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A Novel Mutation of the *GNE* Gene in Distal Myopathy with Rimmed Vacuoles: A Case with Inflammation

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Key Words

Distal myopathy with rimmed vacuoles · Hereditary inclusion body myopathy · UDP-N-acetylglucosamine 2-epimerase and N-acetylmannosamine kinase · Inflammation

Abstract

Distal myopathy with rimmed vacuoles (DMRV) is an autosomal recessive or sporadic early adult-onset myopathy caused by mutations in the UDP-N-acetylglucosamine 2-epimerase and N-acetylmannosamine kinase (*GNE*) gene. Characteristic pathologic features of DMRV are rimmed vacuoles on muscle biopsy and tubulofilamentous inclusion in ultrastructural study. Presence of inflammation in DMRV is unusual. We report a sporadic case of DMRV in a 40-year-old Thai man who presented with slowly progressive distal muscle weakness. Gene analysis revealed a compound heterozygous mutation of the *GNE* gene including a novel mutation c.1057A>G (p.K353E) and a known mutation c.2086G>A (p.V696M). The latter is the most common mutation in Thai DMRV patients. The muscle pathology was compatible with DMRV except for focal inflammation.

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Introduction

Distal myopathy with rimmed vacuoles (DMRV) is caused by mutations in the UDP-N-acetylglucosamine 2-epimerase and N-acetylmannosamine kinase (*GNE*) gene on chromosome 9 [1, 2]. It can be present either in autosomal recessive or in sporadic form. Clinically, DMRV is characterized by slowly progressive myopathy in early adult life. It is also known as Nonaka myopathy, hereditary inclusion body myopathy, inclusion body myopathy type 2,

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and *GNE* myopathy [2–4]. DMRV usually involves the tibialis anterior muscle and spares the quadriceps muscle. The histopathologic hallmark of DMRV is the presence of rimmed vacuoles predominantly in atrophic fibers [5]. It is unusual to have inflammation in DMRV. We report a sporadic case of DMRV in a 40-year-old Thai man with inflammatory cell infiltration and compound heterozygous mutation of the *GNE* gene, a novel mutation at c.1057A>G (p.K353E) and a common mutation in Thai patients at c.2086G>A (p.V696M).

Case Report

A 40-year-old Thai man had developed gradual but progressive left leg and left arm weakness over 7 years. He could not flex his left foot upward and had difficulty using the left hand. He also noticed weakness on his right leg and right hand for the last 4 years. Physical examination revealed muscle atrophy in both arms and legs. The muscle volume and strength of distal muscles on both sides of the extremities were markedly decreased, especially in the forearms, hands, and feet. Motor power of both sides of the body rated by the Medical Research Council Scale was as follows: tibialis anterior 2/5, quadriceps 4/5, gastrocnemius and soleus 5/5, forearm flexors and intrinsic hand muscles 3/5, and triceps and biceps 5/5. The muscle strength of deltoid and supraspinatus on the left side was 4/5 but 5/5 on the right side. The deep tendon reflexes at the ankle were diminished. There was no other neurologic abnormality. There was no clinical or laboratory evidence of systemic or connective tissue diseases. Serum creatine kinase (CK) was mildly increased to 293 IU/l. He was initially treated with corticosteroids but there was no significant clinical improvement. A nerve conduction study and electromyogram were consistent with chronic myopathy predominantly involving the intrinsic hand muscles and tibialis anterior muscles. Whole-spine magnetic resonance imaging was within normal limits. Magnetic resonance imaging of the muscles was not performed. There was no history of muscle disease or consanguineous marriage in his family. The patient was partially wheelchair-bound but could walk with assistance.

Muscle Biopsy

Muscle biopsy was obtained from the left biceps brachii. It showed marked fiber size variation ranging from 10 to 120 μm . There was perivascular and scattered intrafascicular lymphocytic infiltration (fig. 1a) with scattered necrotic and regenerating fibers. Vacuolated fibers were predominantly hypertrophic (fig. 1b). Rimmed vacuoles were highlighted by modified Gomori trichrome (mGT) stain (fig. 1c). There was no fiber type grouping. Atrophic fibers were predominantly type 2. Immunohistochemical study revealed a mixed population of CD3-positive T cells and CD20-positive B cells infiltration. CD3-positive T cells were predominant. Staining for MHC class I was positive. Ultrastructural study showed tubulofilamentous inclusions, myeloid bodies, and autophagic vacuoles in the areas corresponding to rimmed vacuoles (fig. 1d).

Molecular Genetics

Mutation analysis in 11 coding exons (exon 2–12) of the *GNE* gene was performed by PCR amplification, followed by direct DNA sequencing. A heterozygous substitution of adenine (A) to guanine (G) at nucleotide position 1057 (c.1057A>G) in exon 6 was identified, resulting in a lysine to glutamic acid substitution at codon 353 (p.K353E) in the epimerase domain (fig. 2a). A heterozygous substitution of G to A at nucleotide position 2086 (c.2086G>A) in exon 12 was present, resulting in a valine to methionine substitution at

codon 696 (p.V696M) in the kinase domain (fig. 2b). c.1057A>G (p.K353E) was not present in the screening of 376 normal chromosomes from 188 Thai subjects.

Discussion

In this case, the diagnosis of DMRV is confirmed by a molecular genetics study for mutations in the *GNE* gene. Our patient harbors compound heterozygous *GNE* mutations of the epimerase domain at c.1057A>G (p.K353E) on exon 6 and of the kinase domain at c.2086G>A (p.V696M) on exon 12. Interestingly, although c.2086G>A (p.V696M) is a common mutation which is present in all Thai DMRV patients [6, 7], it is also present in Indian, Algerian, and Chinese patients [8, 9]. To our knowledge, the c.1057A>G (p.K353E) mutation has not been reported elsewhere. The novel *GNE* mutation at c.1057A>G (p.K353E) is probably pathogenic for the following reasons (i) the mutation is not detected in 376 ethnically matched control chromosomes, (ii) the mutation affects a residue in the *GNE* protein that is phylogenetically conserved from fugu to man, and (iii) this mutation is predicted to be probably damaging with a score of 0.992 by a prediction of the functional effect software (PolyPhen-2) [10]. The age of onset, a slightly elevated CK level, and pathologic features in this patient including rimmed vacuoles are consistent with the diagnosis of DMRV. However, there are several uncommon presentations and findings noticed. Clinically, while DMRV is typically described as weakness and atrophy of the distal muscles, our patient noticed weakness only on one side of his body, which later progressed to the other side; this prompted the attending neurologists to investigate for vascular or spinal cord abnormalities. Nevertheless, the weakness in this patient preferentially involved the distal muscles, thus the main clinical differential diagnoses are among a group of distal myopathies. Presence of rimmed vacuoles together with inflammation and MHC class I positivity raise the possibility of sporadic inclusion body myositis. On the other hand, the age of onset and distribution of muscles affected in this patient are not typical for sporadic inclusion body myositis. Unusual clinical presentation and the age of this patient could raise the possibility of inclusion body myopathy with Paget's disease of the bone and frontotemporal dementia (IBMPFD) caused by mutations in the vasolin-containing protein (VCP) gene. However, our patient and his family members do not have any other signs or symptoms suspicious for IBMPFD and the genetic analysis is consistent with DMRV. In patients with predominant distal muscle weakness with presence of rimmed vacuoles, DMRV is on the top list of differential diagnoses although rimmed vacuoles alone are one of the nonspecific findings on muscle biopsy [4]. Perivascular and endomysial inflammatory cell infiltration, albeit uncommon, has been reported in DMRV [11–15]. So far, there is no plausible explanation for inflammation in DMRV. It could be either nonspecific cellular responses or primary event that leads to muscle damage. Concurrent polymyositis, dermatomyositis, or connective tissue diseases are also possible but unlikely in this patient, since there is no evidence of corticosteroid response or laboratory supports. In conclusion, we reported a case of DMRV with heterozygous novel (p.K353E) and known (p.V696M) mutations and highlighted atypical but possible clinical and histopathologic features in DMRV. Presence of inflammation in a muscle biopsy with rimmed vacuoles may divert the diagnosis; however, in a possible clinical setting it does not rule out DMRV, and genetic analysis for *GNE* mutations should be conducted [12].

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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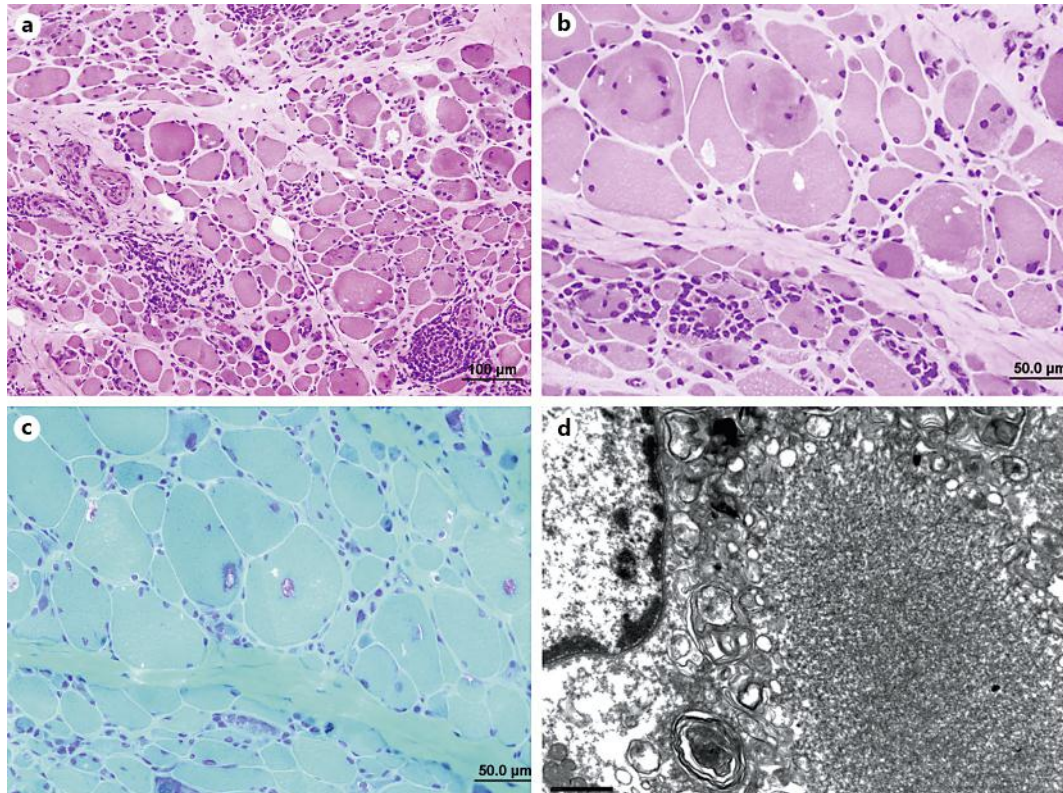


Fig. 1. Moderate degree of fiber size variation with increased endomysial and perimysial connective tissue. Intrafascicular and perivascular lymphoid aggregates are noted (a; HE). Higher magnification reveals hypertrophic vacuolated fibers. Scattered atrophic and necrotic fibers with intrafascicular lymphocytic infiltration are present (b; HE). Rimmed vacuoles are highlighted by mGT stain (c; mGT). Tubulofilamentous inclusion, myeloid bodies, and autophagic vacuoles in the area corresponding to rimmed vacuoles (d; bar = 1 μ m).

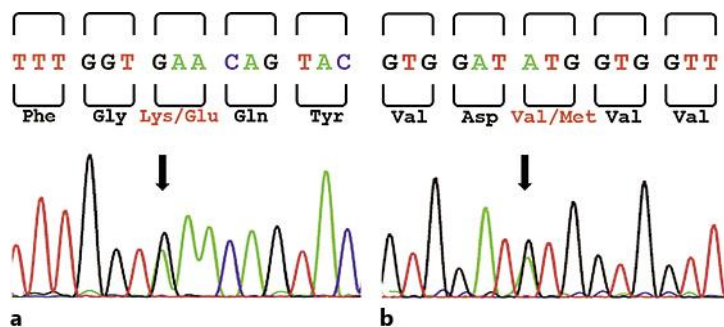


Fig. 2. Electropherogram of compound heterozygous mutations in this patient. A novel mutation c.1057A>G in exon 6 resulting in substitution of lysine to glutamic acid (p.K353E) is presented (a). A known mutation c.2086G>A in exon 12 resulting in substitution of valine to methionine (p.V696M) is presented (b).