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CASO CLÍNICO

Novel *SERPING1* Genetic Variant in Two Family Members with Hereditary Angioedema

Nova Variante Genética no Gene *SERPING1* em Dois Familiares com Angioedema Hereditário

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ABSTRACT

Hereditary angioedema is a rare, autosomal dominant, genetic disorder characterized by recurrent episodes of angioedema. Over 800 *SERPING1* gene variants have been reported, and their clinical profiles and causal genetic variants are highly heterogeneous. We report two cases of hereditary angioedema (HAE) in a Portuguese family: a 27-year-old male, under lanadelumab, and his 57-year-old father, kept on on-demand treatment. Genetic testing was performed following international guidelines. The Hereditary Angioedema Database Annotation highlighted a heterozygous insertion at exon 3 (c.336_337insC). This variant predicts a frameshift of the transcript, with the introduction of a premature STOP codon in C1-INH protein (p.Ser113LeufsTer20). We report the identification of a novel pathogenic *SERPING1* variant in a family with HAE type 1, assisted by the Hereditary Angioedema Database Annotation variant prioritization tool. Our results may contribute to the identification of additional families with the same variant and can further enhance the knowledge about this condition.
Keywords: Angioedemas, Hereditary; Complement C1 Inhibitor Protein/genetics

RESUMO

O angioedema hereditário é uma doença genética rara, autossómica dominante, caracterizada por episódios recorrentes de angioedema. Estão descritas mais de 800 variantes genéticas associadas ao *SERPING1*. No entanto, existe uma elevada heterogeneidade clínica e genética. Descrevem-se dois casos de angioedema hereditário numa família portuguesa: um homem de 27 anos, medicado com lanadelumab, e o seu pai, com 57 anos, sob terapêutica em SOS. Em conformidade com as orientações internacionais, realizou-se o estudo genético, que identificou uma inserção no exão 3 (c.336_337insC), em heterozigotia. Esta nova variante prevê uma alteração *frameshift*, com introdução prematura de um codão STOP na proteína C1-INH (p.Ser113LeufsTer20). Descrevemos a identificação de uma nova variante genética patogénica no gene *SERPING1* numa família com angioedema hereditário tipo 1 assistida pela ferramenta Hereditary Angioedema Database Annotation. Estes resultados poderão contribuir para a identificação de outras famílias portadoras da variante e aumentar o conhecimento sobre esta patologia.
Palavras-chave: Angioedema Hereditário; Proteína Inibidora do Complemento C1/genética

INTRODUCTION

Hereditary angioedema (HAE) is a rare, autosomal dominant, genetic disorder characterized by recurrent episodes of angioedema that affect most commonly the extremities, face, gastrointestinal tract, and upper airways.[1,2] It has an estimated incidence of 1 in 50 000 worldwide.[3] However, its precise incidence may be higher due to the lack of recognition and awareness.

HAE is grouped into three different types based on the C1 inhibitor (C1-INH) levels and activity. HAE type I (C1-INH deficiency) and type II (C1-INH disfunction) are due to pathogenic variants in the *SERPING1* gene, which encodes the C1-INH protein. Patients with normal C1-INH (HAE-nC1-INH) are currently understood to have disease caused by pathogenic variants in one of eight recognized genes, namely factor XII (*FXII*), angiopoietin-1 (*ANGPT1*), plasminogen (*PLG*), kininogen 1 (*KNG1*), myoferlin (*MYOF*), heparan sulfate-glucosamine3-O-sulfotransferase 6 (*HS3ST6*), carboxypeptidase N (*CPN1*) and *DAB2IP*.[4-13]

More than 800 pathogenic and likely pathogenic genetic variants in *SERPING1* have been described as causes of HAE,[14] but not all these variants have been registered in the various genetic databases. The Hereditary Angioedema Database Annotation (HADA, https://github.com/genomicsITER/HADA), a next-generation sequencing tool, has described 471 genetic variants in *SERPING1*.[15] Nevertheless, there is a high heterogeneity of clinical profiles and causal genetic variants,

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making it difficult to reach conclusions about the spectrum of disease expression. Bors *et al* suggested that missense variants (i.e. single-nucleotide variants predicting an amino acid substitution) in *SERPING1* seem to be associated with less severe forms of the disease.[16] Every year new genetic variants are described, contributing to the enhancement of the knowledge about this particular disease.

The authors performed a next-generation genetic study in two members of a family with HAE type I and, with the support of HADA, detected a previously undescribed genetic variant in *SERPING1*.

CASE REPORT

We report two cases of HAE in a Portuguese family. The index case is a 27-year-old man, who experienced episodes of angioedema since the age of six years old. He initially reported angioedema a few times per year (two to four episodes/year), with each episode lasting two to four days, and resolving spontaneously. The most common sites were the extremities (hands and feet), mainly triggered by physical factors. At 16 years-old he was referred to our outpatient clinic for recurrent angioedema, with a monthly frequency of episodes. The investigation revealed markedly reduced levels of C1-INH, functional C1-INH, and C4, confirming a diagnosis of HAE type I [C1-INH < 6 mg/dL (C1-INH: 15-39 mg/dL), fC1-IHN < 25% (fC1-INH: 68% - 120%); and C4 3.2 mg/dL (C4: 10 - 40 mg/dL)]. At that point, the lack of response to antihistamines and the suspicion of HAE led to the prescribing of aminocaproic acid on-demand, with full clinical response. In 2019, at the age of 21, angioedema became more frequent, occurring almost weekly. Aminocaproic acid was started daily, but full adherence was not achieved, and episodes persisted. At the age of 22, the patient presented to the emergency department with a cervical and laryngeal episode that fully resolved after intravenous C1-INH 1000U administration, without the need for intubation. Since then, daily aminocaproic acid has been maintained, resulting in a reduced frequency of episodes (every two to three months). In 2023, despite adherence to preventive therapy, angioedema episodes became weekly, leading to multiple emergency visits and the need for intravenous C1 inhibitor or subcutaneous icatibant. During this period, the patient reported three laryngeal episodes, all without the need for intubation, even though fibrinolytics were kept daily. Androgen therapy was considered; however, the patient refused it due to long-term potential adverse effects. Lanadelumab was started in January 2024, with full disease control.

Family investigations were initiated immediately after the diagnosis of the index case (Fig. 1). Self-reporting provided information of four generations from the paternal side. Unfortunately, most relatives, for whom disease symptoms were known, had already died (grandmother, great-uncle, and great-aunt), thus making it impossible to establish the diagnosis.

The 57-year-old father of the index case had a history of recurrent angioedema, starting at the age of 15, three to four times a year, affecting mainly the upper and lower extremities. These would last two to four days, resolving spontaneously. No clear trigger was identified. Angioedema related to dental procedures was also documented but not diagnosed as HAE. In 2015, at the age of 47 years old, the patient was admitted to the emergency department for abdominal pain, and surgery was performed. At the time, bridle occlusion was admitted, even though abdominal surgery had not been performed previously. In 2020, following the son's diagnosis, laboratory diagnosis was performed. It revealed HAE type 1 diagnosis, with low levels of C1-INH, fC1-IHN and C4 [C1-INH < 3 mg/dL (C1-INH: 15-39 mg/dL), fC1-IHN < 1% (fC1-INH: 68% - 120%); and C4 2.6 mg/dL (C4: 10 - 40 mg/dL)]. The patient was prescribed with aminocaproic acid on-demand, with full clinical response.

The index patient's paternal grandmother reported several episodes affecting mainly the face. Laryngeal angioedema, with multiple evaluations in the emergency department, was mentioned. However, HAE was never suspected, nor was the patient referred to our department. One great-aunt and one great-uncle also reported peripherical episodes, disregarded at the time. These patients' causes of deaths could not be clearly related to the HAE. Further family details were unclear due to lack of close relationships.

In line with international HAE management guidelines, a whole-exome sequencing (i.e. sequencing of primarily all protein-coding regions of the genome) was performed in both patients, by a HiSeq 4000 Illumina platform (Illumina Inc.). Sequencing data was analyzed with the HADA tool[14] for causal and novel candidate variant prioritization within genes *SERPING1, FXII, ANGPT1, PLG, KNG1, MYOF, HS3ST6*, and several other candidate genes described in the literature (information upon request). The HADA tool highlighted a heterozygous 1-pb insertion at the exon 3 (c.336_337insC) of the *SERPING1* gene in both cases. This newly described variant predicts a frameshift of the transcript, with the introduction of a premature STOP codon in the C1-INH protein (p.Ser113LeufsTer20). This possibly triggers the nonsense-mediated decay (NMD), a cellular surveillance mechanism that degrades mRNAs containing premature STOP codons. NMD is, therefore, compatible with the HAE type 1 diagnosis, as it may justify the low serum expression of C1-INH. According to the American College of Medical Genetics and Genomics and pathogenicity prediction tools (CADD Phred Score 16.26,

exceeding the mutational significance cutoff of 14.39 for this gene), this variant is classified as pathogenic (PVS1 very strong, PM2 supporting, PP1 supporting, PP4 supporting).

DISCUSSION

The international World Allergy Organization/European Academy of Allergy & Clinical Immunology guidelines recommend screening family members for HAE, as delayed diagnosis often leads to increased morbidity and reduced quality of life.[1] It is a potential life-threatening disease, with an unpredictable clinical course, making timely recognition and early treatment crucial to prevent fatalities.

In this study, we describe a family with HAE type 1, in whom HADA-assisted variant prioritization helped the identification of a novel pathogenic genetic variant in *SERPING1* gene. Our results may contribute to the identification of further relatives and/or families with the same variant, and can further enhance the knowledge about this condition, as the identification of new genetic variants may help to establish genotype-phenotype correlations in HAE. Genetic testing supports diagnostic accuracy and can justify structured family-screening programmes and access to specific biological therapies, providing a clear basis for health-policy measures. Early diagnosis improves clinical and psychological outcomes, and can reduce healthcare costs by avoiding misdiagnoses, preventing severe attacks, and guiding counselling and targeted care.

Family history based on second-hand accounts from deceased relatives constitutes a limitation, as well as the lack of genetic and laboratory data from deceased family members and the clinical variability that constrains genotype-phenotype correlations. Nonetheless, the authors suggest that this report has important added value in clinical practice, contributing to further establishing data on this subject.

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The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

SFC, AR, FS: Study conception and design, methodology, data analysis and collection, writing and critical review of the manuscript.

AMA, RGM, AC, CF, RC: Study conception and design, methodology, data analysis and interpretation.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

CF received honoraria in educational events from Fundación Instituto Roche.

The authors have no conflicts of interest to declare.

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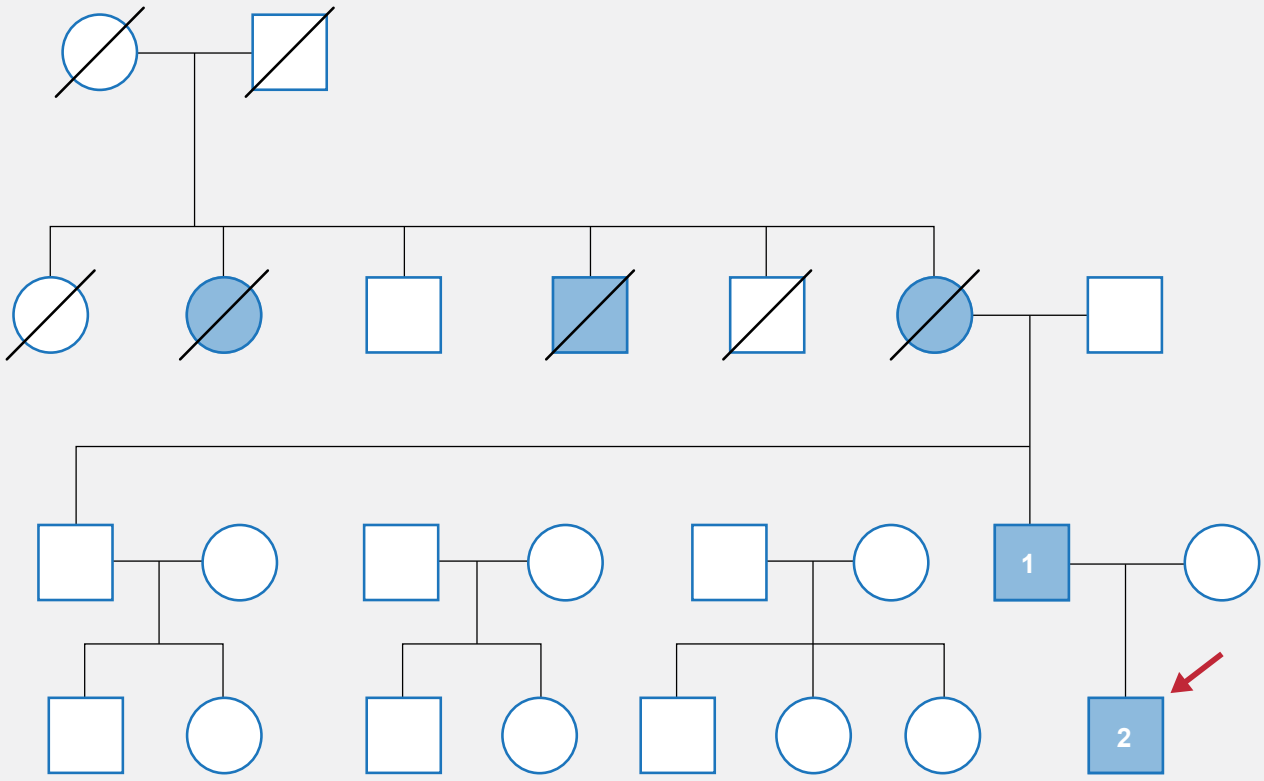

Figure 1 – Pedigree illustrating the inheritance of hereditary angioedema in the studied family. Number 2 refers to the index case, while number 1 refers to his father, for whom clinical, biochemical, and genetic data were obtained.
Circle: female; square: male; filed symbol: genetic trait or symptomatic disease; blank symbol: unaffected or asymptomatic; cross through symbol: deceased; arrow: index case.