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Heterozygous mutations affecting the epimerase domain of the GNE gene causing distal myopathy with rimmed vacuoles in a Taiwanese family

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Abstract

Objectives: Studies of distal myopathy with rimmed vacuoles (DMRV) revealed that most patients had mutations in the UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (GNE) gene. However, the correlation between GNE mutations and clinical features was not fully understood.
Purposes: To report the correlation between the clinical features and genetic analysis of DMRV patients.
Patients and methods: The clinical presentations, histopathological findings, image studies, and genetic analyses of two patients with DMRV from a Taiwanese family were studied.
Results: Two compound heterozygous mutations, Ile 241 Ser and Arg 246 Gln, located in the epimerase domain, were identified in both patients, who were of the same generation. In addition, the elder sister showed a progressive muscular dystrophy course with severe quadriceps and trunk muscle involvement.
Conclusion: The compound heterozygous mutations in the epimerase domain of the GNE gene are important in the severe phenotype of DMRV. However, the mechanisms leading to this phenotypic heterogeneity still remain to be elucidated.
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Keywords: Distal myopathy; Rimmed vacuole; DMRV; GNE gene; Heterozygous mutation

1. Introduction

Adult onset distal myopathy is a primary muscle disorder characterized clinically by progressive muscle weakness and atrophy, beginning in the hands or feet, and pathologically by myopathic changes in the skeletal muscles [1]. Distal myopathy with rimmed vacuoles (DMRV) is characterized by the distinct clinical features of: (1) an autosomal recessive or sporadic disorder with an early adult onset, (2) an involvement of the tibialis anterior muscle with a sparing of the quadriceps muscles, (3) rimmed vacuoles, particularly abundant in atrophic fibers, and the nucleus occasionally containing tubulofilamentous inclusions in muscle biopsies, and (4) a normal or mild elevation of the serum creatine kinase level [2,3].

Hereditary inclusion body myopathy (HIBM), originally called "a vacuolar myopathy sparing the quadriceps", shares characteristic clinical and histopathologic features similar to DMRV, but has been reported mainly from Middle Eastern countries [4]. Both diseases were mapped to the same region on chromosome 9 [5]. The UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (GNE) gene, a bifunctional enzyme, has been found in both HIBM and DMRV patients [6,7]. Thus, these two disorders are thought to be the same disease entity.

In previous studies, homozygous mutations were shown to be common in Japanese patients with V572L mutations and Middle Eastern Jewish patients with the M712T mutation [5,8]. However, compound heterozygous mutations have been found in other ethnic groups [6,9,10]. Interestingly, HIBM patients carrying homozygous M712T mutations

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appeared clinically to have typical HIBM with a sparing of the quadriceps muscles, similar to Japanese DMRV patients with homozygous V572L mutations [5,8]. In addition, a marked weakness of the hands and involvement in the proximal muscles, including the quadriceps muscles in heterozygous mutation were also found in Japanese patients and non-Jewish HIBM patients [5,11,12]. Therefore, the pattern of muscle involvement was proposed to be mutation dependent [10]. However, in a recent study, different mutations in GNE resulted in different enzyme activities, but not in different disease phenotypes in DMRV [13]. In this study, we report the clinical and genetic analyses of two patients with DMRV from a Taiwanese family with prominent quadriceps involvement and heterozygous mutations in epimerase domain.

2. Patients and methods

We examined two patients of the same generation from a Taiwanese family, who were affected with DMRV.

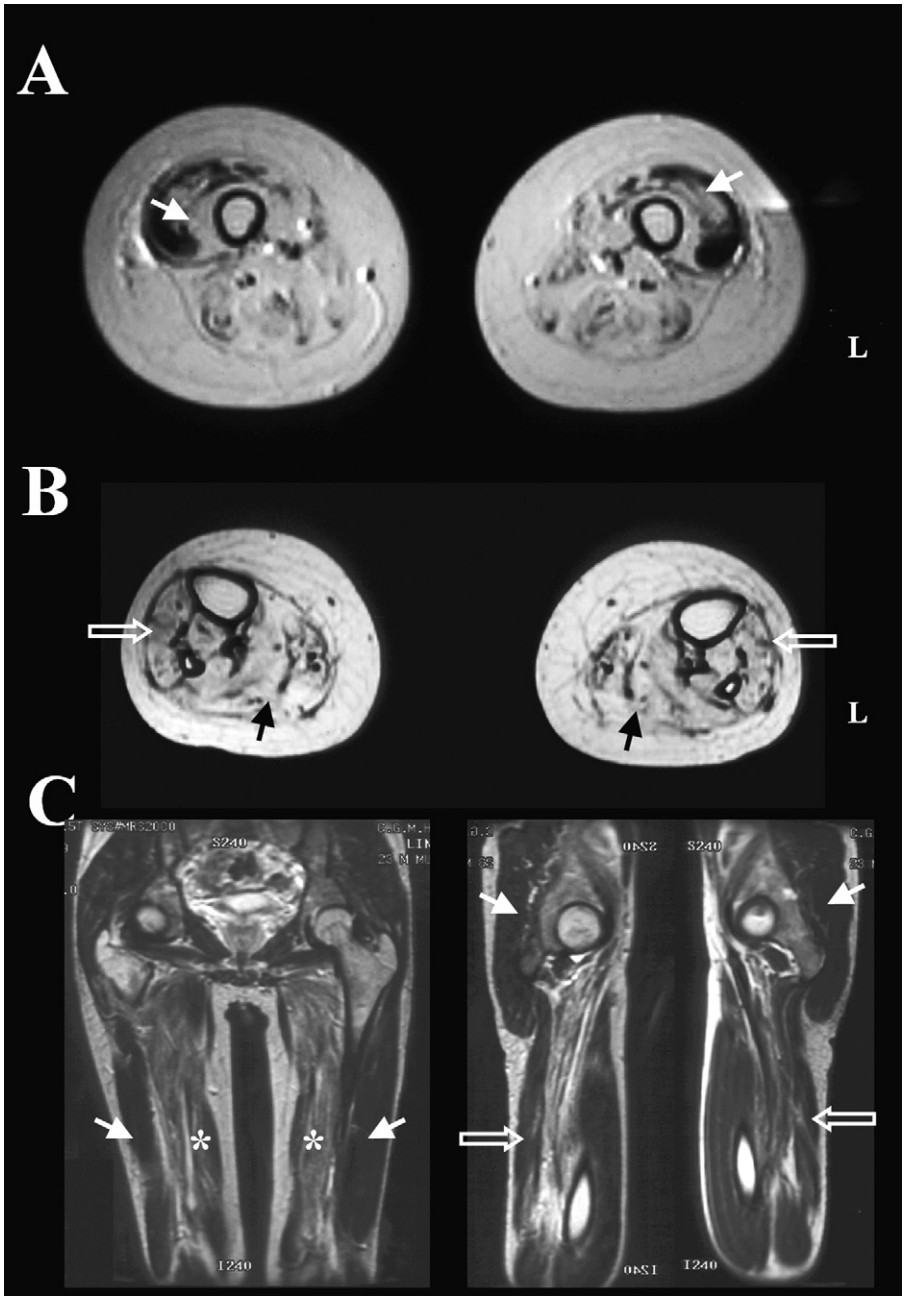

Fig. 1. Muscle T1-weighted magnetic resonance imaging (MRI) of patient II-1 examined at the age of 36, showed (A) prominent atrophy and fatty infiltration in the thigh muscles, including the quadriceps (arrows) at the middle thigh level, (B) severe atrophy and fatty replacement, including the gastrocnemius (black arrows) and tibialis anterior (open arrows) muscles at the distal leg level. Muscle MRI study of patient II-3 examined at the age of 24, showed (C) fatty infiltration in the adductor muscles (asterisks) and anterior tibialis muscles (open arrows) with preservation of the quadriceps muscles (arrows).

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