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LETTER TO THE EDITOR

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A missense mutation of the plasminogen gene in hereditary angioedema with normal C1 inhibitor in Japan

To the Editor,

Hereditary angioedema with normal C1 inhibitor (HAEnCI) is a novel type of HAE, whose genetic background is heterogeneous.[1] Mutations in the factor XII (*F12*) gene have been reported almost exclusively in Caucasians,[2-6] whereas none have been reported for other races, including Asians. The genetic abnormalities that cause HAEnCI in Asians were therefore unknown. Recently, Bork et al[7] and others[8] reported a missense mutation, pLys330Glu (K330E), in exon 9 of the plasminogen (*PLG*) gene in German patients with HAEnCI that did not exhibit *F12* gene mutations. We report here that this new genetic abnormality in the *PLG* gene was identified in 4 members of two unrelated families with HAEnCI in Japan.

Twenty unrelated Japanese families have been registered in our patient registry as having HAEnCI. The criteria for HAEnCI were as follows: (a) two or more patients per blood-related family with recurrent angioedema; (b) normal C1 inhibitor activity in plasma; (c) no urticaria at present or in the patient's history; and (d) no treatment efficacy with antihistamines and corticosteroids. All of the patients were Japanese. These patients were registered in the HAE registry of Kyushu University. The detailed data regarding patient clinical information and genetic analysis from our HAE registry will be published elsewhere. This study was approved by Institutional Review Board of Kyushu University Hospital. Twenty probands from 20 unrelated families with HAEnCI were subjected to direct sequencing of exon 9 of the *PLG* gene. From composite analysis using PCR/SSCP and direct sequencing, these patients did not carry any mutations in the coding regions or the flanking introns of the *F12* gene (Supporting information). In 2 families, two members each carried a heterozygous missense mutation, K330E. The K330E *PLG* gene mutation was absent in the 100 healthy Japanese controls. The

TABLE 1 Characteristics of four patients with HAEnCI that carry a missense mutation in the *PLG* gene

	Family 1		Family 2	
	Patient 1	Patient 2	Patient 3	Patient 4
Age/sex	97/female	65/male	47/female	52/female
Age of onset	94	35	26	34
Age of diagnosis	96	64	47	51
Total number of lifetime attacks	2	1	Many (>50 attacks)	2
Number of attacks affecting each organ				
Tongue	2	0	Common	0
Face	0	1	Common	2
Larynx	0	0	2	0
Extremities	0	0	0	0
Abdomen	0	0	Several	0
Other organs	0	0	0	0
Inducer	None	Surgery	Travel, lack of sleep	Dental treatment
Drugs[a]	ACE inhibitor at the 1st attack	None	None	None
C1-INH activity (reference range: 70%-130%)	104	84	112	ND
C4 concentration (reference range: 13-35 mg/dL)	28	21	19	ND
PLG activity (reference range: 70%-130%)	ND	118	ND	ND
Treatment[b]	Intubation for the 2nd attack	None	Tranexamic acid (effective for 2 y)	None
PLG gene mutation	K330E hetero	K330E hetero	K330E hetero	K330E hetero
F12 gene mutation	None	None	None	None

[a]Drugs known to aggravate HAE (ACE inhibitor or estrogen-containing drugs).
[b]Includes all specific treatments for angioedema including emergency and prophylactic treatments.

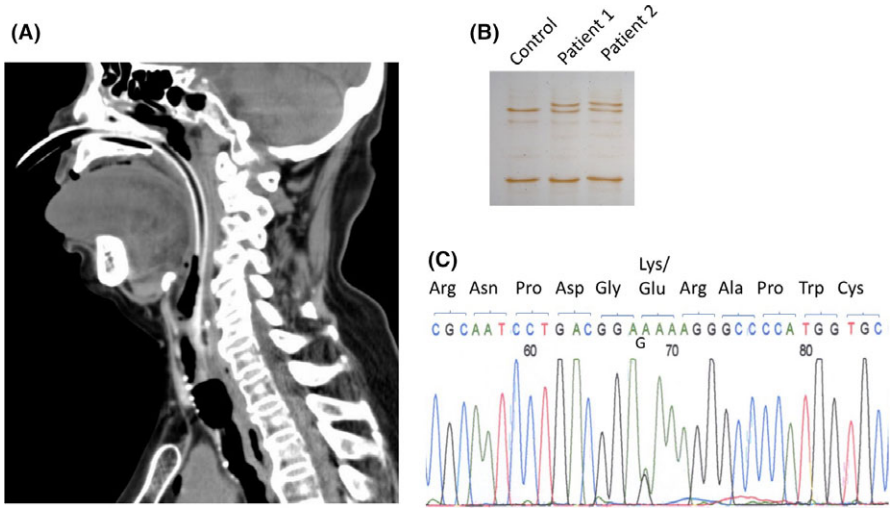

FIGURE 1 A, The CT scan of patient 1 showed remarkable swelling of the tongue. B, PCR-SSCP analysis of exon 9 of the *PLG* gene. In Patient 1 and Patient 2, an additional abnormal band is visible. C, Direct sequencing of exon 9 of the *PLG* gene of Patient 1 shows that a c.988A>G transition caused a missense mutation that changed the codon AAA for Lys to GAA for Glu at amino acid residue 330. Residue numbering is based on the primary translation product.

characteristics of the members of Family 1 (Patient 1 and Patient 2) and Family 2 (Patient 3 and Patient 4) are shown in Table 1.

Patient 1 was a 97-year-old woman. She first experienced angioedema at the age of 94. Her tongue was swollen for 2 days, which gradually subsided after several days without any treatment. She was taking an angiotensin-converting enzyme inhibitor (ACE inhibitor) and was ordered to stop taking it immediately after the episode. Her second attack occurred 3 months later. She had severe tongue swelling and airway obstruction. Intranasal intubation was performed using a fiberscope. The CT scan was performed to examine the extent of edema. Her airway had been occluded from the remarkable edema of the tongue (Figure 1). Intestinal or skin edema, due to the angioedema, was not observed after the onset of the disease. Her two sisters had several, similar attacks that affected their tongues and lips. As both sisters had already died, their medical records were unclear.

Patient 2 was a 65-year-old man, and a son of Patient 1. He experienced lip angioedema at the age of 35, after he underwent surgery for a duodenal ulcer. Among the 8 siblings of Patient 2, a female experienced an episode of eyelid angioedema. However, none of the siblings gave consent for the genetic analysis.

Patient 3 was a 46-year-old woman. She first experienced angioedema at the age of 26. Her symptoms were mainly recurrent swelling of the upper lip and tongue, which subsided within several days. At most, her attacks occurred once a week. She experienced a feeling of suffocation twice during the course of her disease. Travel and/or lack of sleep induced the attacks in this patient. After she began to take 0.75 g/day of tranexamic acid orally 2 years ago, her angioedema attacks terminated completely, except for one attack episode. Patient 3 has two older sisters. One of the sisters (Patient 4) experienced angioedema during dental treatment, which disappeared without any treatment. The other sister did not experience any angioedema attacks. Patient 3 and her older sisters were not married and had no history of pregnancy. Their mother experienced one angioedema attack, whereas their father did not. Genetic analysis has not yet been performed for their parents. We were unable to obtain genetic data from the other family members, so the exact penetrance of the disease could not be estimated.

Our present study might contribute to a detailed understanding of the clinical features and pathogenesis of HAEnCI. First, HAE with a *PLG* gene mutation (HAE-PLG) might be a disease condition common to all ethnic groups, for which HAE-PLG has not yet been reported. It is of note that genetic abnormalities in the *F12* gene[2-6] and angiopoietin-1 (*ANGPT1*) gene[9] have not been reported in patients with HAEnCI in an ethnic group other than Caucasians and their descendants. These two gene mutations might be caused by a founder effect in Caucasians. Second, as Bork et al[7] have already noted, tongue swelling seems to be a characteristic clinical feature of HAE-PLG. Third, tranexamic acid may be a treatment option for HAE-PLG. In 1 of our patients, whose angioedema was so severe that attacks occurred at most once a week, prophylactic administration of tranexamic acid led to an almost complete inhibition of the attacks for 2 years. Bork et al[7] reported that long-term prophylaxis with tranexamic acid completely inhibited attacks in two patients with HAE-PLG for 12 and 4 years, respectively.

In conclusion, we identified a missense mutation, K330E, in the *PLG* gene in four patients from two unrelated families with HAEnCI in Japan. To our knowledge, the *F12* mutations, as well as other genetic abnormalities, have not been reported in Asian patients. We believe that this is the first report to identify the genetic basis of HAEnCI in an ethnic group other than Caucasians. The accumulation of additional HAE-PLG cases from different ethnic groups will contribute to understand the pathophysiology of HAE-PLG in more detail.

CONFLICTS OF INTEREST

Dr. Horiuchi reports speaker fees from CSL Behring. The other authors have no conflict of interests to disclose.

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REFERENCES

1. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. *Allergy*. 2018;73:1575-1596.
2. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun*. 2006;343:1286-1289.
3. Bork K, Wulff K, Meinke P, Wagner N, Hardt J, Witzke G. A novel mutation in the coagulation factor 12 gene in subjects with hereditary angioedema and normal C1-inhibitor. *Clin Immunol*. 2011;141:31-35.
4. Kiss N, Barabás E, Várnai K, et al. Novel duplication in the F12 gene in a patient with recurrent angioedema. *Clin Immunol*. 2013;149:142-145.
5. Veronez CL, Moreno AS, Constantino-Silva RN, et al. Hereditary angioedema with normal C1 inhibitor and F12 mutations in 42 Brazilian families. *J Allergy Clin Immunol Pract*. 2017 Nov 8. pii: S2213-2198(17)30755-9. https://doi.org/10.1016/j.jaip.2017.09.025. [Epub ahead of print]
6. Bork K, Wulff K, Witzke G, Hardt J. Hereditary angioedema with normal C1-INH with versus without specific F12 gene mutations. *Allergy*. 2015;70:1004-1012.
7. Bork K, Wulff K, Steinmüller-Magin L, et al. Hereditary angioedema with a mutation in the plasminogen gene. *Allergy*. 2018;73:442-450.
8. Dewald G. A missense mutation in the plasminogen gene, within the plasminogen kringle 3 domain, in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun*. 2018;498:193-198.
9. Bafunno V, Firinu D, D'Apolito M, et al. Mutation of the angiopoietin-1 gene (ANGPT1) associates with a new type of hereditary angioedema. *J Allergy Clin Immunol*. 2018;141:1009-1017.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.