

# Serological Profiles and *SERPING1* Gene Mutations in a Pedigree with Hereditary Angioedema

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## Abstract

**Background:** Hereditary angioedema (HAE) is a rare disease caused by deficiency or dysfunction of C1-esterase inhibitor (C1-INH), predominantly affecting the skin, gastrointestinal mucosa, and upper airway. In severe cases, it may cause fatal asphyxiation. The disease is primarily caused by mutations in the *SERPING1* gene, although triggering factors also contribute to attacks. In this study, we investigated the serological profiles and *SERPING1* gene mutations in a pedigree with HAE, and clarified the underlying pathogenic mechanism.

**Methods:** A three-generation family with HAE was enrolled. Diagnosis followed international guidelines. Serum complement component 4 (C4) and complement component 1q (C1q) were quantified by immunoturbidimetry, and C1-INH concentration was measured by nephelometry. C1-INH functional activity was assessed by enzyme-linked immunosorbent assay (ELISA). Whole-exome sequencing (WES) was performed using a targeted enrichment strategy. Candidate variants were validated by Sanger sequencing and classified in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines.

**Results:** HAE in this pedigree followed an autosomal dominant inheritance pattern. Family members II-2, II-3, and III-3 exhibited serum C4 levels below the normal range, whereas C1q levels remained normal. Furthermore, C1-INH concentration was below the normal range, and its functional activity was less than 50% of the reference value, consistent with the diagnosis of type I HAE. WES revealed a heterozygous nonsense variant, c.897del (p.(Trp299Ter)), in *SERPING1* exon 6. Sanger sequencing confirmed this pathogenic variant in affected individuals, while unaffected members carried the wild-type allele.

**Conclusion:** This study reported that the *SERPING1* c.897del (p.(Trp299Ter)) nonsense variant leads to type I HAE by triggering protein truncation and subsequent C1-INH functional deficiency. These findings provide a solid basis for molecular diagnosis, familial screening, and genetic counseling of HAE, thereby expanding the spectrum of known pathogenic mutations associated with this disease.

**Keywords:** hereditary angioedema (HAE); C1-INH; *SERPING1*; variant

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## Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent, non-pitting edema of the skin, mucous membranes, and internal organs<sup>[1,2]</sup>. The pathophysiology of HAE stems from dysregulation of the complement, coagulation, and fibrinolytic systems, driven primarily by bradykinin-mediated increases in vascular permeability<sup>[3,4]</sup>. According to international consensus, based on C1-esterase inhibitor (C1-INH) status, HAE is classified into HAE-C1-INH (HAE with C1-INH deficiency) and HAE-nC1-INH (HAE with normal C1-INH) types; the former accounts for the vast majority of cases<sup>[5,6]</sup>. Within HAE-C1-INH, two subtypes are recognized: type I, associated with low C1-INH plasma concentration and function, and type II, characterized by normal or elevated antigenic levels but reduced functional activity. Approximately 85% of HAE patients are classified as type I, which results from *SERPING1* loss-of-function mutations that lead to the production of structurally abnormal C1-INH proteins. These defective proteins are inefficiently secreted, causing markedly reduced serum levels of both antigenic and functional C1-INH. In contrast, type II HAE accounts for about 15% of cases; here, *SERPING1* mutations produce dysfunctional but normally secreted C1-INH proteins, resulting in normal or even elevated antigenic concentrations with significantly impaired functional activity<sup>[7,8]</sup>. In recent years, a rarer form—HAE type III—has been described. Patients with this subtype exhibit normal C1-INH concentration and function, and the majority are female. Type III HAE is often associated with gain-of-function mutations in the *F12* gene (encoding coagulation factor XII) and is frequently triggered or exacerbated by elevated estrogen levels, such as those induced by oral contraceptives containing estrogen or during pregnancy<sup>[8]</sup>.

Epidemiological data indicate a global prevalence of HAE of approximately 1.5 per 100,000 individuals, whereas nationwide statistics remain unavailable in China. Studies conducted at Peking Union Medical College Hospital (PUMCH) reveal a marked predominance of the HAE-C1-INH phenotype (> 98%) among Chinese patients. Specifically, type I accounts for 98.73% of cases, compared to only 1.27% for type II, with no publicly reported cases of HAE-nC1-INH (e.g., mutations in

coagulation factor XII, angiotensin-1, or plasminogen gene) to date<sup>[9]</sup>. Given that C1-INH levels may remain within normal ranges in type II patients—rendering routine biochemical assays prone to false negatives—genetic diagnosis serves as the gold standard. This approach is particularly critical for the screening of asymptomatic carriers and the assessment of familial risk.

Family-based studies are invaluable for elucidating the genetic basis of HAE, as they enable the delineation of mutation transmission patterns and provide critical insights into genotype–phenotype correlations. In this study, we investigated a large Chinese pedigree with HAE using next-generation sequencing to characterize the mutational spectrum of the *SERPING1* gene. We identified a pathogenic variant, correlated it with the clinical phenotype, and evaluated its functional consequences. Our findings not only support informed genetic counseling and targeted intervention for this family but also help address the underrepresentation of *SERPING1* variants in the Chinese population within global mutation databases.

## Materials and methods

### Study subjects

The family spans three generations, with one deceased member (I-1) reported to have a history of HAE (Fig. 1). A clinical diagnosis of HAE was made based on the patient's description of his father's symptoms. The proband (II-3), a 36-year-old male, presented with recurrent abdominal pain and cutaneous edema that responded poorly to conventional therapy. Following hospital admission, detailed medical and family histories were obtained, and comprehensive laboratory testing confirmed an initial diagnosis of HAE. Family member II-2 also exhibited similar clinical symptoms and was subsequently diagnosed with HAE. Family member III-3 was genetically and biochemically consistent with the diagnosis of HAE but has remained phenotypically normal to date. The clinical data of the confirmed patients are summarized in Table 1. To assess the disease status across the pedigree, serum levels of complement component 4 (C4), complement component 1q (C1q), and C1-INH, along with C1-INH functional activity, were measured in all available family members. To

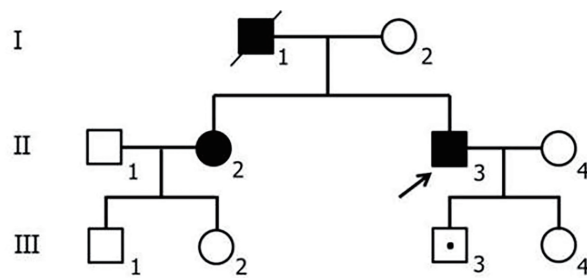


**Figure 1:** Hereditary angioedema (HAE) family tree.

The family consists of 3 generations, I-1 having a history of HAE and having passed away. The proband (II-3) and his older sister (II-2) experienced recurrent abdominal pain and cutaneous edema, and were definitively diagnosed with HAE by laboratory testing. Family member III-3 was genetically and biochemically consistent with the diagnosis of HAE, but remained phenotypically normal, and is therefore a carrier of the pathogenic *SERPINC1* variant.

identify the underlying genetic cause, whole-exome sequencing (WES) was performed on six individuals (II-2, II-3, III-1, III-2, III-3, and III-4). Candidate variants were identified through bioinformatic analysis and confirmed by Sanger sequencing in all participating family members.

### Diagnostic criteria for HAE

The diagnosis was made based on the consensus of Chinese experts on the diagnosis and treatment of

HAE<sup>[10]</sup>, and the International World Allergy Organization/ European Academy of Allergy and Clinical Immunology (WAO/EAACI) Guidelines for the Management of Hereditary Angioedema—2021 Revision and Update<sup>[11]</sup>. The main clinical symptom criteria for HAE: (1) recurrent non-inflammatory, self-limited subcutaneous edema, without urticaria, with an onset duration of more than 12 h; (2) recurrent self-limited abdominal pain, often without obvious induction, with symptoms lasting more than 6 h during the attack; (3) recurrent laryngeal edema. Secondary criteria: family history of recurrent edema and/or abdominal pain and/or laryngeal edema. Laboratory indicators: (1) C1-INH content < 50% of the normal value; (2) C1-INH function < 50% of the normal value; (3) C1-INH gene mutation. Diagnosis can be confirmed by meeting one of the main clinical criteria and one laboratory indicator mentioned above.

### Specimen collection and processing

After obtaining written informed consent, 10 mL of peripheral venous blood was collected from the antecubital vein of each participant into two 5-mL tubes. One tube was used for genomic DNA extraction from white blood cells using a commercial kit (Thermo Fisher Scientific Inc., USA) for subsequent sequencing. The second tube was allowed to clot at room temperature for

**Table 1: Clinical characteristics of patients with hereditary angioedema (HAE).**

| Family members | Sex    | Age (years)    | Age at onset (years) | Main edema site                | Abdominal/ laryngeal involvement                       | Attack frequency | Previous treatments                                                           | Time of sample collection |
|----------------|--------|----------------|----------------------|--------------------------------|--------------------------------------------------------|------------------|-------------------------------------------------------------------------------|---------------------------|
| I-1            | Male   | died at age 54 | 16                   | Extremities and abdomen        | died of laryngeal edema, abdominal pain: 1×/1.5 years  | 1×/month         | Mainly anti-allergic therapy                                                  | No specimens obtained     |
| II-2           | Female | 38             | 14                   | Extremities and abdomen        | Abdominal pain: 1×/year, no laryngeal edema            | 2–3×/year        | Symptomatic anti-allergic therapy during attacks                              | Between attacks           |
| II-3           | Male   | 36             | 14                   | Extremities, face, and abdomen | Laryngeal edema: 1×/2 years; abdominal pain: 1–2×/year | 7×/year          | Treated with danazol for six months, followed by a single dose of lanadelumab | Between attacks           |
| III-3          | Male   | 11             | No attacks           |                                |                                                        | No attacks       | Untreated                                                                     | Between attacks           |

Note: 1×/year, once per year.

30 min, followed by centrifugation to obtain serum. The serum supernatant was then used to measure C1-INH antigenic concentration and functional activity, as well as complement components C4 and C1q.

### **Complement determination**

Serum levels of complement C4 and C1q in family members II-2, II-3, III-1, III-2, III-3, and III-4 were measured by immunoturbidimetry.

### **C1-INH determination**

C1-INH antigenic concentration was quantified by nephelometry, and functional activity was assessed by enzyme-linked immunosorbent assay (ELISA). Both parameters were evaluated in all available family members, including symptomatic individuals with recurrent edema and asymptomatic relatives.

### **Whole-exome sequencing**

WES was performed using targeted region capture-based high-throughput sequencing approach. Genomic DNA was extracted from peripheral blood leukocytes, quantified by fluorometry, and subjected to polymerase chain reaction (PCR) amplification as needed. Targeted sequencing was performed using a liquid-phase hybridization capture system to enrich genomic regions of interest, followed by high-throughput, high-depth sequencing on an Illumina platform. Library preparation and target enrichment were carried out using the Agilent SureSelect XT Custom Kit, in accordance with the manufacturer's instructions and optimized in-house protocols. Briefly, genomic DNA was randomly fragmented to 180–280 bp using a Bioruptor Pico sonicator (Diagenode). Fragmented DNA underwent end repair, 5' phosphorylation, and 3' A-tailing, followed by ligation of indexed adapters to generate sequencing libraries. Indexed libraries were pooled and hybridized in solution with biotinylated RNA baits specific to the target regions. Streptavidin-coated magnetic beads were used to capture probe-bound fragments. Following limited-cycle linear PCR amplification, libraries were assessed for quality and concentration. Libraries meeting quality criteria were sequenced on an Illumina platform using paired-end 150-bp (PE150) chemistry, followed by bioinformatic analysis.

The quality metrics for the targeted region capture high-throughput sequencing data are as follows: a total of 20,858 targeted genes were analyzed, covering a targeted region length of 37,837,472 bp. The targeted region achieved a coverage of 99.70%, with a mean sequencing depth of 107.002×. Furthermore, 97.59% of the targeted bases reached a depth of  $\geq 20\times$ .

### **Bioinformatics analysis**

Raw sequencing reads were assessed for quality using fastp (v0.23+), and low-quality bases as well as adapter-contaminated reads were trimmed or removed. The cleaned reads were aligned to the human reference genome (hg19/GRCh37) using Burrows–Wheeler Aligner. Alignment metrics and on-target capture efficiency were evaluated to assess sequencing performance. Variant calling was performed using the Genome Analysis Toolkit (GATK, v4.x) best practices pipeline to identify single nucleotide variants (SNVs) and small insertions/deletions (indels). Candidate variants were filtered against population frequency databases, including the 1,000 Genomes Project, Genome Aggregation Database (gnomAD) v2.1.1, and Exome Aggregation Consortium, excluding variants with minor allele frequency  $> 1\%$  in any population unless clinically relevant.

The potential pathogenicity of missense and splice-site variants was predicted using multiple algorithms integrated in the database of nonsynonymous single nucleotide polymorphisms functional predictions (dbNSFP) (e.g., SIFT, PolyPhen-2, CADD, and REVEL). Known disease-associated variants were cross-referenced with Online Mendelian Inheritance in Man (OMIM), the Human Gene Mutation Database (HGMD Professional), and ClinVar.

All candidate variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines into five categories: pathogenic, likely pathogenic, uncertain significance, likely benign, or benign. Finally, all putative pathogenic or likely pathogenic variants were validated by Sanger sequencing in the proband and available family members. Primers for Sanger sequencing of *SERPING1* (RefSeqGene: NG\_009625.1) were as follows: forward, 5'-AGCCAGTT AGTCTTCCCATCTG-3'; reverse, 5'-GACTTGCTAA GCCACCAGAGT-3' (amplicon, ~650 bp).

## Results

### Mode of inheritance

The pedigree demonstrates affected individuals across three consecutive generations, consistent with vertical transmission and an autosomal dominant inheritance pattern (Fig. 1). Notably, individual I-1 died at the age of 54 due to airway obstruction caused by laryngeal edema, a known life-threatening complication of HAE.

### Complement C4 and C1q assay results

Serum complement C4 concentrations were below the reference range in the proband (II-3), his older sister (II-2), and his son (III-3), but were normal in the other individuals. C1q levels were within the normal range across all individuals (Table 2).

**Table 2: Determination results of C4 and C1q.**

| Examinee | Complement C4 (g/L) | Complement C1q (mg/L) |
|----------|---------------------|-----------------------|
| II-2     | 0.05                | 114.90                |
| II-3     | 0.04                | 121.50                |
| III-1    | 0.26                | 138.20                |
| III-2    | 0.21                | 126.60                |
| III-3    | 0.07                | 107.30                |
| III-4    | 0.19                | 123.80                |

Note: Normal value, complement C4 0.12–0.36 g/L, complement C1q 50.00–250.00 mg/L.

Abbreviations: C4, complement component 4; C1q, complement component 1q.

### Results of serum C1-INH concentration and functional determination

The results of serum C1-INH concentration and functional determination are shown in Table 3. The serum C1-INH concentrations in the proband and individuals II-2 and III-3 were below the normal range, while their functional activities were less than 50% of the lower limit of normal, indicating functional impairment. These findings are consistent with a diagnosis of type I HAE. Serum C1-INH levels and functional activity in the other family members were within normal limits.

**Table 3: C1-INH concentration and functional determination.**

| Examinee | C1-INH concentration (g/L) | C1-INH functional (%) |
|----------|----------------------------|-----------------------|
| II-2     | 0.07                       | 5.6                   |
| II-3     | 0.09                       | 4.8                   |
| III-1    | 0.25                       | 86.2                  |
| III-2    | 0.31                       | 89.3                  |
| III-3    | 0.12                       | 4.1                   |
| III-4    | 0.28                       | 88.5                  |

Note: The reference interval for C1-INH concentration is (0.21–0.39) g/L, and the reference interval for C1-INH function is  $\geq 68.0\%$ .

Abbreviations: C1-INH, C1 esterase inhibitor.

### Gene sequencing results

A heterozygous frameshift variant, NM\_000062.3: c.897del (p.(Trp299Ter)), was identified in the *SERPING1* gene in the proband (II-3), his older sister (II-2), and his son (III-3). This variant, located in exon 6, results from a single-nucleotide deletion at position 897 of the coding sequence, leading to the substitution of tryptophan at amino acid position 299 with a premature stop codon. The variant has not been reported in the ClinVar database. The variant was classified as pathogenic based on the ACMG guidelines, supported by the following criteria: PVS1\_Very Strong + PS4\_Strong + PM2\_Moderate. In contrast, three unaffected family members (III-1, III-2, and III-4) were homozygous for the wild-type allele at this locus, with no variant detected (Fig. 2).

### Bioinformatics analysis results

The pathogenicity of missense and splice-site variants was assessed using the dbNSFP database. *In silico* prediction by MutationTaster classified the *SERPING1* variant c.897del (p.(Trp299Ter)) as disease-causing. This nonsense mutation introduces a premature termination codon at position 299, which is predicted to result in either a truncated protein or nonsense-mediated mRNA decay, thereby severely compromising C1-INH protein structure and function. Although this variant is absent from the gnomAD population database (v2.1.1), it has been previously reported in affected individuals, with a significantly higher frequency observed in HAE cohorts compared to control populations. Furthermore, it has not been documented in the ClinVar database<sup>[12]</sup>.

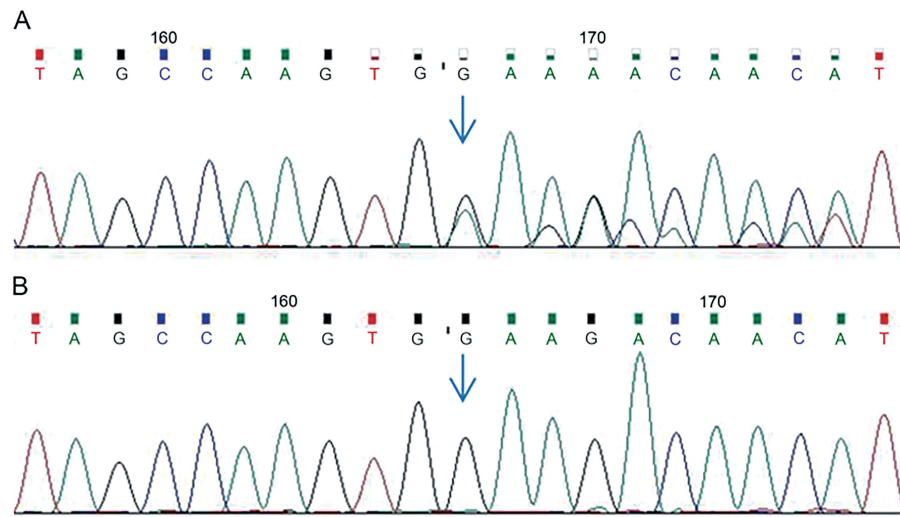


**Figure 2:** Sanger sequencing validation of the *SERPING1* c.897del variant.

(A) Sequencing chromatograms of the proband, his sister, and his son, all carrying the heterozygous variant. The arrow indicates the site of the single-nucleotide deletion. Note the overlapping peaks and distorted signal downstream of the mutation site, characteristic of a heterozygous frameshift. (B) Sequencing chromatogram of an unaffected family member (wild-type homozygote). The sequence shows clean, single peaks with no evidence of the deletion.

## Discussion

Family studies confirm that HAE is inherited in an autosomal dominant manner, consistent with previous reports<sup>[13,14]</sup>. Since individuals I-1, II-2, and II-3 presented with normal phenotypes at birth and developed characteristic HAE symptoms later in life, their clinical course is consistent with delayed onset. Given this mode of inheritance, the risk of disease transmission within the family can be predicted based on the segregation pattern of the pathogenic *SERPING1* variant. Genetic testing enables early identification of at-risk relatives, accurate determination of mutation status, and informed reproductive counseling. These measures facilitate timely clinical surveillance, preventive strategies, and early intervention—ultimately improving outcomes and reducing the burden of HAE in affected families.

Studies on the pathogenic mechanisms of HAE have demonstrated that mutations in the *SERPING1* gene—including deletions, insertions, translocations, and point mutations—can disrupt intracellular protein processing and trafficking. These genetic alterations may introduce premature termination codons or critical amino acid substitutions, ultimately leading to either deficient secretion or functional inactivation of C1-INH<sup>[15,16]</sup>. As a key serine

protease inhibitor, C1-INH normally regulates multiple plasma proteolytic cascades. Loss of its inhibitory function results in uncontrolled activation of the complement, kallikrein–kinin, and fibrinolytic systems, culminating in excessive bradykinin generation. Bradykinin, a potent vasodilator, increases vascular permeability and triggers episodic angioedema<sup>[17,18,19]</sup>. Notably, laryngeal edema—a life-threatening manifestation of HAE—can progress rapidly and carries a reported mortality rate of 11% to 40%, underscoring its status as the most severe complication of the disease<sup>[20]</sup>.

C1-INH, a key serine protease inhibitor, plays a central role in maintaining vascular homeostasis by suppressing the complement system (C1r/C1s), the contact system (factor XIIa and plasma kallikrein), and the fibrinolytic system (plasmin)<sup>[21,22]</sup>. In this study, we identified a heterozygous nonsense variant in exon 6 of the *SERPING1* gene—c.897del (p.(Trp299Ter)). The frameshift nonsense mutation caused by this single-base deletion constitutes definitive evidence of pathogenicity, supported by the PVS1 criterion, its enrichment in patient cohorts (PS4), and its rarity in population databases (PM2). This variant is likely to abolish the inhibitory activity of C1-INH against factor XIIa and plasmin. Such loss of function leads to uncontrolled activation of

the bradykinin-generating pathway, which represents the core pathogenic mechanism underlying angioedema in HAE.

Of particular pathophysiological relevance is the reciprocal amplification between the contact and fibrinolytic systems: factor XIIa activates plasma kallikrein and promotes the conversion of plasminogen to plasmin, while plasmin, in turn, can feedback-activate factor XII, establishing a self-amplifying positive feedback loop<sup>[23]</sup>. In the setting of C1-INH deficiency, this regulatory circuit becomes dysregulated, resulting in excessive bradykinin production and consequent vascular leakage in mucosal and subcutaneous tissues<sup>[24,25]</sup>. This study identified a pathogenic variant in the *SERPING1* gene in a Chinese family with HAE. We report a heterozygous nonsense mutation—c.897del (p.(Trp299Ter))—in exon 6 of *SERPING1*, resulting from a single-nucleotide deletion at position 897 of the coding sequence. This alteration replaces the tryptophan codon at amino acid position 299 with a premature stop codon, leading to a truncated protein product. Antigenic and functional analyses revealed concomitant reductions in C1-INH concentration and activity, along with decreased C4 levels, in family members II-2, II-3, and III-3. Meanwhile, C1q levels were within normal limits, consistent with the diagnostic criteria for type I HAE. The *SERPING1* gene is well established as the causative locus for autosomal dominant HAE characterized by C1-INH deficiency<sup>[26]</sup>.

To investigate the underlying mechanisms of *SERPING1* gene mutations in HAE, erythroblasts expanded from peripheral blood mononuclear cells (PBMCs) of patients with HAE-C1-INH type I (harboring distinct *SERPING1* point mutations, insertions, deletions, or large fragment mutations) were reprogrammed into expanded pluripotent stem cells (EPSCs) and subsequently differentiated into hepatocyte-like cells (HLCs). All patient-derived HLCs exhibited impaired C1-INH secretion. To verify whether these mutations directly drive the observed phenotype, clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9)-mediated genome repair was performed, which successfully restored *SERPING1* mRNA expression and C1-INH secretion. Conversely, introducing the identical patient *SERPING1* mutations into healthy

EPSCs recapitulated the same transcriptional and secretory defects. These findings demonstrate that HAE with C1-INH deficiency is caused by pathogenic *SERPING1* mutations that disrupt the production of the plasma protease inhibitor C1-INH<sup>[27]</sup>. *In vitro* studies were conducted on a patient with type I HAE harboring the *SERPING1* missense mutation p.S150F. The results demonstrated that the p.S150F-mutant C1-INH was stably expressed within human embryonic kidney 293T (HEK293T) cells but was completely absent from the culture medium. Furthermore, the mutant C1-INH was shown to significantly impede the secretion of wild-type C1-INH. These findings suggest that the wild-type protein is not only retained intracellularly but also degraded in the cytoplasm through interaction with the mutant protein. Collectively, this study clearly reveals a dominant-negative effect of the p.S150F-mutant C1-INH against wild-type C1-INH<sup>[28]</sup>. In fibroblasts derived from a heterozygous carrier of the dominant-negative *SERPING1* (c.551\_685del) variant, intracellular aggregation of C1-INH and endoplasmic reticulum (ER) abnormalities were observed; notably, this pathological condition was ameliorated by viral vector-mediated delivery of the *SERPING1* gene. These findings indicate that in patients harboring the c.551\_685del mutation, the abnormal aggregation of serpins impairs the secretion of C1-INH<sup>[29]</sup>.

A novel pathogenic variant of *SERPING1* gene c.708T>G, was discovered in a Han Chinese family affected by HAE. Notably, this variant was closely associated with the aberrant accumulation of C1-INH within the ER, accompanied by a significant upregulation of glucose-regulated protein 75 (GRP75) protein expression. These findings elucidate a distinct pathogenic cascade: ranging from molecular abnormalities triggered by ER stress to GRP75-mediated Ca<sup>2+</sup> homeostasis imbalance, ultimately culminating in mitochondrial structural and functional impairment and apoptosis. Based on these observations, the authors postulate that the detection of intracellular Ca<sup>2+</sup> concentration could serve as a potential biomarker for predicting acute attacks in HAE patients. This discovery not only expands the genotype–phenotype spectrum of *SERPING1* mutations but also provides a crucial theoretical basis for developing precision therapeutic strategies targeting Ca<sup>2+</sup> signaling pathways, holding significant implications for optimizing the clinical management

of HAE<sup>[30]</sup>. A family with HAE type I was caused by intron mutation. A heterozygous nucleotide change was found at -10 position (c.52-10T>A) of intron 2. The effect of the mutation likely leads to a reduction in the expression of full-length C1-INH protein, thereby reducing normal C1-INH activity. This variant has been identified as pathogenic<sup>[31]</sup>. Bork K<sup>[32]</sup> analyzed the various clinical manifestations of HAE in 14 related patients using clinical data, biochemical analysis for C1-INH and C4, as well as gene sequencing. The patients' symptoms were assigned to different forms of HAE. In 10 patients suffering from swelling of the lips or tongue but not of the extremities, a mutation in the *PLG* gene (c.988A>G) was found, whereas in the only four patients with swelling of the gastrointestinal tract and extremities, a mutation in the *SERPING1* gene (c.1480C>T) was identified. An HAE patient in early childhood was found to have the c.686-7C>G (intron) variant of the *SERPING1* gene. Not all variants present in genes cause disease, but given patient clinical history and low C1-INH, reduced function of C1-INH and low C4, the c.686-7C>G (intron) mutation in the *SERPING1* gene is likely pathogenic<sup>[33]</sup>. The wide-ranging spectrum of disease-causing *SERPING1* variants includes everything from missense mutations, nonsense mutations, splice site mutations, smaller insertions, deletions, and larger genomic deletions caused by recombination between Alu repeats<sup>[34]</sup>. Ponard D<sup>[35]</sup> conducted an update on *SERPING1* gene mutations, analyzing diverse variants that included both published data and an additional 120 unpublished cases. These variants were identified as heterozygous ( $n = 729$ ), homozygous (in 10 probands), and compound heterozygous (9 combinations). Notably, gonadal mosaicism was observed in six probands with heterozygous variants. Furthermore, 72 heterozygous and 1 homozygous variant were identified as *de novo* cases. Overall, 58 variants were located at residue positions that are highly conserved among the serpin family. The above reports indicate that the occurrence of C1-INH-HAE exhibits genetic heterogeneity. This study not only confirms the central position of *SERPING1* gene mutation in the pathogenesis of HAE, but also provides key evidence for the molecular diagnosis of HAE patients. Our findings broaden the mutational spectrum of *SERPING1* and provide evidence for accurate diagnosis and predictive genetic counseling.

## Conclusion

This study reported that *SERPING1* gene c.897del (p.(Trp299Ter)) nonsense mutation led to type I HAE, and this variant caused C1-INH functional deficiency by triggering protein truncation. These findings provide a solid basis for molecular diagnosis, familial screening, and genetic counseling of HAE, thereby expanding the spectrum of known pathogenic mutations associated with this disease.

## Author contributions

Guangmou Zhang conceived the study and designed the pedigree investigation. Yichen Li performed the serological assays and *SERPING1* sequencing. Yichen Li and Kefeng Zhang analysed the data and drafted the manuscript. Huijuan Zhai provided clinical resources and critically revised the manuscript for important intellectual content. Zhiqing Yuan supervised the work. All authors reviewed, edited, and approved the final version of the manuscript and agreed to its publication.

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## Ethics statement

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Xinxiang Medical University (Approval No. 2024392).

All figures are either original to this work or properly attributed. No original images have been previously published, and all images comply with research integrity standards without inappropriate manipulation or misrepresentation.

### Patient consent statement

Written informed consent was obtained from all family members, or from their legal guardians for participants under 18 years of age, for participation in this study and for publication of the study results and accompanying images, including pedigree, serological, and genetic data.

### Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

### AI statement

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, analysis, writing, image generation, or image processing of this manuscript.

### Conflicts of interest

The authors declare no conflicts of interest.

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