Genetic Analysis of Prekallikrein Deficiency in a Consanguineously Married Chinese Family

Akraba Evliliği Olan bir Çinli Ailede Prekallikrein Eksikliğinin Genetik Analizi

Yuan Chen[1], Meina Liu[1], Mingshan Wang[1], Huilin Chen[1], Bile Chen[2]

[1]*Department of Clinical Laboratory, Key Laboratory of Clinical Laboratory Diagnosis and Translational Research of Zhejiang Province, The First Affiliated Hospital of Wenzhou Medical University, Zhejiang, China*
[2]*Department of Blood Transfusion, The First Affiliated Hospital of Wenzhou Medical University, Zhejiang, China*

To the Editor,

As a part of the contact activation system, prekallikrein (PK) is not associated with an increased bleeding tendency but connected with thrombosis and hypertension [1,2]. Patients with PK deficiency do not experience bleeding, but they typically exhibit an isolated and significantly prolonged activated partial thromboplastin time (aPTT) depending on the degree of deficiency, while their other coagulation indices remain within the normal range [3].

Herein, we reported a case of hereditary PK deficiency resulting from a homozygous mutation in the *KLKB1* gene. The proband, a 29-year-old Chinese female, was presented to our hospital with Hoshimoto's thyroiditis. There was no history of bleeding or thromboembolic events and abnormal liver and kidney functions. Remarkably, her mother and father were first cousins. The preoperative coagulation test revealed a prolonged aPTT of 112.1 s, which was corrected with mixing studies. However, her clotting activity of coagulation factors VIII, IX, XI, and XII all fall within the normal range. Based on these findings, PK or high-molecular-weight kininogen (HMWK) deficiency was strongly suspected. Subsequent analysis of PK and HMWK activities confirmed a significant reduction in PK activity.

With informed consent, blood samples were taken from the family members of the proband to analyze their coagulation indices. The results revealed that both the proband and her brother had PK activity below 1% and significantly prolonged aPTT. Apart from her grandfather and husband, the other family members showed a decrease of varying degrees in their PK activity but normal aPTT (Table 1). This observation aligns with the autosomal recessive nature of hereditary PK deficiency, as heterozygous individuals do not exhibit prolonged aPTT [4]. Next, all the exons and flanking regions of the *KLKB1* genes were amplified and directly sequenced. We identified a homozygous mutation c.417_418insCATTCTTA (p.Arg140Hisfs*3) in exon 5 of the *KLKB1* gene in the proband and her brother. Additionally, we found a heterozygous p.Arg140Hisfs*3 mutation in her two grandmothers, mother, father, sister, and son (Figure 1). The transcript and peptide numbers we used in this paper are NM_000892.5 and NP_000883.2, respectively.

The p.Arg140Hisfs*3 mutation was predicted to be "Disease-causing" by Mutation Taster. This mutation would lead to the termination of PK protein at p.Thr142. Consequently, the final mature PK protein was estimated to have only 122 amino acid residues (the first 19 amino acids being a signal peptide).

Table 1. Phenotypes and genotypes of the hereditary PK deficiency family.

Patient	PT (S)	aPTT (S)	FVIII:C (%)	FIX:C (%)	FXI:C (%)	FXII:C (%)	PK (%)	HMWK (%)	p.Arg140Hisfs*3
Grandmother (II_2)	13.5	39.3	109	91	89	79	33.1	85.6	Heterozygous
Grandmother (II_3)	12.6	40.2	92	82	120	77	29.5	88.7	Heterozygous
Grandfather (II_4)	14.3	37.7	128	79	94	88	96.5	99.8	Wild type
Father (III_1)	13.5	31.9	90	121	112	100	42.5	83.4	Heterozygous
Mother (III_2)	14.7	34.1	89	125	108	107	43.6	98.6	Heterozygous
Husband (IV_1)	13.6	38.8	114	99	120	99	94.2	97.9	Wild type
Proband (IV_2)	12.5	112.1	137	112	103	98	<1	89.8	Homozygous
Sister (IV_3)	12.8	35.4	129	107	91	95	37.9	82.1	Heterozygous
Brother (IV_4)	11.9	122.2	113	111	88	111	<1	90.0	Homozygous
Son (V_1)	14.0	33.7	130	109	123	94	33.6	99.1	Heterozygous
Reference range	11.5~14.8	29.0~43.0	80~134	72~136	84~122	72~114	80~120	80~120	

aPTT: Activated partial thromboplastin time, PK: prekallikrein, HMWK: high-molecular-weight kininogen

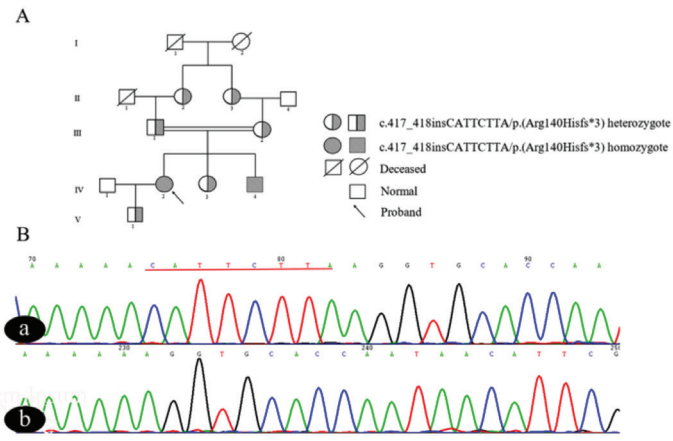

Figure 1. Family pedigree investigation, genetic sequencing of *KLKB1* c.417_418insCATTCTTA/p.(Arg140Hisfs*3) mutation. (A) The family pedigree investigation. (B) Chromatogram of DNA sequencing. (a) c.417_418insCATTCTTA/p.(Arg140Hisfs*3) mutation sequence in exon 5 of the *KLKB1* gene; (b) The wild-type sequence of exon 5 in the *KLKB1* gene.

The presence of this truncated protein can be degraded by the cellular defense mechanism [5].

Hereditary PK deficiency is a rare condition commonly caused by homozygous or compound heterozygous mutations in the *KLKB1* gene. The Human Gene Mutation Database (HGMD, https://www.hgmd.cf.ac.uk/docs/login.html) has collected only 14 cases of this condition, with only two reports in Chinese individuals [6].

In conclusion, we have identified a homozygous p.Arg140Hisfs*3 mutation in the *KLKB1* gene. This mutation has the potential to disrupt the protein's spatial structure of the protein and subsequently result in decreased PK activity. Nonetheless, the specific pathogenic mechanism needs to be demonstrated by expression study in vitro.

Acknowledgements

We are grateful to the patient and his family members for cooperation. All authors stated that they had no interests which might be perceived as posing a conflict or bias.

Keywords: Prekallikrein deficiency, Blood coagulation, Genetic mutation

Anahtar Sözcükler: Prekallikrein eksikliği, Koagülasyon, Genetik mutasyon

Ethics

Ethics Committee Approval: Our study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (China). (KY2022-R193).

Informed Consent: Informed consent was obtained from this family.

Authorship Contributions

Surgical and Medical Practices: Y.C.; Design: B.C.; Data Collection or Processing: M.L.; Analysis or Interpretation: M.W.; Literature Search: H.C.; Writing: Y.C.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Financial Disclosure: This work was funded by Key Laboratory of Clinical Laboratory Diagnosis and Translational Research of Zhejiang Province (2022E10022), Science and Technology Plan Fund of Wenzhou (2022Y0744).

References

1. Nakao T, Yamane T, Katagami T, Shiota M, Izumi Y, Samori T, Hino M, Iwao H. Severe prekallikrein deficiency due to a homozygous Trp499Stop nonsense mutation. Blood Coagul Fibrinolysis 2011;22:337-339.
2. Bojanini EU, Loaiza-Bonilla A, Pimentel A. Prekallikrein deficiency presenting as recurrent cerebrovascular accident: case report and review of the literature. Case Rep Hematol 2012;2012:723204.
3. Barco S, Sollfrank S, Trinchero A, Adenaeuer A, Abolghasemi H, Conti L, Häuser F, Kremer Hovinga JA, Lackner KJ, Loewecke F, Miloni E, Vazifeh Shiran N, Tomao L, Wuillemin WA, Zieger B, Lämmle B, Rossmann H. Severe plasma prekallikrein deficiency: Clinical characteristics, novel KLKB1 mutations, and estimated prevalence. J Thromb Haemost 2020;18:1598-1617.
4. Abraham RM, Viswanathan GK, Dass J, Dhawan R, Aggarwal M, Kumar P, Seth T, Mahapatra M. Prekallikrein deficiency due to homozygous *KLKB1*(+) mutation c.444_445insT (p.Ser151PhefsTer34). Int J Lab Hematol 2022;44:e132-e134.
5. Kurosaki T, Popp MW, Maquat LE. Quality and quantity control of gene expression by nonsense-mediated mRNA decay. Nat Rev Mol Cell Biol 2019;20:406-420.
6. Lu X, Zhao W, Huang J, Li H, Yang W, Wang L, Huang W, Chen S, Gu D. Common variation in *KLKB1* and essential hypertension risk: tagging-SNP haplotype analysis in a case-control study. Hum Genet 2007;121:327-335.

Address for Correspondence/Yazışma Adresi: Bile Chen, M.D., Department of Blood Transfusion, The First Affiliated Hospital of Wenzhou Medical University, Zhejiang, China
Phone : +8657788069594
E-mail : zjwzcbl@163.com ORCID: orcid.org/0009-0004-8404-1922

Received/Geliş tarihi: September 27, 2023
Accepted/Kabul tarihi: November 17, 2023
DOI: 10.4274/tjh.galenos.2023.2023.0351