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Case Report

Phenotypic Heterogeny of Hereditary Angioedema Within a Single Family

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INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by episodic angioedema, affecting approximately 1 in 50,000 people.[1] It is most caused by mutations in the *SERPING1* gene, which encodes the C1 esterase inhibitor (C1-INH) protein. Less commonly, HAE results from gain-of-function mutations in the *F12*, *PLG*, or *ANGPT1* genes, leading to increased bradykinin activity.[2]

C1-INH plays a critical role in regulating the complement system, bradykinin formation, coagulation factors, and the fibrinolytic protease plasmin.[3] Deficiency or dysfunction of C1-INH leads to unregulated bradykinin production and excessive C4 consumption, resulting in angioedema. These biochemical markers help distinguish HAE from other forms of angioedema (Table 1).

While most *SERPING1* mutations involve deletions, duplications, or indels, over 748 variants have been identified, including missense, splice-site, and nonsense mutations.[4] Missense mutations, which alter a single amino acid, are generally associated with milder symptoms.[4] However, HAE severity can vary even among affected family members, and genotype-phenotype correlations remain unclear.[1,4] The lack of definitive associations between specific mutations and clinical presentation limits the ability to predict disease severity based on genetic findings.

This case report highlights the genotypic and phenotypic variability of HAE within a family, providing additional insights into this rare disease and underscoring the importance of comprehensive evaluation and monitoring of affected relatives.

Table 1. Angioedema subtypes and complement levels.[5]

	C4 Level	C-INH Level	C1-INH Function	C1q Level
HAE Type I	Low	Low	Low	Normal
HAE Type II	Low	Normal-High	Low	Normal
HAE with normal C1-INH- levels	Normal	Normal	Normal	Normal
Acquired C1-INH deficiency	Low	Low	Low	Low
ACE-I angioedema	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal

Adapted with permission from Bernstein, Severity of Hereditary Angioedema, Prevalence, and Diagnostic Considerations, 2018. Permission to use adapted table obtained from author.

CASE REPORT

We present a 40-year-old male proband, the father of three children: a 14-year-old daughter (Daughter A), a 5-year-old daughter (Daughter B), and a 7-year-old son. Three of these family members have a clinical diagnosis of HAE, though with differing characteristics. Daughter A has a different mother than Daughter B and the son.

The proband was diagnosed with Type II HAE in his teens, characterized by absent C4 protein, a normal C1 esterase inhibitor level, and reduced C1 esterase inhibitor function. He experiences episodic angioedema and has a family history of HAE; his father died from the disease, though specific genetic mutations were not identified. Genetic testing of the proband revealed a pathogenic *SERPING1* p.Arg466Cys heterozygous mutation. He is managed prophylactically with short-acting (icatibant) and long-acting (lanadelumab) kallikrein inhibitors.

Daughter A (14 years old) tested positive for the same *SERPING1* mutation, but her laboratory results were inconclusive, and she remains asymptomatic post-puberty (Table 2). She keeps icatibant on hand for acute attacks and was advised to avoid estrogen-containing contraceptives, which can increase the frequency and severity of HAE attacks.[6]

Daughter B (5 years old, half-sister of Daughter A) also tested positive for the *SERPING1* p.Arg466Cys heterozygous mutation, with similarly inconclusive lab results (Table 2). However, she has experienced extremity and abdominal angioedema, and therapeutic intervention is pending.

The son (7 years old) tested negative for mutations in *SERPING1*, *F12*, *PLG*, and *ANGPT1*, with normal lab results (Table 2). He has never exhibited symptoms of HAE, consistent with his wild-type *SERPING1* genotype.

Table 2. Complement protein quantity and levels of function of proband and offspring.

		C4 (normal levels)	**C1 esterase inhibitor level** (normal levels)	**C1 esterase inhibitor function** (normal levels)
Father	2016	<8 mg/dL (10-49)	59 mg/dL (19-37)	<10% (<41 abnormal)
Type II HAE				
Daughter A	2019	9.0 mg/dL (10-49)	90 mg/dL (19-37)	55% (41-67 equivocal)
Not typed	2021	<8 mg/dL (10-49)	41 mg/dL (19-37)	55% (41-67 equivocal)
	2023	<8 mg/dL (10-49)	26 mg/dL (19-37)	50% (41-67 equivocal)
Daughter B	2019	14 mg/dL (10-49)	92 mg/dL (19-37)	84% (>67)
Not typed	2021	<8 mg/dL (10-49)	39 mg/dL (19-37)	43% (41-67 equivocal)
	2023	<8 mg/dL (10-49)	16 mg/dL (19-37)	55% (41-67 equivocal)
	2024	3 mg/dL (10-34)	54 mg/dL (21-39)	90% (>67)
Son	2019	16 mg/dL (10-49)	35 mg/dL (19-37)	87% (>67)
	2022	34 mg/dL (10-49)	40 mg/dL (19-37)	>90% (>67)
	2023	24 mg/dL (10-49)	31 mg/dL (19-37)	106% (>67)

DISCUSSION

While the reason for the vastly different phenotypic presentations in this male proband and his two affected children remains unclear, they are not unique. One study described four family members with the *SERPING1* p.Met1Val missense mutation in exon 2, each exhibiting wide variation in the severity and frequency of HAE attacks.[6] Environmental and epigenetic factors, including hormonal and inflammatory signals, have been proposed to explain these variations.[4,7] For example, HAE attacks have been linked to an imbalance of pro- and anti-inflammatory cytokines.[7] Additionally, Cancian et al.[8] reported that HAE due to C1-INH deficiency tends to be more severe in females and can worsen after puberty.

Environmental influences, epigenetic modifications, pro-inflammatory states, and hormonal factors may contribute to the differing phenotypic presentations observed in this family.

In conclusion, we report a case of a male proband with Type II HAE and the variable phenotypic expressions of his offspring. This highlights the importance of early genetic screening and close monitoring of all family members for potential disease manifestation over time.

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