Novel Heterozygous variant of the SERPING1 gene associated with hereditary angioedema in an Italian family based in Australia

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Abstract

Hereditary angioedema (HAE) is a relatively uncommon condition, affecting estimated 1 in 50,000 people and presents with potentially life threatening angioedema involving mucosal and/or cutaneous surfaces [1-3]. We describe a case of a newly identified a likely pathogenic heterozygous variant of Leu197Pro Serping 1 of the SERPING1 gene associated with hereditary angioedema in an Italian family based in Australia.

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Abstract

Hereditary angioedema (HAE) is a relatively uncommon condition, affecting estimated 1 in 50,000 people and presents with potentially life threatening angioedema involving mucosal and/or cutaneous surfaces [1-3]. We describe a case of a newly identified a likely pathogenic heterozygous variant of Leu197Pro *Serping 1* of the *SERPING1* gene associated with hereditary angioedema in an Italian family based in Australia.

Introduction

Hereditary angioedema (HAE) is a relatively uncommon condition. Three major types have been described [1-3]. The estimated prevalence of HAE is estimated to be 1 in 50,000 people, without major difference in prevalence between gender or ethnicity [3]

Type 1 is associated reduced total levels of C1 Inhibitor, a protease inhibitor, which is important negative regulator of the Complement cascade, preventing the proteolytic cleavage of complement components C2 and C4. Type 2 is associated with normal serum levels of C1 inhibitor, but defects in the function of the protein. Type 1 and 2 HAE are typically associated with heterozygous genetic mutations within to the serine protease inhibitor G1 (SERPING1) gene. *SERPING 1* is located on chromosome 11 (11q12-q13.1), with 8 exons and 7 introns. While C1 inhibitor inhibits several complement cascade proteases (C1r,

C1s, MASP-1, and MASP-2), it also inhibits contact system proteases plasma kallikrein and activated Hageman factor [coagulation factors XIIa and XIIf], fibrinolytic protease plasmin, and the coagulation protease factor Xia. Type 3 HAE is associated with defects in the factor XII (F12) pathway, and pathogenic variants in angiopoietin 1(ANGPT 1), plasminogen (PLG) [1,2], myoferlin (MYOF) and Kininogen 1 (KNG1) have been described in this category of hereditary angioedema.

A large number of missense, nonsense, frameshift, deletion, and insertion mutations in *SERPING1* have been previously associated with type 1 HAE. These result in truncated or misfolded proteins that cannot be secreted, manifesting as a deficiency in serum C1 INH levels and/or function. Here we describe a novel mutation in the *SERPING1* gene which was identified in an Australian family of Italian heritage with a history of type 1 hereditary angioedema affecting three generations. Several members of the family were diagnosed based on standard protein-based assays before genetic testing was routinely available.

Discussion

The index case is a 38-year-old gentleman who presented with a history consistent with adult-onset recurrent angioedema of the limbs. He has a family history of confirmed hereditary Type 1 angioedema (Fig1). Both his father (68-year-old male) and sister (40-year-old female) had long standing histories of recurrent characteristic attacks of angioedema affecting limbs, gut and upper respiratory airways with both having repeatedly documented low levels of C1 inh protein and low C4 during attacks. Both had been on treatment with danazol and tranexamic acid. The sister had been treated for several years with prophylactic C1nh replacement therapy because of the severity and frequency of her attacks.

The index case was also found to have reduced serum levels of C1inh and proceeded to genetic testing, which demonstrated an uncommon heterozygous variant LRG_105t1 (SERPING1): c.590T>C, p.(Leu197Pro). This was deemed a variant of unknown significance. Subsequent genetic analysis of the index's father and sister confirmed the presence of the same variant.

Two of the three children of the index case have developed angioedema symptoms, with one daughter having her first attack of HAE at age of 9 years, and one son having his first attack at age 4 years. These children have low levels of C1inh. Genetic testing performed on each of the children (two daughters and one son) has confirmed the presence of the same variant in each of them (Table 1). We have performed further testing on two unaffected family members, the index case's paternal aunt's daughter (1st degree cousin) and index case's sister's daughter both of whom had normal C1 esterase levels and function, and there no abnormal genetic variants noted in the *SERPING1* gene in these family members.

On further questioning of the index case, additional family members report symptoms of angioedema but have not have genetic testing performed. It is likely that the patient's deceased paternal grandfather had differential of HAE attacks given his symptom history taken from the index case. Further, the paternal uncle has a clinical diagnosis of type 1 HAE made decades ago with documented C1inh deficiency but has not consented to genetic testing.

Interestingly, despite having the same genetic variant, the clinical manifestations within this family are highly variable. The ranges from index case's sister having had very early onset, severe, frequent (approximately 2 weekly) attacks mostly affecting her gut or upper respiratory tract despite prophylaxis with both high dose Danazol and bi weekly high dose subcutaneous Berinert, through to the index case who has had 2 mild attacks affecting his limbs only, with age of onset in his mid 30's who is managed only with an emergency supply of Icatibant. It is also noteworthy that two the of index cases children with the variant have had attacks at a young age, the older of whom had her first attack involving her face and larynx (hoarse voice). The family tree is outlined in figure 1, with the relevant investigations outlined in figure 2.

Figure 1 :Family tree

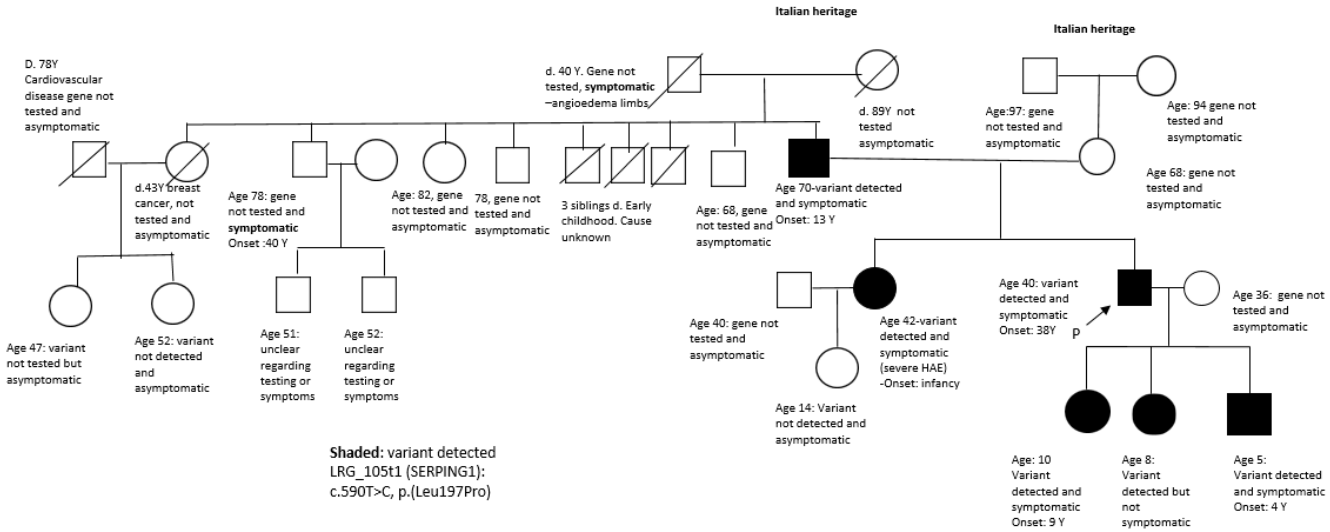

Figure 2: Relevant family clinical history with biochemical and genetic result

Relationship with Index	Gender	Current age	Age of first HAE symptoms	Symptoms	C3 (g/L) (NR 0.8-1.8)	C4 (g/L) (NR 0.15-0.45)	CH100	C1 inhibitor level g/l (Normal range 0.21-0.38 g/L)	C1 inhibitor function	C1 q	Leu197Pro *SERPING1* variant identified
Index	M	40	38	Yes	1.03	0.07	Normal	0.11	Abnormal	N/T	Yes
Sister	F	42	5	Yes	0.94	0.06	Normal	0.08	Abnormal	Normal	Yes
Father	M	70	13	Yes	0.9	0.12	Normal	0.13	Abnormal	Normal	Yes
daughter #1	F	10	9	Yes	NA	0.04	N/T	0.09 g/L	48%(Abnormal)	N/T	Yes
daughter #2	F	8	N/A	No	N/A	0.05	N/T	0.07g/L	21% (abnormal)	N/T	Yes
Son	M	5	4	Yes	0.96	0.08	N/T	0.11g/L	13% (abnormal)	N/T	Yes
Sister's Daughter	F	14	N/A	No	1.42	0.27	Normal level	0.3	Normal	N/T	No
cousin (Paternal Auntie's Child)	F	52	N/A	No	1.22	0.51	Normal	0.35	Normal	N/T	No

N/T not tested

The American College of Medical Genetics and Genomics (ACMG) have developed criteria for classifying the pathogenicity of new variants [3]. Based on these criteria [3-4], this genetic variant would classify as likely pathogenic. Given its absence in the gnomAD population database, it would classify as PM2 (moderate) for the population data. In silico analysis of pathogenicity, using REVEL (ensemble), of the novel variant suggests that this missense variant is

highly deleterious to the C1 inhibitor protein-with score of 0.95. Given the REVEL score, based on the paper by Pejaver et al [5], the genetic variant can be upgraded from PP3 to strong. The effect of the variant on the protein has not been elucidated, however it is predicted to result in a protein that is affecting the C1 inhibitor function. Segregation data, with N= 1/32 (calculated by 1 x1/2x1/2x1/2x1/2x1/2), based on the ACMG criteria will be PP1, however in the paper by Jarvik et. al (year here) suggesting this potentially can be upgraded from supporting to strong given 1/32 suggestive of strong evidence of segregation [5]. There was no de novo data, alleic data, or other database data relating to this particular genetic variant. The affected family members hereditary angioedema phenotype is highly specific for the mutation in the SERPING1 gene, hence other data criteria would be PP4 (supporting). In summary based on the current criteria, the Leu197Pro *Serpin 1* variant identified would be classified as likely pathogenic variant. However, if based on the paper by Jarvik et al on the role of segregation data, then this variant potentially can be upgraded to pathogenic, given patient would have met two strong criteria [6]]

Conclusion

In summary, we have identified a likely pathogenic heterozygous variant of Leu197Pro *Serpin 1* of the *SERPING1* gene associated with hereditary angioedema in an Italian family with variable clinical presentation based in Australia. This adds to our knowledge of pathogenic variants identified in this gene, and its clinicopathological manifestations.

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