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The World's Largest Nonprofit Organization Focused on GNE Myopathy (also known as HIBM)

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The Neuromuscular Disease Foundation (NDF) is the world's largest GNEM patient advocacy organization. Our programs fund scientific research and gene therapy as well as provide comprehensive resources, support and advocacy to affected individuals and their families/caregivers. Annual NDF symposia provide outreach and education to the public and convene scientists and physicians to collaborate and share data to facilitate proper diagnosis and encourage timely genetic screening to prevent the disorder from being passed down to future generations.

The Neuromuscular Disease Foundation is a registered 501(c)(3) based in Los Angeles, with a presence in 23 countries and counting. Contact us to learn more about GNEM and grant opportunities.

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Overview of GNE myopathy

Sponsored by the Neuromuscular Disease Foundation

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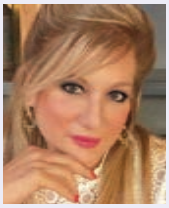

Lale' Welsh
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What is GNE myopathy?

GNE myopathy also known as hereditary inclusion body myopathy (HIBM) and Nonaka distal myopathy, is a rare genetic muscle wasting disease.[1-4] It has an autosomal recessive pattern of inheritance with an incidence of 1-9 in 1,000,000.[5] It is estimated that ~40,000 GNE myopathy patients exist worldwide.[6] Onset is typically in early adulthood (between 20-40 years old), presenting with bilateral foot drop and weakness of the tibialis anterior muscle, with relative sparing of quadricep muscles (Figure).[7] Cardiac and respiratory functions are rarely affected.

Foot drop is an early indicator of GNE myopathy.

How does GNE myopathy affect quality of life?

GNE myopathy is a slow progressing disease, taking decades for late-stage symptoms to manifest. Early stage muscle weakness in GNE myopathy patients typically leads to:

- Disturbed gait 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 rate of progression is different in each patient, most patients end up wheelchair-bound within 10-20 years of disease onset. In later stages of the disease, patients may experience complete loss of skeletal muscle function and require aid from caregivers for activities of daily life.

The Neuromuscular Disease Foundation, a patient-entric organization dedicated to outreach, support and research for GNE myopathy offers information for the community at www.CureHIBM.org.

How is GNE myopathy diagnosed?

Patients receive a definitive genetic diagnosis* when pathogenic mutations are identified in both alleles of the GNE gene. Usually targeted sequencing of the GNE gene is performed in relatives of affected patients, particularly in ethnicities with founder effects. For example, GNE founder mutations are associated with specific ancestries such as Japanese (Cys44Ser) 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. Carrier testing and genetic counseling are recommended for families of affected individuals.

No routine diagnostic test can identify GNE myopathy on its own. However, a combination of mutation analysis, histopathology, and muscle magnetic resonance imaging (MRI) can provide a cumulative body of evidence for diagnosis of GNE myopathy. Histopathology is usually performed on biopsies from affected muscle groups and will typically reveal atrophic fibers, variation in fiber size and a characteristic "rimmed" vacuole appearance.[1,2] T1-weighted MRI of GNE myopathy patients is associated with progressive muscle weakness, fat replacement and fibrosis of affected muscle groups.[8] Characteristic pattern of muscle involvement begins with atrophy of lower extremities, progressing to the posterior thigh muscles, and finally affecting the quadricep muscles in advanced stages of the disease.[2] Other clinical tests that may be informative include serum creatine kinase levels, electromyograms and nerve conduction studies.

*Patients who receive a diagnosis of GNE myopathy are encouraged to register the details of their diagnosis in registries such as TREAT-NMD or Remudy for monitoring and clinical trial readiness.

What causes muscle weakness in GNE myopathy patients?

The GNE gene encodes a bifunctional enzyme responsible for biosynthesis of sialic acid, and regulator of cell surface sialylation.[9,10] In GNE patients, decreased GNE function results in hyposialylation of muscle glycans, thought to play a role in disease pathophysiology.[11,12] Missense mutations are reported to result in decreased enzyme activity,[13] with as yet no patients reported to harbor two null mutations. This corroborates findings that knock-out of GNE in mice is embryonic lethal, which suggests a potentially critical role for the gene during development.[14] Experts suspect GNE plays additional undiscovered cellular roles that may contribute to disease pathology. Recent evidence pointing to potential roles for GNE in muscle regeneration post-injury, skeletal muscle organization and proliferation is subject to further investigation.[6]

How do we treat GNE myopathy?

In the absence of specific treatment for GNE myopathy, patients are encouraged to pursue a balanced physical exercise regime, as well as avoiding over-use or under-use of affected muscles. Several efforts are underway to develop therapies specific for GNE myopathy, including substrate replacement and gene therapy. Encouraging preclinical evidence for efficacy of sialylation increasing therapies such as sialic acid, ManNAc and siallactose in mouse models of GNE myopathy may translate to a therapeutic benefit in patients after disease onset. Despite negative results emerging from the phase 3 trial of extended release sialic acid (SA-ER) conducted by Ultragenyx, patients can look forward to a multicenter trial of ManNAc conducted by the National Institutes of Health (https://www.genome.gov/27567243/). With the promising success of adeno-associated virus (AAV)-based gene therapy trials in muscular dystrophy, spinal muscular atrophy and congenital myopathy, GNE gene replacement therapy to deliver an unaffected copy of the gene presents as a viable therapeutic approach.[15] Additional funding and research are required to establish safety, re-dosing and systemic delivery to all muscles in the body. As an alternative to gene replacement therapy, correction on a genomic level is also a viable approach to correcting pathogenic mutations in GNE. CRISPR technology to perform gene-editing is currently being explored as a strategy to correct common founder mutations.

What are the current challenges in the field?

1. Incomplete understanding of disease pathophysiology: Current assumption is that disease primarily manifests due to defects in sialic acid synthesis. Efforts to increase sialylation through pathway substrates such as ManNAc and sialic acid may not result in a therapeutic benefit if GNE has other important cellular functions implicated in the disease process.

2. Difficulties in establishing a preclinical animal model of the disease: Several mouse models (knock-in and knock-out) have been developed but none have faithfully recapitulated the muscle disease pathology of GNE myopathy patients. Going forward, a preclinical animal model is important for both disease understanding and therapeutic efficacy testing.

3. Lack of reliable clinical biomarkers, GNE-specific assays and antibodies: The development of these research tools is critical for assessing upcoming clinical trials, and will also help to determine pathogenicity of novel sequence variants for diagnosis.

4. Understanding variability in disease onset and progression: Biallelic mutations in GNE can result in clinical variability, affected by genetic modifiers and environmental factors. A better understanding of these variables through natural history studies and genome sequencing will lead to more accurate prognoses, patient care, and development of clinical trial outcomes.

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