CASE REPORT
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An Unexpected Association of a Novel *MYOF* Variant with Generalized Myopathy and HAE-nl-C1-INH

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ABSTRACT

Myoferlin (encoded by MYOF) is a highly expressed protein in myoblasts and endothelial cells; mutations in MYOF are linked to malignancies, skeletal and cardiac myopathy, and hereditary angioedema with normal C1-inhibitor (HAE-nl-C1-INH).

We present a 31- year-old female with recurrent severe abdominal angioedema attacks since late childhood. Mucocutaneous angioedema attacks began in early adolescence, triggered by stress and mechanical stimuli, and hormonal changes, often proceded bya fatigue or chest discomfort. Assessment of C1INH level and function had not shown any deficiency C1-INH protein level and function. Because C1-INH protein level and function were normal, whole exome sequencing (WES) was performed, identifying a novel heterozygous missense mutation in MYOF. Family screening revealed the same mutation in her mother and brother.

Her angioedema symptoms were partially controlled using daily tranexamic acid and weekly anti-androgenic agents, while fresh frozen plasma or Berinert reserved for severe attacks.

Over the past two years, she developed slowly progressive weakness in her facial, proximal, and distal extremity muscles, causing fatigue, bilateral ptosis, and difficulty climbing stairs or rising from a chair. Neurological examination, EMG-NCV studies, and elevated serum creatine kinase (CK) and lactate dehydrogenase (LDH) levels confirmed reduced muscle strength and generalized myopathy. Additionally, she experienced palpitations and unprovoked sinus tachycardia, likely reflecting cardymyopathy secondary to myoferlin deficiency.

Keywords: C1 esterase inhibitor; Dysferlin; Hereditary angioedema; Myoferlin; SERPING1

INTRODUCTION

The clinical condition of hereditary angioedema (HAE) leads to short-term swelling of skin and mucous membrane tissues, which typically affect the face, lips, and oropharynx, and occasionally, the gastrointestinal

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tract. *SERPING1* gene mutations that cause HAE result in deficiency or dysfunction of C1 esterase inhibitors (C1-INH). The most common form (85% of the cases described) is due to a reduction in the C1-INH level, also known as the type I HAE-C1INH. Other cases are normal levels of non-functional C1-INH proteins (also known as HAE-C1INH II).[1]

However, some patients presented typical symptoms of HAE but had normal levels of C1-INH (HAE-nC1INH) and no detectable mutations in *SERPING1*. The identified cases require scientists to investigate different genetic factors because they contradict our present knowledge of angioedema genetics.

In recent years, studies have highlighted the potential role of other genes, such as *ANGPT1*, *F12*, *HS3ST6*, *KNG1*, *PLG*, and *MYOF*.[2]

Myoferlin (MYOF) is a membrane-anchored protein in the Ferlin family.[3] The *MYOF* gene is located on chromosome 10q23.33. Initially, it was found to be a highly similar compound to dysferlin, with 69% of the similarities between them being myoferlin and dysferlin sequences.[4] Although dysferlin is found mainly in muscle tissue, MYOF is found in many other tissues and cells, including cardiac muscle, human pulmonary epitheliums, human placenta, vascular tissues, and endothelial cells (ECs).[3,5] Myoferlin, initially identified for its role in muscle cell fusion and repair, is also highly expressed in endothelial cells. Its involvement in stabilizing membrane proteins, such as VEGFR-2, indicates that myoferlin may play a broader role in maintaining vascular integrity and function.[6]

A pioneering study in 2020 demonstrated that enhanced VEGF-mediated intracellular signaling cascades may contribute to vascular leakage and hereditary angioedema with normal C1 inhibitor (HAE-nC1INH) in an Italian family; further, recent studies also indicated *MYOF* gene mutations in patients with HAE-nC1INH.[7-10] In the present study, we report the first Iranian family identified with a novel variant in the *MYOF* gene, which is associated with HAE-nC1INH.

CASE PRESENTATION

A 31-year-old female was referred to the Immunology, Asthma and Allergy Research Institute (IAARI) for evaluation of recurrent, abdominal angioedema attacks. Her symptoms began in early adolescence (aged 10 years) and were often triggered by stress, mechanical stimuli, or hormonal changes, preceded by prodromal symptoms of fatigue and chest discomfort. She underwent an appendectomy at age 17 years for what was likely an undiagnosed angioedema attack.

Initial investigations ruled out C1 inhibitor deficiency, as both C1-INH protein level and function were within normal limits (Table 1).

Table 1. Complement components levels in the patient.

Complement component	Patient	Range
CH50 (SRID)	130	70–160 U
C1q	140	118–244 mg/L
C3	155	83–177 mg/L
C4	22	15–45 mg/L
C1-inhibitor quantitative	35	19–37 mg/L
C1-inhibitor functional	Normal (>67%)	67%–92.5%

SRID: single radial immunodiffusion.

Over the past 2 years, the patient developed slowly progressive muscle weakness, affecting facial, proximal, and distal extremity muscles. This resulted in fatigue, bilateral ptosis, and difficulty with tasks, such as rising from a chair or climbing stairs, with symptoms worsening as the day progressed. Neurological examination and electromyography with nerve conduction studies (EMG/NCS) were consistent with a generalized myopathic process. Serum creatine kinase (CK) and lactate dehydrogenase (LDH) levels were elevated. The differential diagnosis included limb-girdle muscular dystrophy. Furthermore, she experienced palpitations and unprovoked sinus tachycardia. An echocardiogram showed a left ventricular ejection fraction (LVEF) of 55%, raising the possibility of an associated cardiomyopathy, as described in literature related to myoferlin and dysferlin defects. Consequently, whole exome sequencing (WES) was

performed, revealing a novel heterozygous missense variant in the *MYOF* gene (NM_013451.4: c.4943G>A, p.Arg1648His) in exon 44. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, this variant was classified as a variant of uncertain significance (VUS). Subsequent familial segregation analysis revealed that her symptomatic mother and brother also carried the variant, while asymptomatic family members did not (Figure 1).

Her angioedema symptoms were partially controlled with daily tranexamic acid and weekly anti-androgenic therapy. Severe breakthrough attacks were managed with fresh frozen plasma or human C1-inhibitor concentrate. Also, she received supportive treatment by a neurologist regarding her myopathy. Subsequent use of supporting medications has improved her muscle weakness. Recently, she gave birth and had a safe pregnancy with a cesarean delivery with no HAE attack.

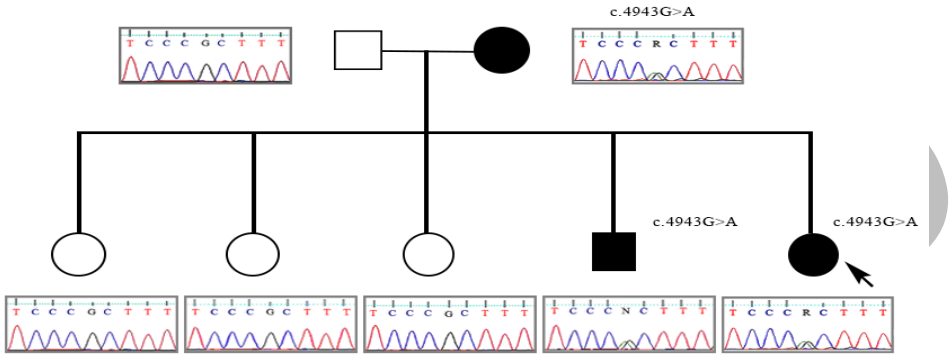

Figure 1. Pedigree and sequencing results of the patient and her family members. The proband has been shown with an arrow.

DISCUSSION

The present case describes a 31-year-old female with a novel heterozygous *MYOF* variant (p.R1648H), recurrent angioedema, and a progressive myopathy with possible cardiac involvement. This study expands the clinical and genetic spectrum of hereditary angioedema associated with myoferlin gene mutations (HAE-MYOF). Our patient exhibits features that both align with and profoundly differentiate from previously reported cases, suggesting a more complex and multisystemic phenotype than previously recognized.

The angioedema phenotype in our patient shares several characteristics with the cases described by Fomina et al (2025) and the seminal Italian family reported by Ariano et al (2020).[7,8] Onset in adolescence, recurrent abdominal attacks culminating in surgical interventions (eg, appendectomy), and triggers, such as stress and hormonal fluctuations, are consistent across these studies. Normal C1-INH level and function in our patient support a diagnosis of HAE with HAE-nC1INH. The positive response to tranexamic acid in our case parallels the excellent prophylactic control achieved in the 2 unrelated patients described by Fomina et al, supporting the use of tranexamic acid as a viable first-line prophylactic option in HAE-MYOF in our country.[1]

The proposed mechanism, as suggested by Fomina et al, may involve tranexamic acid's protective effect on vascular endothelial integrity, thereby counteracting the enhanced VEGF signaling implicated in HAE-MYOF pathogenesis.[7,8]

Our case introduces several novel features. Most notably, the development of a progressive myopathy with bilateral ptosis, proximal and distal muscle weakness, elevated CK/LDH, and myopathic findings on EMG represents a previously unreported phenotype in the context of HAE-MYOF. While the patient's symptom of worsening weakness as the day progressed could raise concern for a neuromuscular junction disorder, comprehensive evaluation did not support myasthenia gravis. The pattern of proximal muscle weakness, elevated creatine kinase, and myopathic changes on EMG were most consistent with a primary myopathy. However, we acknowledge that the presence of ptosis and diurnal fatigue warrants continued clinical surveillance for overlapping neuromuscular junction pathology. This muscular involvement is not described in the clinical reports accompanying recent publications.[7-9] Gao et al (2025) extensively document the genetic landscape of HAE-nC1INH in a Chinese cohort, including 4 novel *MYOF* variants; their focus remains on the angioedema phenotype, with no mention

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of myopathy.[9] Similarly, the patients in the Fomina and Ariano studies exhibited no muscular symptoms.[7,8] Taken together, these observations suggest that the clinical spectrum of HAE-MYOF may be broader and more multisystemic than previously appreciated.

This finding compellingly links HAE-MYOF to the known biology of myoferlin. Myoferlin is a paralog of dysferlin, the protein deficient in limb-girdle muscular dystrophy type 2B (LGMD2B) and Miyoshi myopathy, which are characterized by progressive muscle weakness and elevated CK levels.[3] Our patient's clinical presentation, including the difficulty rising from a chair (proximal weakness), closely mirrors the LGMD spectrum. The EMG diagnosis of a "myopathic process" with a differential of limb-girdle myopathy further supports this connection. Therefore, our case provides the first case that certain *MYOF* mutations can cause a combined phenotype of angioedema and a dysferlin-like myopathy, implying a critical, nonredundant role for myoferlin in skeletal muscle.

The patient's cardiac evaluation revealed an LVEF of 55%, which is within the normal reference range, and no clinical signs of heart failure. However, given the known association of dysferlin and myoferlin defects with cardiac involvement, further evaluation with advanced imaging or strain echocardiography may be warranted to assess for subclinical myocardial dysfunction.[1,10] Together, this observation suggests that the clinical monitoring of HAE-MYOF should extend beyond angioedema to include neuromuscular and cardiac assessments, particularly in patients harboring specific *MYOF* variants.

The genetic findings in our case further contribute to the understanding of HAE-MYOF. The p.R1648H variant was initially classified as a VUS. However, the segregation analysis, showing that her symptomatic mother (aged 58 years) and brother (aged 37 years) carry the variant while asymptomatic relatives do not, provides strong evidence for its pathogenicity and an autosomal dominant inheritance with variable expressivity. However, the affected family members of our patients have presented mild HAE manifestations, and only her brother has tiredness complaints; unfortunately, they did not refer to our center for further investigation. This pattern of incomplete penetrance and variable phenotypes is also seen in the family of patient 3 in the Gao et al study and the asymptomatic brother of patient 2 in the Fomina et al report, indicating that this is a common characteristic of HAE-MYOF (Table 2).[8,9]

Table 2. Summary of genetic and clinical findings in HAE-MYOF cases.

Source/patient	*MYOF* variant (cDNA)	*MYOF* variant (protein)	Exon	ACMG classification	Inheritance and penetrance	Key clinical correlation
Our patient	c.4943G>A	p.Arg1648His	44	VUS	Autosomal dominant (variable expressivity). Mother and brother symptomatic.	Novel phenotype: recurrent angioedema + progressive myopathy and cardiac symptoms.
Fomina et al (2025)—patient 1	c.2225C>T	p.Ser742Leu	33	VUS	Autosomal dominant (incomplete penetrance). Mother was an asymptomatic carrier.	First symptomatic male reported. Angioedema only.
Fomina et al (2025)—patient 2	c.3508C>T	p.His1170Tyr	33	VUS	De novo or germline mosaic suspected. Parents and siblings negative; asymptomatic brother carries the variant.	Angioedema only.

Table 2. Continued...

Source/patient	*MYOF* variant (cDNA)	*MYOF* variant (protein)	Exon	ACMG classification	Inheritance and penetrance	Key clinical correlation
Gao et al (2025)—patient 1	c.5923G>A	p.Glu1975Lys	52	VUS	No family data.	Persistent swelling, abdominal pain, laryngeal involvement.
Gao et al (2025)—patient 2	c.6001C>G	p.Arg2001Gly	53	VUS	Autosomal dominant (incomplete penetrance). Daughters negative; mother (deceased) was symptomatic.	Severe abdominal and laryngeal angioedema.
Gao et al (2025)—patient 3	c.3965C>G	p.Ala1322Gly	36	VUS	Autosomal dominant (incomplete penetrance). Mother is an asymptomatic carrier.	Angioedema with allergic comorbidities.
Gao et al (2025)—patient 4	c.1097G>T	p.Arg366Leu	12	VUS	No family data.	Recurrent angioedema.
Ariano et al (2020)—Italian family	c.651G>T	p.Arg217Ser	7	VUS, but functional data supports pathogenicity.	Mother and 2 daughters	Recurrent angioedema

ACMG: American College of Medical Genetics and Genomics; cDNA: complementary DNA; HAE: hereditary angioedema; MYOF: myoferlin; VUS: variant of uncertain significance.

In conclusion, our case demonstrates that HAE-MYOF is not solely a vascular disorder but can present as a systemic disease affecting both the vascular endothelium and skeletal muscle. This expands the differential diagnosis for patients presenting with both angioedema and myopathy. Future research should include functional studies to confirm the gain-of-function mechanism of this specific variant on VEGF signaling and to elucidate its loss-of-function impact on muscle biology. We recommend that patients diagnosed with HAE-MYOF, particularly those with variants in domains critical for myoferlin's muscular functions, undergo routine neurological evaluation and serum CK testing to screen for subclinical myopathic involvement.

STATEMENT OF ETHICS

This research was approved by the Ethics Committee of the Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences (IR.TUMS.IAARI.REC.1403.003).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The data will be available upon reasonable request from correspondence author.

AI ASSISTANCE DISCLOSURE

The authors declare that an artificial intelligence tool (Sider) was used for grammatical editing of the manuscript.

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