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【 CASE REPORT 】

A Missense Mutation of the Plasminogen Gene in a Japanese Family with Hereditary Angioedema with Normal C1 Inhibitor: Third Family Survey in Asia

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Abstract:
Hereditary angioedema (HAE) is a life-threatening disease associated with recurrent episodes of subcutaneous and mucosal swelling, painful abdominal cramping, and asphyxiation. HAE has long been thought to be caused by genetic defects of C1 inhibitors (C1-INH). Recently, HAE with a normal C1 inhibitor expression (HAEnCI) was reported, and the missense mutation p.Lys330Glu (K330E) in exon 9 of the plasminogen (*PLG*) gene was shown to be responsible for a subset of HAEnCI. HAE with the K330E mutation in the *PLG* gene-PLG (HAE-PLG) has been reported in only two Japanese families in Asia. We herein report a third family with HAE-PLG in Japan.

Key words: hereditary angioedema (HAE), hereditary angioedema with normal C1 inhibitor (HAEnCI), plasminogen, factor XII, mutation

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Introduction

Hereditary angioedema (HAE) is a life-threatening disease associated with recurrent episodes of subcutaneous and mucosal swelling, painful abdominal cramping, and asphyxiation caused by swelling of the tongue and/or pharynx/larynx. The incidence is estimated to be from 1 in 50,000 to 1 in 100,000 in European countries (1). HAE has long been thought to be caused by genetic defects of protease inhibitors, known as C1 inhibitors (C1-INH), referred to as HAE-C1-INH. In 2000, HAE with normal C1 inhibitor expression (HAEnCI) was reported as a novel disease entity of HAE (2). HAEnCI does not carry typical defects in the C1-INH (*SERPING1*) gene but is caused by abnormalities in a number of genes other than the *SERPING1* gene (3).

The missense mutation p.Lys330Glu (K330E) in exon 9 of the plasminogen (*PLG*) gene has been shown to be responsible for a subset of HAEnCI (4). To date, 146 HAEnCI patients from 33 families have been reported to carry the K330E mutation in the *PLG* gene (HAE-PLG) worldwide (5). We previously demonstrated the K330E mutation in the *PLG* gene in four patients from two Japanese families with HAEnCI, the first account in Asia (6). No other genetic mutations in HAEnCI have been identified in Asia thus far. In contrast to HAE-C1-INH, the clinical and genetic features of HAEnCI remain unclear in Asia, including Japan (7).

We herein report a third family with HAE-PLG in Japan. This detailed family survey revealed a mode of HAE-PLG inheritance and clarified the clinical features of Japanese patients with HAE-PLG.

Case Report

In 2019, a 65-year-old woman (index patient, Fig. 1; patient II-1) was hospitalized because of a severely swollen tongue and lips. The swelling occurred without any triggers

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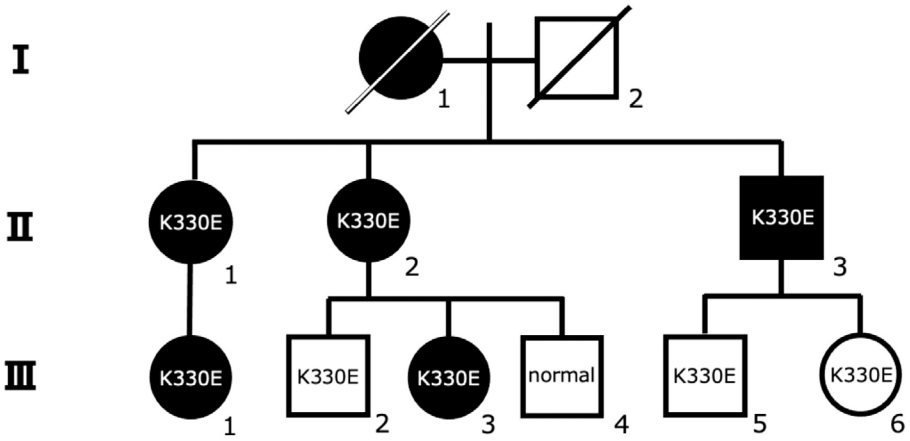

Figure 1. A pedigree of a family with HAE-PLG. Circles indicate female family members, while squares indicate male members. Black-filled symbols indicate affected individuals with a history of recurrent episodes of angioedema. A slash indicates a deceased individual. Roman numerals indicate generations, Arabic numerals indicate individuals within a generation. "K330E" in circles or squares indicates the presence of the mutation p.Lys330Glu (K330E) in exon 9 of the plasminogen (PLG) gene: If the p.Lys330Glu mutation in the *PLG* gene was absent, the family member was indicated as "normal" (in corresponding circle or square). Patients I-1 and I-2 are deceased, so genetic testing was not available.

and was not resolved by steroids or antiallergic drugs but disappeared after a few days. Her symptoms began at 64 years old in 2018 and occurred several times before hospitalization. Her mother (patient I-1) had had unexplained suffocation, and her sister (patient II-2) and younger brother (patient II-3) had shown similar symptoms. These family histories and clinical features were compatible with a diagnosis of HAE; however, there were no abnormalities in complement C4 protein levels (a common feature of HAE) or C1-INH activity.

We strongly suspected HAEnCI in this family and performed genetic analyses of the *SERPING1*, *PLG*, and factor XII (*F12*) genes for all members. Mutations in the *F12* gene are most commonly identified in Caucasian patients with HAEnCI (8). In the index patient (patient II-1), direct sequencing of all the exons and their flanking introns of the *SERPING1* gene and the *F12* gene did not show any mutations. Subsequent direct sequencing of exon 9 of the *PLG* gene revealed a heterozygous missense mutation, K330E. This mutation was also found in her daughter (patient III-1), sister (patient II-2), brother (patient II-3), nephews (patients III-2 and III-5), and nieces (patient III-3 and III-6). The characteristics of the members of the family are shown in Table. The medical histories of all nine living members of this family were also studied.

Discussion

This family study, the first detailed family survey performed for HAE-PLG in Asia, revealed and confirmed a number of important clinical aspects of these Japanese HAE-PLG patients. First, the onset of disease varies between family members, but autosomal dominant inheritance is concluded to be the most likely mode of inheritance, in line with findings reported in European patients (5). As a result, the three asymptomatic patients (patients III-2, III-5, and III-6) may suffer angioedema attacks as they age. Second, the frequency and site of HAE-PLG attacks in this family are distinctive. The frequency of symptoms is up to 10 times a year but low in relation to the overall HAE patient population. Most attacks occurred in the tongue or facial area, followed by abdominal symptoms, while swelling in the extremities was absent. As Bork et al. noted in Caucasian HAE-PLG patients (5), tongue swelling is an important clinical feature of Asian HAE-PLG. The reason for the localization of the site of the onset is unknown. Third, it is important to perform genetic analyses while paying close attention to the K330E mutation in the *PLG* gene. The present case is the third family with HAE-PLG in Asia. No mutations in the *F12* gene have been reported in Asian HAE patients. Defects in the *F12* gene cause 25% of cases of HAEnCI in Caucasians (8), suggesting the existence of a distinction in the genetic background between Japanese/Asian and Caucasian HAEnCI. Finally, tranexamic acid, noted to be effective for some Caucasian HAE-PLG patients (9), seemed to be at least partially effective in treating the attacks in several family members of the case family. On-demand treatment is recommended for HAE attacks, including plasma-derived C1-INH concentrates (pdC1-INH), kallikrein inhibitors, and bradykinin B2 receptor antagonists (icatibant) (3). Only pdC1-INH and icatibant are available in Japan. Icatibant and probably to a lesser extent pdC1-INH are effective against HAEnCI (5, 10).

We first used tranexamic acid, which is inexpensive, easy to use, and has been reported to be effective both prophylactically and during HAE-PLG attacks (4). The symptom re-

Table. **Clinical Features of 8 Patients of the HAE-PLG Case Family.**

Characteristic	Patient							
	II-1	II-2	II-3	III-1	III-2	III-3	III-5	III-6
Age	68	66	61	45	41	38	23	22
Sex	Female	Female	Male	Female	Male	Female	Male	Female
Age at onset	20	42	35	18	NA	25	NA	NA
Age at diagnosis	64	63	58	45	38	35	20	19
Frequency of attacks/year	2	1	2	2	NA	10	NA	NA
C1-INH activity (reference range 70-130%)	125	84	ND	98.8	ND	112	ND	ND
C4 (reference range 13-35 mg/dL)	21.7	21	ND	15.3	ND	19	ND	ND
PLG activity (reference range 70-130%)	ND	118	ND	ND	ND	ND	ND	ND
Treatment	TXA	TXA	TXA	TXA	NA	TXA	NA	NA
Affected organs:								
Tongue	+	+	-	-	NA	-	NA	NA
Face	+	+	+	-		+		
Larynx	-	+	-	-		-		
Extremities	-	-	-	-		-		
Abdomen	+	-	-	+		+		
Other organs	-	-	-	-		-		
Inducer	None	None	None	None	NA	None	NA	NA

NA: not applicable, ND: not determined, TXA: tranexamic acid

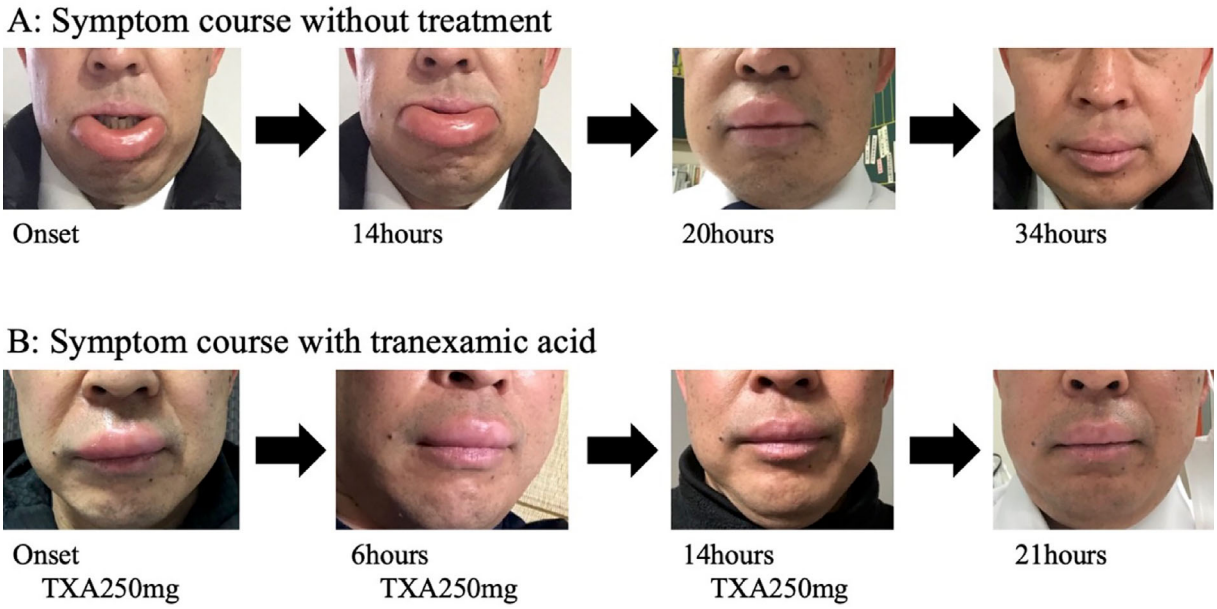

Figure 2. **(A) Symptom course without treatment. It took 34 hours for the swollen lips to disappear completely. (B) Symptom course after taking tranexamic acid (TXA) at the same time of the onset of swelling. The progress of swelling was mild, and the swelling had vanished almost completely after 14 hours.**

lief time and frequency of swelling attacks were improved in patient II-3 when tranexamic acid was used (Fig. 2). Four other members were also prescribed tranexamic acid for long-term prophylaxis or treatment of attacks, which led to a reduction in the frequency of swelling attacks in one patient (III-3). Tranexamic acid, a synthetic lysine derivative, binds to the lysine binding site of plasminogen, inhibiting its transformation to plasmin, a multifunctional proteolytic enzyme that plays an important role in inflammation, in addition to its fibrinolytic function (11). Although the functional outcome of K330E in the *PLG* gene remains unknown, the present findings demonstrate that this is the only mutation commonly identified in Japanese and Caucasian HAE patients, suggesting that this mutation upregulates the formation or function of plasmin. K330E may increase plasmin activity, leading to activation of substances involved in the cascade of HAE, such as coagulation factor XII (4). Plasmin has an extremely short half-life in blood and is difficult to

measure directly, but the alpha2-plasmin inhibitor-plasmin complex may permit the indirect measurement of the plasmin function. Further studies will be needed to clarify the pathophysiology.

In conclusion, we report a Japanese family recently diagnosed with HAE-PLG. This family study not only suggested a mode of inheritance for HAE-PLG in the Japanese population but also confirmed its clinical characteristics. Although the actual status of HAEnCI in Japan is gradually becoming clearer, an active diagnosis by genetic testing is desirable for further pathological clarification and epidemiological evaluations.

All study participants provided their informed consent, and this study was approved by the Institutional Review Board of Kyushu University Hospital (586-03).

Author's disclosure of potential Conflicts of Interest (COI).
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