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CORRESPONDENCE

Hereditary angioedema with a novel mutation, c.1481G>C, in the *SERPING1* gene

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent episodes of localized angioedema, potentially life-threatening when involving upper airways. The pathophysiology of HAE has been identified as bradykinin-mediated angioedema caused by deficiency or dysfunction of C1-inhibitor, because of a mutation in serpin family G member (*SERPING1*) gene, which encodes the serine protease C1-inhibitor (C1-INH).[1] Up to now, more than 450 different HAE-causing *SERPING1* gene variants have been identified,[2] but the genotype-phenotype relationships has not been elucidated. Here, we report a case with HAE carrying a novel point mutation, c.1481G>C, in *SERPING1*, resulting in p.Arg494Pro.

A 27-year-old woman presented to our hospital with recurrent swelling of extremities over 20 years. She had her first swelling attack on her thigh when she was a preschooler. After entering a university, once in a few months, she had hands or feet edema, which resolved within a few days. Some attacks were triggered by fatigue, cold, or heavy loads. She never had laryngeal or facial swelling but had abdominal pain after exercise. Her mother and maternal grandfather also had similar symptoms, but neither was diagnosed or treated. With increasing frequency, more than three times in a month, she decided to visit our hospital. Her laboratory test revealed decreased levels of serum complement C1-INH activity and C4 (Table 1).

We obtained informed consent from the patient for genetic analysis. The study protocol was approved by the institutional review boards of Kyoto University. Sequencing of *SERPING1* was carried out using the patient's genomic DNA purified from peripheral blood cells. The result identified a heterogeneous mutation at c.1481G>C of exon 8 in *SERPING1*, resulting the amino acid transition at p.Arg494Pro. Although other single base pair transitions (G to A or T, resulting in p.Arg494Gln or p.Arg494Leu) at the same nucleotide position have been reported,[3] this variant has not been reported previously. We made a diagnosis of HAE and prescribed her icatibant, bradykinin B2 receptor antagonist, but fortunately until now she has not experienced a serious attack requiring icatibant self-administration.

The current HAE treatment which is available in Japan and recommended by the international guideline[1] includes on-demand treatment with either C1-INH or icatibant, short-term preprocedural prophylaxis with C1-INH concentrate, and long-term prophylaxis with attenuated androgens. Considering the side effects, long-term prophylaxis should be provided for only severely symptomatic patients.

TABLE 1 Levels of C1-INH and complements in our case

Test	Result	Unit	Reference range
C1-INH (activity)	16	%	70-130
C4	3.1	mg/dL	10.6-33.0
C3	76.0	mg/dL	70.5-125.6
CH50	23	U/mL	30-46

Like our case, the majority of HAE patients are heterozygous carriers of a mutated *SERPING1* allele. Nevertheless, their heterozygous mutations lead to unexpectedly low C1-INH levels: our case showed only 16% activity of C1-INH.[4] For this mechanism, the current research revealed that mutant C1-INH induces protein-protein interactions between normal and mutant C1-INH, creates the larger intracellular C1-INH aggregates trapped in the endoplasmic reticulum, and affects the secretion of normal C1-INH protein in a dominant-negative way.[4] As HAE is rare but potentially fatal, early diagnosis and appropriate treatment are essential. We believe that accumulation of gene mutations and clinical reports will facilitate further elucidation of disease pathogenesis and the development of more effective care for HAE.

DECLARATION SECTION

Approval of the research protocol: Yes.
Informed Consent: Yes.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

CONFLICT OF INTEREST

Dr Kenji Kabashima is a member of the Journal of Cutaneous Immunology and Allergy Editorial Board. Management of the peer review process, and all editorial decision-making for this article was undertaken by Editor in Chief. The authors declare that they have no conflicts of interest.

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