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The First Korean Case of High-Molecular-Weight Kininogen Deficiency, With a Novel Variant, c.488delG, in the *KNG1* Gene

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Dear Editor,

High-molecular-weight kininogen (HK) circulates bound to prekallikrein (PK), which can bind to negatively charged phospholipids. It is a non-enzymatic cofactor for kallikrein binding to negatively charged phospholipids. Kallikrein activates factor XII, which then activates factor XI, leading to activation of the intrinsic coagulation pathway [1].

Deficiencies in HK and PK can cause isolated activated partial thromboplastin time (aPTT) prolongation with normal levels of intrinsic coagulation factors (VIII, IX, XI, and XII). In PK deficiency, pre-incubation of patient plasma with an aPTT reagent before aPTT assay shortens the aPTT, whereas in HK deficiency, such pre-incubation does not correct aPTT prolongation [2]. Several cases of HK deficiency have been reported in the Japanese population [3]. Herein we report the first Korean case of congenital HK deficiency that resulted in a prolonged aPTT without a change in the pre-incubation aPTT assay. HK deficiency was confirmed by plasma HK levels and identification of two pathogenic variants, one of which was novel (c.488delG). This study was approved by the institutional review board (IRB) of Seoul National University Hospital (IRB 1911-116-1080). Informed consent for performing genetic testing along with additional coagulation assays was obtained from the patient.

A 37-year-old man visited the CHA Bundang Medical Center, Seongnam, Korea, for lipoma surgery. He underwent preoperative assessment, including coagulation assays, during which aPTT prolongation was found. He had suffered from peptic ulcer bleeding in his twenties and had no other medical history related to bleeding or thrombosis. The patient's peripheral blood specimen was sent to the Seoul National University Hospital (SNUH), Seoul, Korea for further analysis. The results of laboratory workup performed in SNUH are presented in Table 1: Prothrombin time (PT) and aPTT before preincubation were 12.2 and 177.9 s, respectively. Prolonged aPTT was corrected after a mixing study. Factors VIII, IX, and XII were within normal ranges, whereas factor XI was slightly decreased (Table 1).

To exclude immunologic causes of aPTT prolongation, lupus anticoagulant, anti-cardiolipin antibody, anti-β_2GPI antibody, and anti-nuclear antibody were tested, which all turned out to be negative. Under suspicion of PK deficiency, aPTT was measured after preincubation with an aPTT reagent for 20 minutes. However, aPTT shortening was not observed: the re-tested aPTT was

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Table 1. Results of laboratory coagulation workup

Laboratory parameter	Value	Reference range
Coagulation assay		
PT (sec)	12.2	10.3–12.7
aPTT (sec)	177.9	26.0–31.3
Factor assay		
Factor VIII (%)	98	52–190
Factor IX (%)	114	74–137
Factor XI (%)	51	60–150
Factor XII (%)	46	42–131
vWF antigen (%)	89	50–160
PK assay		
PK activity (%)	48	70–150
PK antigen (ng/mL)	1.98	1.70–2.68
HK assay		
HK activity (%)	<0.1	67–125
HK antigen (ng/mL)	3.68	29.86–43.01

Abbreviations: aPTT, activated partial thromboplastin time; HK, high-molecular-weight kininogen; PK, prekallikrein; PT, prothrombin time; vWF, von Willebrand factor.

169.7 seconds, and after preincubation it was 132 seconds. PK activity was of borderline deficiency and PK antigen level was within the reference range. Sanger sequencing of the *KLKB1* gene revealed a normal sequence. On the other hand, HK activity was below the detection limit, and HK antigen was very low (Table 1).

Sanger sequencing of the *KNG1* gene (exons 1–11 and the flanking regions; NM_000893) revealed compound heterozygous variants c.488delG and c.1165C>T. A novel variant, c.488delG in exon 4, which resulted in a frameshift mutation (p.Gly163-Alafs*20), was assessed as a pathogenic variant based on the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines: PVS1 (a frameshift variant that leads to a truncated protein), PM2 (absent from controls in the Exome Aggregation Consortium and Genome Aggregation Database), and PP4 (highly specific patient phenotype) [4]. A nonsense mutation caused by c.1165C>T generates a premature stop codon at position 389 (p.Arg389*). The same variant has been reported in a patient with severe HK deficiency [5]. Thus, our patient was confirmed as having HK deficiency with compound heterozygous *KNG1* variants. We could not perform a family study because the patient was lost to follow up.

In HK deficiency, PK activity and factor XI have been reported to be decreased or normal [3, 6]. In our case, PK activity was low, which was measured by the clotting method, and factor XI was reduced. Both PK and factor XI circulate bound to HK, which explains the decreased levels of PK and factor XI in our patient.

Patients with HK deficiency are mostly asymptomatic, with prolonged aPTT. Despite their role in triggering the coagulation pathway, deficiency in any contact activation system components, including HK, does not lead to bleeding [1]. A few cases of HK deficiency with thrombosis have been reported: left vertebral basilar artery thromboses, deep vein thrombosis with pulmonary embolism, and splenic infarction [3, 7, 8]. However, the association between HK deficiency and thrombosis has not been clarified. Deletion of murine kininogen gene 1 (*mKng1*) delayed thrombosis in an arterial injury model [9]. A recent study using a murine model revealed that HK deficiency protects mice from ischemic neurodegeneration [10]. In our case, the patient did not have any thrombosis-related medical history. Because of conflicting results and limited data on the relationship between HK deficiency and thrombosis, we suggest that in cases of HK deficiency with thrombosis, other causes of thrombosis should be thoroughly investigated to clarify whether the finding is coincidental, and thrombosis formation should be closely followed up.

AUTHOR CONTRIBUTIONS

Jeong D performed the research, analyzed data, and wrote the paper; Goo JY performed the research; Kim HK designed the research, analyzed data, and wrote the paper; Chong SY and Kang MS performed the research.

CONFLICTS OF INTEREST

None declared.

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REFERENCES

1. Schmaier AH. Antithrombotic potential of the contact activation pathway. Curr Opin Hematol 2016;23:445-52.
2. Asmis LM, Sulzer I, Furlan M, Lämmle B. Prekallikrein deficiency: the characteristic normalization of the severely prolonged aPTT following increased preincubation time is due to autoactivation of factor XII. Thromb Res 2002;105:463-70.
3. Fukushima N, Itamura H, Wada H, Ikejiri M, Igarashi Y, Masaki H, et al. A novel frameshift mutation in exon 4 causing a deficiency of high-molecular-weight kininogen in a patient with splenic infarction. Intern Med 2014;53:253-7.
4. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
5. Barco S, Sollfrank S, Trinchero A, Tomao L, Zieger B, Hovinga Kremer J, et al. Detection and differential diagnosis of PK deficiency: genetic study of new families and systematic review of the literature. Hämostaseologie 2019;39:S1-S92.
6. Davidson SJ, Burman JF, Rutherford LC, Keogh BF, Yacoub MH. High molecular weight kininogen deficiency: a patient who underwent cardiac surgery. Thromb Haemost 2001;85:195-7.
7. Krijanovski Y, Proulle V, Mahdi F, Dreyfus M, Muller-Esterl W, Schmaier AH. Characterization of molecular defects of Fitzgerald trait and another novel high-molecular-weight kininogen-deficient patient: insights into structural requirements for kininogen expression. Blood 2003;101:4430-6.
8. Cheung PP, Kunapuli SP, Scott CF, Wachtfogel YT, Colman RW. Genetic basis of total kininogen deficiency in Williams' trait. J Biol Chem 1993; 268:23361-5.
9. Merkulov S, Zhang WM, Komar AA, Schmaier AH, Barnes E, Zhou Y, et al. Deletion of murine kininogen gene 1 (mKng1) causes loss of plasma kininogen and delays thrombosis. Blood 2008;111:1274-81.
10. Langhauser F, Gob E, Kraft P, Geis C, Schmitt J, Brede M, et al. Kininogen deficiency protects from ischemic neurodegeneration in mice by reducing thrombosis, blood-brain barrier damage, and inflammation. Blood 2012;120:4082-92.

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