

선천성 혈소판감소증을 동반한 GNE 근육병증

연세대학교 의과대학 ¹신경과학교실, ²병리학교실, ³이화여자대학교 의과대학 신경과학교실
허준녕¹, 김세훈², 신하영¹, 이정환^{1,3}, 최영철¹

GNE Myopathy with Congenital Thrombocytopenia

Joon Nyung Heo, MD, MS¹, Se Hoon Kim, MD, PhD², Ha Young Shin, MD, PhD¹, Jung Hwan Lee, MD, MS^{1,3},
Young-Chul Choi, MD, PhD¹

Departments of ¹Neurology, ²Pathology, Yonsei University College of Medicine, Seoul; ³Department of Neurology, Ewha Womans University College of Medicine, Seoul, Korea

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GNE myopathy is a distal dominant myopathy with characteristic sparing of quadriceps, which is known to be caused by mutation of the *GNE* gene. Recently, there were some reports of thrombocytopenia that concurred with GNE myopathy. We also present a case of GNE myopathy with thrombocytopenia, having c.1664C>T (p.A555V) and c.1807G>C(p.V603L) mutations. These two are already well-known mutations, found commonly in multiple reports. We reviewed other cases of thrombocytopenia in GNE myopathy and concluded that thrombocytopenia may not be restricted to any specific mutation in the *GNE* gene or any one of two enzymes. Even so, a *GNE* gene defect can be the causative mutation for these cases of congenital thrombocytopenia, considering that hyposialylation of platelets may cause shortening of its lifespan, and the incidence of thrombocytopenia in GNE myopathy is much higher than in the normal population.

Mutations in the *GNE* gene are known to cause myopathy with characteristic clinical features.¹ Symptoms typically begin in the 2nd to 3rd decade of life and include weakness progressing slowly from the distal leg to proximal parts, including the arms, with sparing of the quadriceps.

A few reports of congenital thrombocytopenia in concurrence with GNE myopathy have recently been published,²⁻⁴ and mutations in the *GNE* gene are considered as

the underlying genetic etiology of thrombocytopenia in these cases. Here, we report a case of GNE myopathy with congenital thrombocytopenia, and explore the possibility of thrombocytopenia as a clinical manifestation of mutations in the *GNE* gene.

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Address for correspondence: Jung Hwan Lee, MD, MS

Department of Neurology, Ewha Womans University College of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea
Tel: +82-2-2650-6161, Fax: +82-2650-2652, E-mail: blubear@hanmail.net

Young-Chul Choi, MD, PhD

Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea
Tel: +82-2-2019-3323, Fax: +82-2-3462-5904, E-mail: ycchoi@yuhs.ac

Case

A 19-year-old male was referred to our hospital due to bilateral leg weakness from the age of 17. He was previously a soccer player, indicating that he had normal functionality before symptom onset. At the age of 17, his toe gait first became impaired, followed by impairments in running. Upper extremity involvement was minimal, but sit-ups and pushups became more difficult a year after onset. At the age of 19, the patient's proximal leg weakness progressed so that he needed to use his arms to stand up from sitting on the floor, and he could no longer run.

In terms of family history, the patient's younger brother had been diagnosed with thrombocytopenia of uncertain etiology (Fig. 1A). He was 3 years younger than the patient, and had complained of running difficulty for a year. However, he refused further evaluation, including genetic

testing for a *GNE* mutation.

Neurologic examination showed distal dominant lower extremity weakness with sparing of the quadriceps. Sensory examinations were normal and deep tendon reflexes were hyporeflexive.

Lab tests showed elevation of creatine kinase (CK, 401 units/L), aldolase (13.4 units/L), and lactate dehydrogenase (522 IU/L). Complete blood count revealed thrombocytopenia (100 k/ μ L) without clumping on a peripheral blood smear. Hematology was consulted for evaluation of thrombocytopenia, and abdominal sonography showed splenomegaly (13.8 cm) without any remarkable findings in other organs. However, a definite etiology for thrombocytopenia could not be found.

An electrophysiological study revealed active myopathy without any evidence of neuropathy. Myopathic changes were found on a muscle biopsy, but there was no evidence

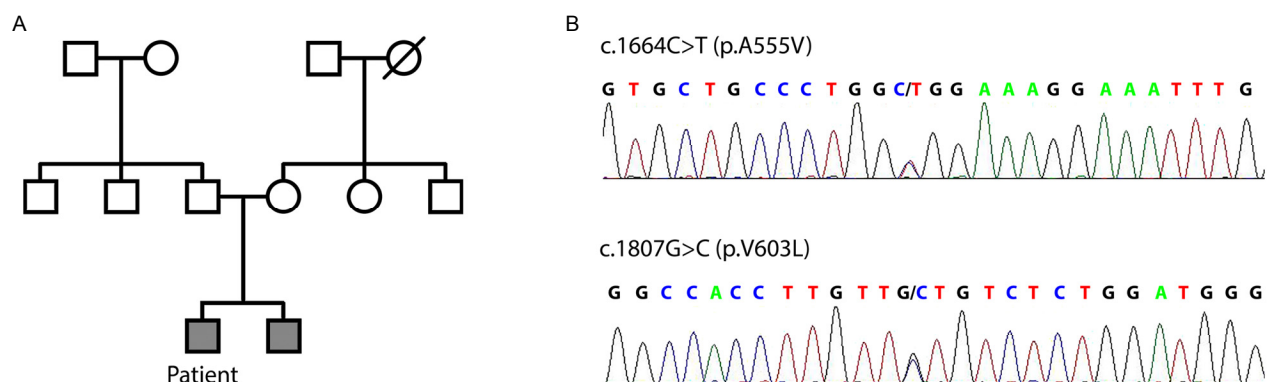


Figure 1. (A) Pedigree showing the two affected siblings without any involvement in their parents. (B) Sequence chromatograms containing pathogenic variant of p.A555V and p.V603L.

Table 1. The review of previously reported and current cases of *GNE* myopathy with thrombocytopenia

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Genomic variants	p.Y217H D515Qfs*2	p.V603L p.R39X	p.V603L p.414insT	p.V603L p.R451X	p.V603L p.G739S	p.V603L p.A555V
Age of onset	25	N/A	N/A	N/A	14-16 (middle adolescence)	17
Age at diagnosis	29	N/A	N/A	N/A	20	19
Clinical presentation	Distal dominant weakness	N/A	N/A	N/A	Proximal lower limb dominant	Distal dominant weakness
Serum creatine kinase (IU/L)	330	N/A	N/A	N/A	300-600	401
Platelet count (k/ μ L)	36	N/A	N/A	N/A	1.7-16.2	100
Pathologic finding	Myopathic changes with rimmed vacuoles	N/A	N/A	N/A	Myopathic changes with rimmed vacuoles	Nonspecific myopathic changes
Reference	Zhen et al. ⁴ (2014)	Mori-Yoshimura et al. ³ (2014)			Izumi et al. ² (2014)	Current case

N/A, not applicable.

of myositis or rimmed vacuoles in muscle staining.

Clinical features of distal myopathy with sparing of the quadriceps, and relatively late onset with slow progression to proximal muscles raised suspicion for GNE myopathy. Direct sequencing of the *GNE* gene was performed with NM_001128227.2 as a reference sequence. Two missense mutations of c.1664C>T (p.A555V) and c.1807G>C (p.V603L) were found, confirming the diagnosis of GNE myopathy (Fig. 1B).

Conclusion

Defects in the *GNE* gene are known to cause hypoglycosylation of muscles, which is thought to be the etiology for the resulting myopathy. Sialic acid is also present in the membrane of platelets, and forms during the process of glycosylation. Sialic acid deficiencies in the platelet membrane can shorten the lifespan of a platelet, causing thrombocytopenia.⁵ In this context, the incidence of thrombocytopenia in a patient registry from Japan was found to be 158 times higher than the general population.³ Considering the aforementioned role of sialic acid in platelet lifespan and the familial occurrence of both myopathy and thrombocytopenia in both siblings, a *GNE* gene mutation may be the causative etiology for thrombocytopenia in these patients.

The two mutations found in our patients were already well-known mutations in the *GNE* gene. The p.V603L mutation is the most common type found in Korea and Japan,^{6,7} while the p.A555V mutation was designated as the second most common in a patient series in China.⁸ However, thrombocytopenia was not a typical feature in patients with these same mutations.

In 6 cases from 4 reports of thrombocytopenia,^{2,4} including ours, five cases (83%) had the p.V603L mutation (Table 1). However, considering all five cases with the p.V603L mutation were from Korea and Japan, and this mutation is the most common in these areas, its significance is questionable. Also, 3 of the 6 cases (50%) had mutations in both the epimerase and kinase domain, while the other half only had mutations in the kinase domain. Considering the above results, thrombocytopenia may not

be restricted to any specific mutation in the *GNE* gene or in any one of the two enzymes. No assumption could be made for any association between other clinical features and thrombocytopenia. Case 5 showed proximal lower limb weakness as the dominant clinical feature, and no clinical features were described for 3 of 6 cases (Table 1).

We present a case of GNE myopathy with thrombocytopenia. The mutations identified in this case were commonly found in other GNE myopathy cases, and no specific genotype-phenotype correlation could be determined for the thrombocytopenia. However, considering that hypoglycosylation in platelets can cause shortening of their lifespan and the prevalence of thrombocytopenia in GNE myopathy is higher than in the general population, congenital thrombocytopenia may be a feature of mutations in the *GNE* gene.

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