is the world's largest GNEM patient advocacy organization.

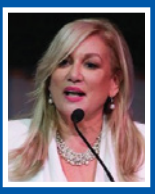
Our scientific programs fund scientific research to advance therapies, including gene therapy. Annual NDF symposia provide outreach and education to the public and convene scientists and physicians to collaborate and share data.

Our clinical programs facilitate proper diagnosis and encourage timely genetic screening, and provide comprehensive resources, support and advocacy to affected individuals and their families and caregivers.

The Neuromuscular Disease Foundation is 501(c)(3) based in Los Angeles, with a presence in 35 countries, and counting.

**CureGNEM.org**
**(310) 721-1605**

Nuria Carrillo, MD



Lale' Welsh
Chief Executive Officer, NDF

Angela Lek, PhD
NDF Scientific Advisor
Research Scientist at,
Lek Lab, Yale University

DEVELOPED UNDER THE DIRECTION AND SPONSORSHIP OF

**NEUROMUSCULAR DISEASE FOUNDATION**

The Neuromuscular Disease Foundation (NDF) is the world's largest GNEM patient advocacy organization. Our scientific programs fund scientific research to advance therapies, including gene therapy. Annual NDF symposia provide outreach and education to the public and convene scientists and physicians to collaborate and share data. Our clinical programs facilitate proper diagnosis and encourage timely genetic screening, and provide comprehensive resources, support and advocacy to affected individuals and their families and caregivers.

NEUROMUSCULAR DISEASE FOUNDATION

The Neuromuscular Disease Foundation is 501(c)(3) based in Los Angeles, with a presence in 35 countries, and counting.

To reach our scientific team:
science@CureGNEM.org
www.CureGNEM.org
(310) 721-1605

# OVERVIEW OF GNE myopathy

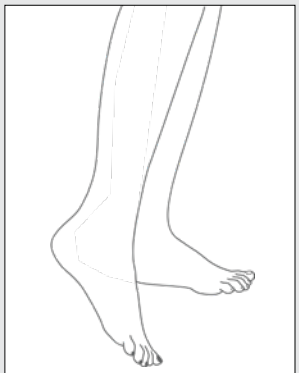
GNE myopathy, previously known as hereditary inclusion body myopathy (HIBM), distal myopathy with rimmed vacuoles (DMRV), or Nonaka myopathy, is a rare genetic muscle disease.[1-4] It has an autosomal recessive pattern of inheritance with an estimated prevalence of 1-9 in 1,000,000 in the general population. It is estimated that ~40,000 GNE myopathy patients exist worldwide.[5] Onset is typically in early adulthood (between 20-40 years old), presenting with bilateral foot drop caused by weakness of the anterior tibialis muscles, with relative sparing of quadriceps muscles (Figure).[6] Cardiac and respiratory functions are rarely affected.[6]

## How does GNE myopathy affect thequality of life?

GNE myopathy is a slowly progressing disease, taking decades to affect skeletal muscles throughout the body. As the disease progresses, muscle weakness typically leads to the following:

- Gait changes and decreased stability, leading to frequent falls.
- Difficulty in climbing stairs, running and getting up from a seated position.
- Use of assistive devices such as orthotics, canes, walkers.

Even though the progression rate is different among individuals, patients typically require a wheelchair within 10-20 years of disease onset.



Foot drop is an early indicator of GNE myopathy.

Muscles of the upper extremities are involved within five to ten years after disease onset, causing difficulty raising arms above head and grip weakness. In later stages of the disease, patients may experience a complete loss of skeletal muscle function and require aid from caregivers for activities of daily life.

## How is GNE myopathy diagnosed?

Patients with characteristic clinical findings, such as young adults presenting with bilateral foot drop, should be evaluated for GNE myopathy. The typical pattern of muscle involvement begins with atrophy of lower leg muscles, progressing to the posterior thigh, and finally affecting the quadriceps muscles in advanced stages of the disease.[2-3,6]

Serum creatine kinase levels may be normal to moderately elevated. Electromyograms and nerve conduction studies do not help reaching a specific diagnosis. Histopathology performed on biopsies from affected muscle groups (not yet replaced by fat) typically reveals atrophic fibers, variation in fiber size and the characteristic "rimmed" vacuoles on Gomori-stained cryosections.[2,3] Muscle MRI shows STIR hyperintensity followed by progressive fat replacement as muscles become affected.[7]

In patients with typical clinical characteristics, genetic testing may be sufficient.[2-3,6] Histopathology of muscle biopsies are needed in instances such as patients with variants of uncertain significance (VUSs) on genetic testing.

Patients receive a definitive diagnosis when pathogenic mutations are identified in both alleles of the ***GNE*** gene.[4-6] Usually, sequencing of the entire gene is needed as there are more than 200 mutations responsible.[5] In relatives of affected patients, or in ethnicities with founder effects, targeted sequencing of the GNE gene can be performed. For example, GNE founder mutations are associated with specific ancestries such as Japanese (Cys44Ser), Roma Gypsy (Ile618Thr), and Middle Eastern (Met743Thr).[4,6] The application of next-generation sequencing panels is expected to increase the identification of GNE myopathy patients from undiagnosed neuromuscular disease cohorts worldwide. However, further investigations are needed when variants of uncertain significance (VUSs) are identified by these methods. Carrier testing and genetic counseling are recommended for patients and families of affected individuals.

## What causes muscle weakness in GNE myopathy patients?

The ***GNE*** gene encodes the bifunctional enzyme responsible for the biosynthesis of sialic acid, and the regulation of cell surface sialylation.[8,9] In patients with GNE myopathy, decreased GNE function and hyposialylation of muscle glycoproteins, are thought to play a role in disease pathophysiology.[10,11] Decreased, but not absent, enzyme activity results from ***GNE*** mutations, which are most commonly missense,[5] with no patients known to harbor two null mutations. This corroborates findings that ***GNE*** knock-out in mice is embryonic lethal, which suggests a potentially critical role for the gene during development.[13] Experts suspect GNE plays additional undiscovered cellular roles that may contribute to disease pathology.[13]

## How can we treat GNE myopathy?

Patients with GNE myopathy should be managed by a multidisciplinary team to establish the extent of the disease and address individual needs as the disease progresses. Ambulatory and assistive devices provide support for motor function and activities of daily living. Patients are encouraged to pursue a healthy diet and a balanced physical exercise regime to avoid muscle ***under***-use. Muscle over-use, such as lifting weights or performing activities that result in severe muscle pain, should also be avoided.[6]

Several efforts are underway to develop therapies specific for GNE myopathy, including sialylation-increasing treatments and gene therapy. Encouraging preclinical evidence for the efficacy of sialic acid and ManNAc in mouse models,14 led to the start of clinical trials to test therapeutic benefit in patients. Negative results emerging from the phase 3 trial of extended-release sialic acid (SA-ER) conducted by Ultragenyx led to the termination of their program.15 ManNAc continues to be evaluated in clinical trials.[16]

Adeno-associated virus (AAV)-based gene therapy preclinical studies to deliver an unaffected copy of the gene are being pursued. Additional funding and research are required to establish safety, dosing, and delivery strategies before moving into clinical trials. Gene editing is being explored as approach to correct common founder mutations in ***GNE*** using CRISPR technology.

## What are the current challenges in the field?

*1. Delayed diagnosis:*

Patients with GNE Myopathy continue to have a delayed diagnosis with an average of 10 years from the onset of symptoms to definitive diagnosis and are frequently misdiagnosed with other conditions.

*2. Incomplete understanding of disease pathophysiology:*

It is being studied how defects in the sialic acid biosynthesis pathway affect cellular functions that lead to muscle atrophy in GNE Myopathy.

*3. Difficulties in establishing a preclinical animal model of the disease:*

Several mouse models (knock-out, knock-in, and transgenic) have been developed. The first two do not recapitulate the muscle disease phenotype of patients with GNE myopathy. The transgenic model develops a muscle phenotype between 20-40 weeks of age, but it has been difficult to replicate in some laboratories. As we move forward, a relevant and reliable preclinical animal model is critical to characterize the mechanisms of disease and perform preclinical testing for potential therapies.

*4. Lack of reliable biomarkers and GNE-specific assays, such as enzyme assays and antibodies:*

These research tools are needed for preclinical assessments, to support clinical trials, and to determine the pathogenicity of novel sequence variants for the diagnosis of patients.

*5. Understanding variability in disease onset and progression:*

It is important to understand the factors that can result in clinical variability, such as the severity of ***GNE*** mutations and their interplay with genetic modifiers and environmental factors. A better understanding of these variables through analysis of natural history and genomic data may lead to more accurate prognoses, patient care, and development of therapies.

**REFERENCES**


1. Eisenberg, I. et al. The UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene is mutated in recessive hereditary inclusion body myopathy. *Nat. Genet.* 29, 83–87 (2001).
2. Nishino, I., Carrillo-Carrasco, N. & Argov, Z. GNE myopathy: current update and future therapy. *J. Neurol. Neurosurg.* Psychiatry. 86, 385–392 (2015).
3. Carrillo, N., Malicdan, M. C. & Huizing, M. GNE Myopathy: Etiology, Diagnosis, and Therapeutic Challenges. *Neurotherapeutics.* 000, 900–914 (2018).
4. Huizing, M., Carrillo-Carrasco, N., Malicdan, M. C. V, Noguchi, S., Gahl, W. A., Mitrani-Rosenbaum, S., Argov, Z. & Nishino, I. GNE myopathy: new name and new mutation nomenclature. *Neuromuscul. Disord.* 24, 387–389 (2014).
5. Celeste, F. V. et al. Mutation update for GNE gene variants associated with GNE myopathy. *Hum Mutat* 35, 915–926 (2014).
6. Carrillo N, Malicdan MC, Huizing M. GNE Myopathy. In: Adam MP et al, editors. GeneReviews® (online). Seattle (WA): University of Washington, Seattle; updated 2020 Apr 9.
7. Liu CY, Yao J, Kovacs WC, Shrader JA, Joe G, Ouwerkerk R, Mankodi AK, Gahl WA, Summers RM, Carrillo N. Skeletal muscle magnetic resonance biomarkers in GNE myopathy. *Neurology.* 2020 Nov 20
8. Hinderlich, S., Weidemann, W., Yardeni, T., Horstkorte, R. & Huizing, M. UDP-GlcNAc 2-Epimerase/ManNAc Kinase (GNE): A Master Regulator of Sialic Acid Synthesis BT - SialoGlyco Chemistry and Biology I: Biosynthesis, structural diversity and sialoglycopathologies. in (eds. Gerardy-Schahn, R., Delannoy, P. & von Itzstein, M.) 97–137 (Springer Berlin Heidelberg, 2015). doi:10.1007/128_2013_464.
9. Keppler, O. T., Hinderlich, S., Langner, J., Schwartz-Albiez, R., Reutter, W. & Pawlita, M. UDP-GlcNAc 2-Epimerase: A Regulator of Cell Surface Sialylation. *Science.* 284, 1372–1376 (1999).
10. Chan, Y. M., Lee, P., Jungles, S., Morris, G., Cadaoas, J., Skrinar, A., Vellard, M. & Kakkis, E. Substantial deficiency of free sialic acid in muscles of patients with GNE myopathy and in a mouse model. *PLoS One.* 12, e0173261 (2017).
11. Noguchi, S., Keira, Y., Murayama, K., Ogawa, M., Fujita, M., Kawahara, G., Oya, Y., Imazawa, M., Goto, Y., Hayashi, Y. K., Nonaka, I. & Nishino, I. Reduction of UDP-N-acetylglucosamine 2-Epimerase/N-Acetylmannosamine Kinase Activity and Sialylation in Distal Myopathy with Rimmed Vacuoles. *J. Biol. Chem.* 279, 11402–11407 (2004).
12. Schwarzkopf, M., Knobeloch, K. P., Rohde, E., Hinderlich, S., Wiechens, N., Lucka, L., Horak, I., Reutter, W. & Horstkorte, R. Sialylation is essential for early development in mice. *Proc. Natl. Acad. Sci.* 99, 5267–5270 (2002).
13. Mitrani-Rosenbaum, S., Yakovlev, L., Becker Cohen, M., Telem, M., Elbaz, M., Yanay, N., Yotvat, H., Ben Shlomo, U., Harazi, A., Fellig, Y., Argov, Z. & Sela, I. Sustained expression and safety of human GNE in normal mice after gene transfer based on AAV8 systemic delivery. *Neuromuscul. Disord.* 22, 1015–1024 (2012).
14. Malicdan, M. C. V., Noguchi, S., Hayashi, Y. K., Nonaka, I. & Nishino, I. Prophylactic treatment with sialic acid metabolites precludes the development of the myopathic phenotype in the DMRV-hIBM mouse model. *Nat. Med.* 15, 690–695 (2009).
15. Lochmüller, H. et al. A phase 3 randomized study evaluating sialic acid extended-release for GNE myopathy. *Neurology* 92, e2109–e2117 (2019).
16. Xu X, Wang AQ, Latham LL, Celeste F, Ciccone C, Malicdan MC, Goldspiel B, Terse P, Cradock J, Yang N, Yorke S, McKew JC, Gahl WA, Huizing M, Carrillo N. Safety, pharmacokinetics and sialic acid production after oral administration of N-acetylmannosamine (ManNAc) to subjects with GNE myopathy. *Mol. Genet. Metab.* 122, 126–134 (2017).

NEUROMUSCULAR
DISEASE FOUNDATION
JOIN THE GLOBAL EFFORT TO CURE NEUROMUSCULAR DISEASES

CureGNEM.org
info@CureGNEM.org

**Los Angeles**
269 S. Beverly Drive
Suite 1206
Beverly Hills, CA 90212
(310) 721-1605

**New York**
10 Bond Street
Suite 330
Great Neck, NY 11021
(516) 441-7126

**Tax ID**
06-1789643
Registered 501(c)(3)