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Clinical Spectrum and Phenotypic Variability of GNE Myopathy: Insights from Two Sibling Cases

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Abstract: ***Background**: GNE myopathy (GNEM), also known as hereditary inclusion body myopathy (HIBM), distal myopathy with rimmed vacuoles (DMRV), or Nonaka myopathy, is a rare autosomal recessive myopathy caused by biallelic pathogenic variants in the GNE gene, which encodes the bifunctional enzyme responsible for the rate-limiting steps of sialic acid biosynthesis. The estimated worldwide prevalence of GNE myopathy is approximately 1–9 cases per million population. Clinically, the disorder is characterized by slowly progressive distal muscle weakness beginning in early adulthood, classically presenting with bilateral foot drop and selective sparing of the quadriceps muscles until the advanced stages of the disease. Owing to its rarity, phenotypic heterogeneity, and overlap with other inherited neuromuscular disorders, diagnosis is frequently delayed. **Case Presentation**: We report two siblings with a classical clinical phenotype suggestive of GNE myopathy who exhibited marked phenotypic variability despite sharing the same familial background. The elder sibling, a 39-year-old man, presented with a nine-year history of slowly progressive bilateral foot drop, characterized by selective weakness of the ankle dorsiflexors and hip adductor muscles. Despite the chronic course of the disease, he remained independently ambulant and was able to continue his occupational activities without significant functional limitation. In contrast, his younger sibling, a 32-year-old woman, experienced symptom onset at an earlier age and demonstrated a more severe clinical phenotype with involvement of both distal and proximal lower-limb muscles. She reported progressive difficulty in climbing stairs, rising from a chair, and standing from a squatting position, reflecting greater functional impairment. Electrophysiological evaluation in both patients revealed preserved sensory nerve conduction studies with chronic myopathic changes on needle electromyography, consistent with a primary myopathic process. Muscle magnetic resonance imaging demonstrated selective fatty infiltration and involvement of the tibialis anterior and hip adductor muscles in both siblings. Additionally, the younger sibling exhibited gluteal muscle involvement, which correlated with her more pronounced proximal muscle weakness and greater disease severity. These findings highlight the marked phenotypic heterogeneity that can occur within the same family in GNE myopathy, emphasizing the importance of comprehensive clinical, electrophysiological, and radiological evaluation for accurate phenotypic characterization. **Discussion**: The clinical, electrophysiological, and radiological findings in both patients were consistent with the characteristic phenotype of GNE myopathy. The younger sister demonstrated earlier onset and more extensive proximal lower-limb involvement than her brother, despite the shared familial background. These findings highlight the substantial intrafamilial phenotypic variability that may occur in GNE myopathy. **Conclusion**: These cases emphasize the importance of recognizing the characteristic clinical and radiological pattern of GNE myopathy while acknowledging its variable expression within the same family. Early-adult-onset bilateral foot drop, preserved sensation, normal sensory nerve conduction, relative quadriceps sparing, and selective muscle involvement on MRI should prompt molecular evaluation of the GNE gene.*

Keywords: GNE myopathy, hereditary inclusion body myopathy, distal myopathy with rimmed vacuoles, Nonaka myopathy, bilateral foot drop, quadriceps sparing, muscle magnetic resonance imaging, electromyography, intrafamilial phenotypic variability

1. Introduction

GNE myopathy (GNEM) is a rare inherited neuromuscular disorder characterized by slowly progressive skeletal muscle weakness caused by pathogenic variants in the GNE gene. Historically described as hereditary inclusion body myopathy (HIBM), distal myopathy with rimmed vacuoles (DMRV), and Nonaka myopathy, these entities are now recognized as a single disorder following the identification of a common molecular basis. Consequently, the unified term GNE myopathy is now universally accepted.[1-3]

The GNE gene, located on chromosome 9p13.3, encodes the bifunctional enzyme UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase, which catalyzes the first two rate-limiting steps in sialic acid biosynthesis. Deficient enzyme activity results in hyposialylation of skeletal muscle glycoproteins, leading to progressive muscle degeneration. In addition to impaired sialylation, defective autophagy, protein aggregation, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, and impaired muscle regeneration are believed to contribute to disease pathogenesis.[4-5]

GNE myopathy is an ultra-rare disorder with an estimated prevalence of 1–9 cases per million population[2-3]. Although reported worldwide, founder mutations have been identified in Japanese, Middle Eastern, Bulgarian Roma, Chinese, Korean, and Indian populations. The true prevalence is likely underestimated because of delayed diagnosis and limited access to molecular genetic testing.[6-7]

Clinically, GNE myopathy typically presents during the second to fourth decades of life with insidious onset of bilateral foot drop due to selective involvement of the tibialis anterior muscles. Weakness gradually progresses to involve the extensor hallucis longus, hamstrings, gastrocnemius, soleus, hip adductors, gluteal muscles, finger extensors, and axial musculature. Relative preservation of quadriceps strength until advanced stages is a distinctive hallmark and an important clue that helps differentiate GNE myopathy from hereditary neuropathies and other inherited or acquired myopathies.[1-3,8]

Diagnosis remains challenging because routine laboratory investigations are often non-specific. Serum creatine kinase levels are usually normal or mildly elevated, and nerve conduction studies are frequently preserved despite significant muscle weakness. Needle electromyography typically demonstrates a chronic myopathic pattern with low-amplitude, short-duration motor unit potentials and early recruitment. Muscle magnetic resonance imaging (MRI) has emerged as a valuable diagnostic modality by demonstrating selective fatty infiltration of the tibialis anterior, hamstrings, gastrocnemius, soleus, and hip adductor muscles with relative preservation of the quadriceps. Although muscle biopsy classically reveals rimmed vacuoles and chronic myopathic changes, histopathological findings may be inconclusive, particularly in early disease. Therefore, identification of biallelic pathogenic variants in the GNE gene remains the diagnostic gold standard.[8-10]

Despite significant advances in understanding disease pathogenesis, treatment remains largely supportive. Physiotherapy, orthotic support, occupational rehabilitation, prevention of contractures, and genetic counselling constitute the cornerstone of management. Meanwhile, targeted therapeutic approaches, including substrate replacement with sialic acid and N-acetylmannosamine (ManNAc), adeno-associated virus-mediated gene replacement, and genome-editing strategies, are under active investigation and offer promise for future disease-modifying therapy.[2,4,11-12]

We report two siblings with a clinically characteristic phenotype of GNE myopathy who demonstrated differences in age at onset, disease severity, functional status, and muscle involvement on MRI. These cases emphasize the importance of recognizing both the classical phenotype and the broader spectrum of intrafamilial variability.

2. Case 1

History

A 39-year-old right-handed man from Hyderabad, India, presented to the neurology outpatient department with a 9-year history of gradually progressive bilateral foot drop. He had completed formal education up to the ninth standard and was employed as a heavy-duty truck driver. His medical history was unremarkable, with no diabetes mellitus, hypertension, thyroid disease, alcohol misuse, toxin exposure, or previous neurological illness. His birth and developmental histories were normal, with no history suggestive of perinatal insult or delay in milestones.

The illness began insidiously at 30 years of age, when he noticed difficulty changing gears while riding his motorcycle. He observed that he was unable to lift the forefoot adequately because of weakness of ankle dorsiflexion and extension of the great toe. Plantar flexion remained relatively preserved, and he did not experience difficulty applying the brake while driving.

During the following months, he developed difficulty clearing thresholds while walking and frequently struck the front of his foot against thresholds and other small obstacles. To compensate for the weakness, he gradually adopted a high-stepping gait.

The progression of the illness remained remarkably slow. During the subsequent 9 years, he continued to walk independently and work as a heavy-duty truck driver without significant occupational disability. He denied difficulty climbing stairs, rising from a chair, rising from a squatting position, or performing overhead activities. There was no history of upper-limb or neck weakness, dysphagia, dysarthria, diplopia, ptosis, facial weakness, sensory symptoms, bladder or bowel dysfunction, muscle cramps, fasciculations, or exercise intolerance. He also denied symptoms suggestive of respiratory muscle involvement.

During the course of the illness, he noticed that his thighs tended to drift apart while sitting, suggesting weakness of the hip-adductor muscles. However, he did not report subjective proximal lower-limb weakness, and his daily activities remained largely unaffected.

3. Examination

General physical examination revealed a moderately built and adequately nourished man with stable vital signs. Higher mental functions and cranial nerve examination were normal. There was no facial weakness, tongue wasting, fasciculation, ophthalmoplegia, ptosis, or clinical evidence of bulbar involvement.

The upper limbs had normal muscle bulk, tone, and strength, with power graded 5/5 throughout. In the lower limbs, tone was reduced distally, and bilateral ankle contractures were present. Muscle bulk was preserved in the thighs, while the legs showed wasting predominantly in the anterior compartment, with relative preservation of the posterior compartment.

Manual muscle testing demonstrated predominantly distal lower-limb weakness. Hip adduction was markedly weak, with strength graded 2/5 bilaterally. Ankle dorsiflexion was also graded 2/5. Great-toe extension was weak, whereas toe flexion and intrinsic toe-grip strength were relatively preserved. Plantar flexion was substantially better preserved than dorsiflexion. Hip flexion and knee extension remained normal.

Deep-tendon reflexes were symmetrically preserved in the upper and lower limbs, and superficial reflexes were normal. Sensory examination, including pinprick, temperature, vibration, proprioception, and joint-position sense, revealed no abnormalities. Cerebellar testing was normal, and there were no pyramidal signs.

4. Investigations

Nerve-conduction studies demonstrated normal motor and sensory conduction velocities and amplitudes. Needle electromyography of the tibialis anterior demonstrated low-amplitude, short-duration motor-unit action potentials with early recruitment, consistent with a myopathic pattern. Similar changes were observed in the adductor magnus muscle.No active denervation or neurogenic motor-unit remodeling was detected.

5. Muscle MRI

T1-weighted muscle MRI demonstrated selective fatty replacement involving the tibialis anterior, (Figure 1). Corresponding short-tau inversion recovery (STIR) sequences demonstrated patchy hyperintensity within the affected muscles, suggesting active muscle involvement superimposed on chronic fatty degeneration. The quadriceps muscles remained relatively preserved. The combination of selective tibialis anterior and hip-adductor involvement with relative quadriceps sparing was strongly suggestive of GNE myopathy. Muscle MRI may demonstrate this characteristic pattern even when proximal muscle weakness is not clinically apparent.

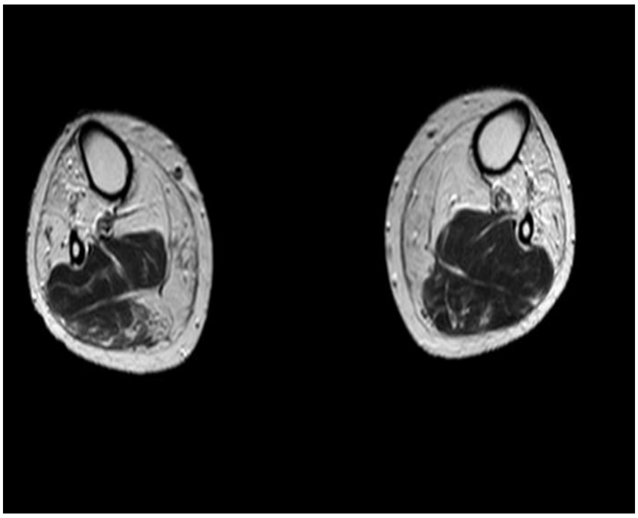

Figure 1 (A)

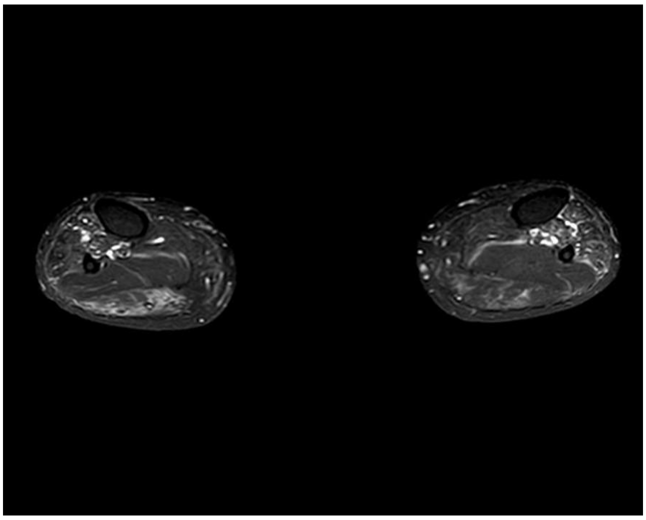

Figure 1 (B)

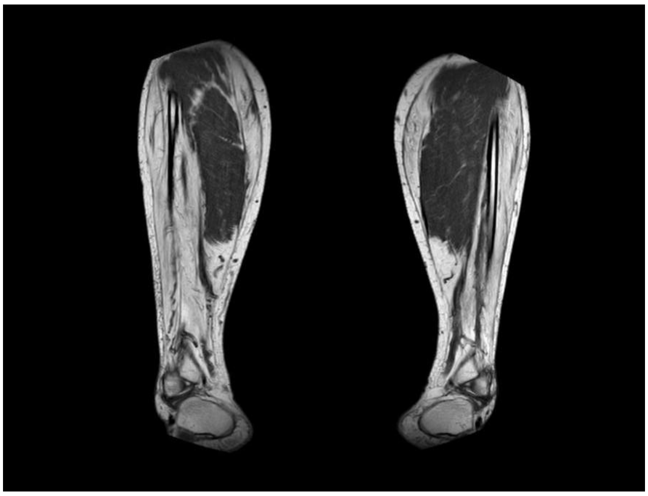

Figure 1 (C)

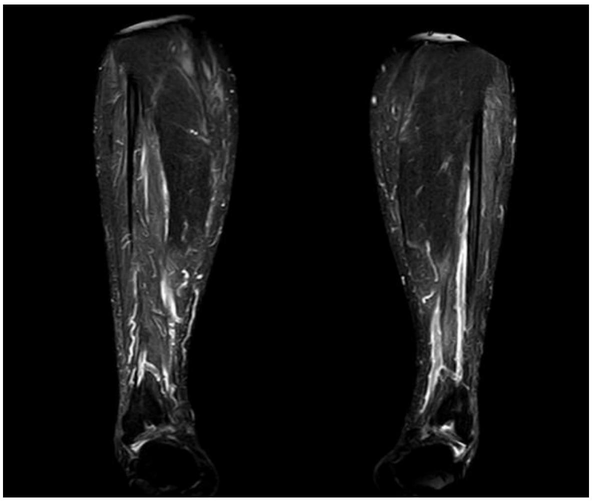

Figure 1 (D)

(A) Axial T1-weighted images demonstrate selective fatty replacement of the anterior compartment muscles, predominantly involving the tibialis anterior, with relative preservation of the posterior compartment muscles. B) Axial STIR images demonstrate mild hyperintense signal within the affected anterior compartment muscles, indicating ongoing muscle edema and active myopathic changes. C) Coronal T1-weighted images demonstrate bilateral selective involvement of the tibialis anterior with relative sparing of the posterior compartment muscles. (D) Coronal STIR images reveal corresponding oedema-like signal changes in the affected muscles.

6. Clinical impression

The clinical, electrophysiological, and radiological findings strongly suggested GNE myopathy. The diagnosis was supported by the early-adult onset, slowly progressive bilateral foot drop, preserved plantar flexion, marked hip-adductor weakness, normal sensory nerve conduction, myopathic electromyography, and relative quadriceps preservation. Molecular confirmation was not available at the time of evaluation; therefore, the diagnosis was considered clinically and radiologically probable. Although molecular genetic testing was not performed in the elder sibling, the remarkably similar clinical presentation, electrophysiological findings, and molecular confirmation obtained in his affected younger sister strongly support the diagnosis of familial GNE myopathy.

Case 2

History

A 32-year-old woman, the younger sister of Case 1, presented with a 7-year history of gradually progressive weakness involving both lower limbs. She was apparently healthy until the age of 25 years, when she first noticed difficulty lifting the front of her feet while walking, resulting in difficulty walking and frequently hitting thresholds. Over the following months, she developed bilateral foot drop associated with a high-stepping gait.

Unlike her elder brother, the disease progressed to involve both distal and proximal lower-limb muscles. She experienced increasing difficulty climbing stairs, rising from a chair, standing from a squatting position, and walking long distances.

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She also reported frequent slipping of footwear while walking because of progressive weakness of the intrinsic foot muscles. She required assistance to rise from a squatting position and from a chair.

There was no history of upper-limb weakness, neck weakness, dysphagia, dysarthria, diplopia, ptosis, facial weakness, sensory disturbances, bladder or bowel dysfunction, respiratory symptoms, or exercise intolerance. The occurrence of similar symptoms in her elder brother strongly suggested an inherited neuromuscular disorder.

7. Examination

General examination was unremarkable. Higher mental functions and cranial nerve examination were normal, with no evidence of facial weakness, ophthalmoplegia, ptosis, tongue wasting, fasciculations, or bulbar involvement.

The upper limbs demonstrated normal muscle bulk, tone, and strength (Medical Research
Council [MRC] grade 5/5). Examination of the lower limbs revealed generalized hypotonia with bilateral ankle contractures. Muscle bulk was relatively preserved in the anterior aspect of thighs.

Manual muscle testing demonstrated both distal and proximal lower-limb weakness. Hip adduction was markedly weak, while weakness was also evident in the hip extensors, hip abductors, knee flexors, and ankle dorsiflexors. Plantar flexion was relatively preserved. Knee extension remained stronger than the surrounding muscle groups, indicating relative quadriceps sparing despite progression of the disease.

Deep tendon reflexes were preserved in the upper limbs and mildly reduced in the lower limbs. Plantar responses were flexor. Sensory examination, including superficial and deep sensory modalities, was normal. Cerebellar examination was unremarkable, and no pyramidal signs were present.

8. Investigations

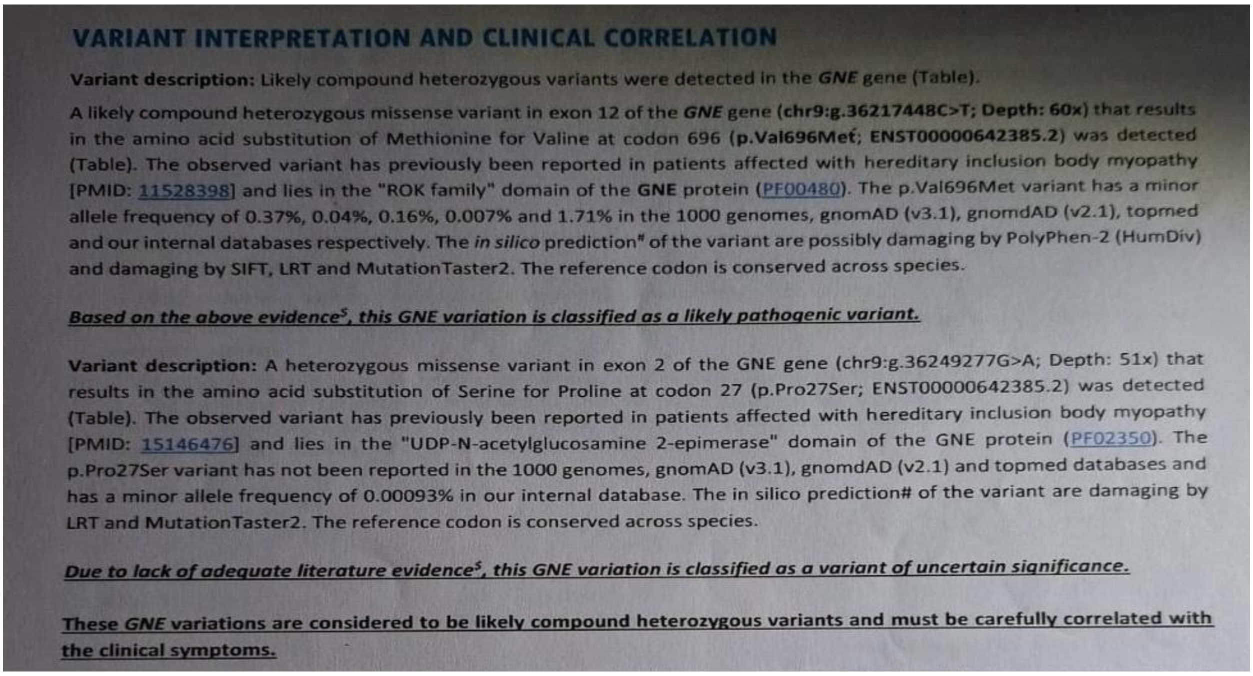
Motor nerve conduction studies demonstrated no evidence of neuropathy. Sensory nerve action potentials were preserved. Needle electromyography of the tibialis anterior, adductor muscles, and gluteus maximus demonstrated low-amplitude, short-duration motor unit action potentials with early recruitment, consistent with a chronic myopathic process. No significant spontaneous denervation activity was observed.

9. Molecular Genetic Analysis

Whole-exome sequencing (WES) was performed on genomic DNA extracted from peripheral blood using a clinically validated next-generation sequencing platform (MedGenome Laboratories, Bangalore, India). Molecular analysis identified likely compound heterozygous variants in the GNE gene (NM_001128227.3), consistent with an autosomal recessive inheritance pattern for GNE myopathy (Nonaka myopathy; OMIM #605820).

The first variant, c.2086G>A (p. Val696Met) located in exon 12, was classified as likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines. This missense variant has previously been reported in patients with GNE myopathy and is considered to have significant disease-causing potential.

The second variant, c.79C>T (p. Pro27Ser) located in exon 2, was classified as a variant of uncertain significance (VUS) based on the currently available evidence. Although this variant has been reported in individuals with GNE myopathy, the existing literature remains insufficient to establish its pathogenicity conclusively.


VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant description: Likely compound heterozygous variants were detected in the *GNE* gene (Table).

A likely compound heterozygous missense variant in exon 12 of the *GNE* gene (**chr9:g.36217448C>T; Depth: 60x**) that results in the amino acid substitution of Methionine for Valine at codon 696 (**p.Val696Met; ENST00000642385.2**) was detected (Table). The observed variant has previously been reported in patients affected with hereditary inclusion body myopathy [PMID: 11528398] and lies in the "ROK family" domain of the **GNE** protein (PF00480). The p.Val696Met variant has a minor allele frequency of 0.37%, 0.04%, 0.16%, 0.007% and 1.71% in the 1000 genomes, gnomAD (v3.1), gnomdAD (v2.1), topmed and our internal databases respectively. The *in silico* prediction# of the variant are possibly damaging by PolyPhen-2 (HumDiv) and damaging by SIFT, LRT and MutationTaster2. The reference codon is conserved across species.

Based on the above evidence$, this GNE variation is classified as a likely pathogenic variant.

Variant description: A heterozygous missense variant in exon 2 of the GNE gene (chr9:g.36249277G>A; Depth: 51x) that results in the amino acid substitution of Serine for Proline at codon 27 (p.Pro27Ser; ENST00000642385.2) was detected (Table). The observed variant has previously been reported in patients affected with hereditary inclusion body myopathy [PMID: 15146476] and lies in the "UDP-N-acetylglucosamine 2-epimerase" domain of the GNE protein (PF02350). The p.Pro27Ser variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomdAD (v2.1) and topmed databases and has a minor allele frequency of 0.00093% in our internal database. The in silico prediction# of the variant are damaging by LRT and MutationTaster2. The reference codon is conserved across species.

Due to lack of adequate literature evidence$, this GNE variation is classified as a variant of uncertain significance.

These *GNE* variations are considered to be likely compound heterozygous variants and must be carefully correlated with the clinical symptoms.

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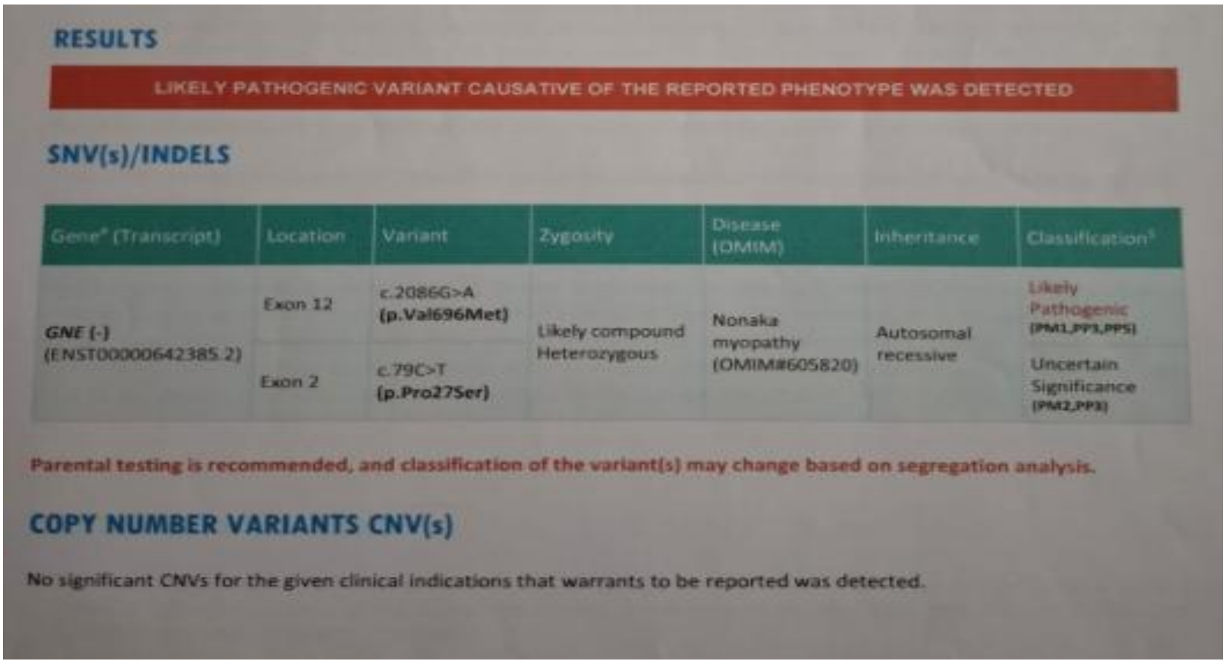

RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene* (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
GNE (-) (ENST00000642385.2)	Exon 12	c.2086G>A **(p.Val696Met)**	Likely compound Heterozygous	Nonaka myopathy (OMIM#605820)	Autosomal recessive	Likely Pathogenic (PM1,PP3,PP5)
	Exon 2	c.79C>T **(p.Pro27Ser)**				Uncertain Significance (PM2,PP3)

Parental testing is recommended, and classification of the variant(s) may change based on segregation analysis.

COPY NUMBER VARIANTS CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

In the context of the patient's characteristic clinical phenotype, electrophysiological findings, and the identification of these likely compound heterozygous variants in the *GNE* gene provided molecular confirmation of the diagnosis of GNE myopathy. Copy number variant (CNV) analysis did not identify any clinically significant genomic deletions or duplications.

Figure 2. Molecular genetic confirmation of GNE myopathy in Case 2. (A) Whole-exome sequencing identified likely compound heterozygous variants in the GNE gene, comprising c.2086G>A (p. Val696Met), classified as likely pathogenic, and c.79C>T (p. Pro27Ser), classified as a variant of uncertain significance according to ACMG criteria. No clinically significant copy number variants were detected. (B) Variant interpretation and clinical correlation demonstrating that the identified GNE variants are consistent with autosomal recessive GNE myopathy and support the molecular diagnosis in the appropriate clinical context.

10. Clinical Impression

The younger sibling demonstrated an earlier age at onset and a more advanced phenotype than her elder brother, with involvement of both distal and proximal lower-limb muscles while retaining the characteristic relative preservation of quadriceps strength. Preserved sensory nerve conduction studies together with chronic myopathic changes on needle electromyography excluded neuropathy and supported a primary myopathic process. The characteristic pattern of selective muscle involvement together with quadriceps sparing despite progression of the disease and whole-exome sequencing demonstrating likely compound heterozygous variants in the GNE gene, established the diagnosis of genetically confirmed GNE myopathy.

11. Discussion

Overview and Principal Findings

The present report describes two siblings with the characteristic clinical phenotype of GNE myopathy and highlights the marked intrafamilial phenotypic variability that may occur despite a shared familial background. Both patients presented in early adulthood with slowly progressive bilateral foot drop due to preferential involvement of the tibialis anterior muscles, with quadriceps strength relatively preserved until late in the disease course. Neurological examination revealed marked weakness of the ankle dorsiflexors and hip adductors, with relative quadriceps sparing, a characteristic clinical feature of GNE myopathy.Electrophysiological studies revealed preserved sensory nerve conduction studies and chronic myopathic changes on needle electromyography, while muscle MRI demonstrated selective involvement of the tibialis anterior and hip adductor muscles.These findings closely resemble the characteristic clinicoradiological phenotype described in previous studies and emphasize the importance of integrating clinical examination, electrophysiological evaluation, and muscle MRI for early diagnosis.

Clinical Spectrum and Clinicoradiological Correlation

GNE myopathy typically presents during the second to fourth decades of life with slowly progressive weakness of the ankle dorsiflexors, resulting in bilateral foot drop. Patients commonly report difficulty clearing thresholds while walking, inability to walk on their heels, and adoption of a high-stepping gait. As the disease progresses, weakness gradually extends to involve the extensor hallucis longus, hamstrings, gastrocnemius, soleus, hip adductors, gluteal muscles, finger extensors, and axial musculature. Despite progressive weakness of several muscle groups, the quadriceps muscles remain relatively preserved until the later stages of the disease, representing one of the most characteristic clinical features of GNE myopathy.

Both siblings in the present report demonstrated this classical clinical evolution. The elder sibling maintained a predominantly distal pattern of weakness even after nine years of disease and remained independently ambulant while continuing his occupation as a heavy-duty truck driver. In contrast, the younger sibling developed earlier and more extensive proximal lower-limb weakness involving the gluteal muscles, resulting in greater functional impairment. These observations are consistent with previous reports demonstrating substantial variability in disease severity and progression among affected individuals, including members of the same family.

A notable clinical finding in both patients was early weakness of the hip adductor muscles. Although bilateral foot drop is widely recognized as the hallmark presentation of GNE myopathy, involvement of the hip adductors is often under-recognized during routine neurological examination. In our patients, marked hip adductor weakness was present despite preserved quadriceps strength, suggesting that careful assessment of the adductor compartment may provide an additional bedside clue to the diagnosis. Recognition of this characteristic distribution of weakness may facilitate differentiation of GNE myopathy from hereditary motor neuropathies and other inherited distal myopathies.

Electrophysiological studies further supported the diagnosis. Motor and sensory nerve conduction studies were preserved in both patients, effectively excluding hereditary motor-sensory neuropathy. Needle electromyography demonstrated low-amplitude, short-duration motor unit action potentials with early recruitment, consistent with a chronic myopathic process. Similar findings have been consistently reported in previous studies and emphasize the value of electromyography in distinguishing distal myopathies from neuropathic disorders.

Muscle MRI demonstrated excellent correlation with the clinical findings. It showed selective fatty replacement involving the tibialis anterior and hip adductor muscles. Relative preservation of the quadriceps muscles was observed, further supporting the diagnosis. Muscle MRI not only assists in diagnosis but also identifies clinically occult muscle involvement, guides muscle biopsy when required, and provides an objective method for monitoring disease progression.

12. Genetics and Pathophysiology

GNE myopathy is an autosomal recessive disorder caused by biallelic pathogenic variants in the GNE gene located on chromosome 9p13.3. The GNE protein functions as a bifunctional enzyme possessing UDP-*N*-acetylglucosamine 2-epimerase and *N*-acetylmannosamine kinase activities, catalyzing the first two rate-limiting steps in sialic acid biosynthesis. Defective enzyme activity results in reduced sialylation of skeletal muscle glycoproteins, leading to progressive muscle fiber degeneration.

Although impaired sialylation represents the primary biochemical abnormality, increasing evidence suggests that disease pathogenesis is multifactorial. Defective autophagy, accumulation of abnormal protein aggregates, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, and impaired muscle regeneration have all been implicated in disease progression. The selective vulnerability of the tibialis anterior muscle and the relative preservation of the quadriceps remain incompletely understood and continue to be important areas of research.

In the present study, whole-exome sequencing performed in the younger sibling demonstrated likely compound heterozygous variants in the GNE gene comprising c.2086G>A (p. Val696Met) and c.79C>T (p. Pro27Ser). The p. Val696Met variant has previously been reported in patients with GNE myopathy and is classified as likely pathogenic, whereas the p. Pro27Ser variant is currently classified as a variant of uncertain significance because of limited published evidence. In the presence of a highly characteristic clinical phenotype, preserved sensory nerve conduction studies, typical muscle MRI findings, and autosomal recessive inheritance, these molecular findings strongly support the diagnosis of GNE myopathy. Further parental segregation analysis would help establish whether the two variants are present in trans and clarify the pathogenic significance of the p. Pro27Ser variant.
More than 200 pathogenic variants have been identified worldwide. However, genotype–phenotype correlation remains imperfect, and patients carrying identical pathogenic variants may demonstrate markedly different clinical phenotypes. The marked difference in disease severity observed between our two siblings, despite their shared familial background, further illustrates the considerable intrafamilial phenotypic variability characteristic of GNE myopathy. The younger sibling exhibited an earlier disease onset with more extensive proximal muscle involvement, whereas the elder sibling retained a predominantly distal pattern of weakness despite a longer disease duration. These observations suggest that factors beyond the primary GNE mutations, including modifier genes, epigenetic influences, environmental factors, and lifestyle, may contribute significantly to the clinical heterogeneity and variable disease expression observed among affected individuals.

13. Differential Diagnosis and Diagnostic Approach

The differential diagnosis of GNE myopathy includes hereditary motor-sensory neuropathies, distal hereditary motor neuropathy, dysferlinopathy, tibial muscular dystrophy, myofibrillar myopathies, mitochondrial myopathies, and sporadic inclusion body myositis. Preservation of sensation together with normal sensory nerve conduction studies effectively excludes most hereditary neuropathies. Similarly, the absence of fasciculations, upper motor neuron signs, and neurogenic electromyographic changes argues against motor neuron disease. Sporadic inclusion body myositis generally presents after the age of 50 years and is characterized by preferential involvement of the quadriceps and finger flexors rather than quadriceps sparing.

Diagnosis of GNE myopathy should therefore be suspected in young adults presenting with slowly progressive bilateral foot drop, selective tibialis anterior weakness, preserved quadriceps strength, normal sensory nerve conduction studies, and chronic myopathic changes on electromyography. Muscle MRI provides valuable supportive evidence by demonstrating a characteristic pattern of selective muscle involvement, while molecular genetic testing remains the definitive diagnostic investigation.

14. Current Management and Emerging Therapeutic Strategies

Although considerable progress has been made in understanding the molecular pathogenesis of GNE myopathy, no universally approved disease-modifying therapy is currently available. Consequently, management remains primarily supportive and aims to preserve mobility, maintain functional independence, prevent secondary complications, and improve quality of life. However, recent advances in substrate replacement therapy and gene-based therapeutics have generated optimism for disease-modifying treatment.

15. Supportive Management

Physiotherapy and Rehabilitation

Physiotherapy forms the cornerstone of management in GNE myopathy. Individualized exercise programs focusing on stretching, range-of-motion exercises, balance training, and low-impact aerobic activities help preserve mobility and delay secondary musculoskeletal complications. Particular attention should be directed toward preventing Achilles tendon contractures through regular stretching exercises, as progressive weakness of the ankle dorsiflexors predisposes patients to equinus deformity.

Resistance training should be tailored carefully. Moderate-intensity strengthening exercises may help maintain muscle function, whereas excessive eccentric exercise and high-intensity resistance training should be avoided because they may exacerbate muscle fiber injury. Aquatic therapy, cycling, and supervised endurance exercises are generally well tolerated and may improve cardiovascular fitness without imposing excessive mechanical stress on weakened muscles.

Orthotic Support and Assistive Devices

Progressive ankle dorsiflexor weakness frequently results in foot drop, gait instability, and recurrent falls. Ankle-foot orthoses (AFOs) improve gait efficiency by preventing toe drag during the swing phase and reducing the risk of falls. As weakness progresses, walking sticks, canes, walkers, or wheelchairs may be required to maintain mobility and independence.Occupational therapy complements rehabilitation by recommending adaptive equipment, workplace modifications, and energy-conservation techniques that enable patients to continue daily activities for longer periods.

Prevention of Contractures and Musculoskeletal Complications

Progressive muscle imbalance predisposes patients to tendon contractures, particularly involving the Achilles tendon. Regular stretching exercises, splinting when appropriate, and maintenance of joint range of motion are essential to delay fixed deformities. Early intervention helps preserve gait mechanics and functional mobility.

Patients should also undergo periodic assessment for scoliosis, spinal deformity, and postural abnormalities, especially in advanced disease.

Respiratory, Nutritional, and Multidisciplinary Care

Clinically significant respiratory involvement is uncommon in GNE myopathy but may occur in advanced disease. Periodic pulmonary function testing should therefore be considered in patients with advanced weakness or symptoms suggestive of respiratory muscle involvement.

Bulbar dysfunction is relatively rare; however, patients should be monitored for dysphagia and aspiration when disease progression involves cervical or bulbar musculature.

Nutritional counselling, psychological support, and multidisciplinary rehabilitation involving neurologists, physiotherapists, occupational therapists, orthotists, respiratory physicians,

Rehabilitation specialists, and genetic counsellors remain essential components of comprehensive care.

Genetic Counselling

As GNE myopathy follows an autosomal recessive pattern of inheritance, genetic counselling is recommended for affected individuals and their families. Identification of the pathogenic variants allows carrier detection among at-risk relatives, facilitates prenatal diagnosis when appropriate, and assists reproductive decision-making. Early molecular diagnosis has become increasingly important because several ongoing clinical trials require genetic confirmation for patient enrolment.

Disease-Modifying Therapies

Sialic Acid Supplementation

The discovery that GNE myopathy results from defective sialic acid biosynthesis led to the development of substrate replacement therapy using free sialic acid and extended-release formulations. Preclinical studies demonstrated restoration of muscle sialylation and improvement in muscle pathology. Although early clinical studies suggested stabilization of muscle strength, larger randomized controlled trials evaluating extended-release sialic acid failed to demonstrate a significant clinical benefit over placebo. Consequently, this therapeutic approach has not achieved widespread clinical use.

Nevertheless, these studies provided important proof-of-concept that metabolic correction of the underlying biochemical defect is feasible.

N-Acetylmannosamine (ManNAc)

N-Acetylmannosamine (ManNAc), a naturally occurring precursor of sialic acid, bypasses the feedback inhibition of the epimerase step and enhances intracellular sialic acid synthesis despite reduced GNE enzyme activity.

Phase I and Phase II clinical trials have demonstrated that oral ManNAc is generally safe and well tolerated. Treated patients exhibited sustained increases in plasma sialic acid concentrations and a slower decline in muscle strength compared with historical controls. Ongoing studies are evaluating long-term efficacy, optimal dosing, and functional outcomes. Currently, ManNAc represents one of the most promising disease-modifying therapies under investigation for GNE myopathy.[4]

Gene Replacement Therapy

Gene replacement therapy aims to correct the underlying molecular defect by delivering a functional copy of the GNE gene using recombinant adeno-associated viral (AAV) vectors.

Experimental studies have demonstrated restoration of GNE enzyme activity, increased sialic acid production, improved muscle histology, and delayed disease progression in animal models. Although human clinical trials remain in the early stages, gene replacement therapy offers the potential to address the primary cause of disease rather than merely slowing progression.

Important challenges include achieving efficient transduction of skeletal muscle, overcoming immune responses to viral vectors, ensuring long-term transgene expression, and determining the optimal therapeutic window.

Genome Editing and RNA-Based Therapies

Rapid advances in molecular medicine have stimulated interest in mutation-specific therapeutic approaches, including CRISPR-Cas9 genome editing, antisense oligonucleotides, messenger RNA replacement, and RNA interference technologies.

Although these strategies remain experimental, they hold promise for precise correction of pathogenic variants and may ultimately provide personalized treatment for selected patients.

16. Future Directions

Future management of GNE myopathy is expected to shift from supportive care toward precision medicine. Advances in molecular diagnostics, natural history studies, imaging biomarkers, and gene-targeted therapies are likely to transform patient care over the coming decade. Earlier diagnosis through heightened clinical awareness and timely genetic testing will be critical, as emerging therapies are anticipated to be most effective before irreversible muscle degeneration and fatty replacement occur.[2]

17. Strengths and Limitations

The principal strength of the present report is the comprehensive clinical, electrophysiological, radiological, and molecular characterization of two siblings with GNE myopathy demonstrating marked intrafamilial phenotypic variability. A limitation of this study is that molecular confirmation was available only in the younger sibling, while genetic testing was not performed in the elder sibling. Furthermore, parental segregation analysis was not available; therefore, the phase of the detected variants could not be conclusively established. Nevertheless, the characteristic clinicoradiological phenotype together with molecular confirmation in one affected sibling strongly supports the diagnosis of familial GNE myopathy.

18. Conclusion

The present report highlights the characteristic clinical, electrophysiological, radiological, and molecular spectrum of GNE myopathy while emphasizing the marked intrafamilial phenotypic variability that may occur despite a shared familial background. Recognition of slowly progressive bilateral foot drop, selective weakness of the tibialis anterior and hip adductor muscles, relative quadriceps sparing, preserved sensory nerve conduction studies, and characteristic muscle MRI abnormalities should raise a high index of suspicion for GNE myopathy. Early recognition of these clinicoradiological features should prompt timely molecular genetic testing, which not only establishes a definitive diagnosis but also facilitates genetic counselling, family screening, prognostication, and access to emerging disease-modifying therapies and future clinical trials.

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