Brief Communication

Yonsei Med J 2018 Jan;59(1):148-153
https://doi.org/10.3349/ymj.2018.59.1.148

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Variants of Lipolysis-Related Genes in Korean Patients with Very High Triglycerides

Chan Joo Lee[1,2], Chi-Yoon Oum[3], Yunbeom Lee[4,5], Sungha Park[1,2], Seok-Min Kang[1,2], Donghoon Choi[1,2], Yangsoo Jang[1,2], Ji Hyun Lee[5], and Sang-Hak Lee[1,2]

[1]Division of Cardiology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul;
[2]Cardiovascular Research Institute, Yonsei University College of Medicine, Seoul;
[3]Department of Biostatistics and Computing, The Graduate School, Yonsei University, Seoul;
[4]Department of Medicine, Graduate School, Kyung Hee University, Seoul;
[5]Department of Clinical Pharmacology and Therapeutics, College of Medicine, Kyung Hee University, Seoul, Korea.

We investigated the prevalence and characteristics of variants of five lipolysis-related genes in Korean patients with very high triglycerides (TGs). Twenty-six patients with TG levels >885 mg/dL were selected from 13545 Korean subjects. Five candidate genes, *LPL*, *APOC2*, *GPIHBP1*, *APOA5*, and *LMF1*, were sequenced by targeted next-generation sequencing. Predictions of functional effects were performed and matched against public databases of variants. Ten rare variants of three genes were found in nine (34.6%) patients (three in *LPL*, four in *APOA5*, and three in *LMF1*). Five were novel and all variants were suspected of being disease-causing. Nine were heterozygous, and one (3.8%) had a homozygous rare variant of *LPL*. Six common variants of four genes were observed in 25 (96.2%) patients (one in *LPL*, one in *GPIHBP1*, two in *APOA5*, and two in *LMF1*). The c.G41T variant of *GPIHBP1* and c.G533T variant of *APOA5* were most frequent and found in 15 (57.7%) and 14 (53.8%) patients, respectively. Rare homozygous variants of the genes were very uncommon, while diverse rare heterozygous variants were commonly identified. Taken together, most study subjects may be manifesting the combined effects of rare heterozygous variants and common variants.

Key Words: *LPL* protein, human; *GPIHBP1* protein, human; *APOA5* protein, human; *LMF1* protein, human; High-Throughput Nucleotide Sequencing

Although it is not common, very high triglyceride (TG) levels (>885 mg/dL) may cause clinical complications, and effective therapeutic approaches for this metabolic disorder are under investigation.[1] Although previous studies have described genetic information of patients with very high TG, data from Asian countries are highly limited.[2-4] Particularly, the prevalence and characteristics of patients in Korea have not been analyzed before. The aim of this study was to investigate the prevalence and characteristics of variants of five lipolysis-related genes in Korean patients with very high TG. We selected 26 patients meeting the lipid criteria from 13545 people and performed targeted next generation sequencing of *LPL*, *APOC2*, *GPIHBP1*, *APOA5*, and *LMF1* to identify rare and common variants.

Unrelated patients with very high TG levels were included in this study. Between November 2000 and March 2011, 13545 subjects were enrolled in the Cardiovascular Genome Center Cohort, Yonsei University College of Medicine, Seoul, Korea. Men and women were recruited in the cohort when they visited Severance Hospital, Seoul, Korea for cardiovascular diseases or health check-ups. Patients were interviewed about their medical histories, and then underwent physical examinations. Among them, 26 subjects with fasting TG >885 mg/dL, documented at least two times, were finally included in this study. Patients with obesity (body mass index >30 kg/m^2), un-

Received: May 10, 2017 **Revised:** September 1, 2017
Accepted: September 7, 2017
Co-corresponding authors: Dr. Sang-Hak Lee, Division of Cardiology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: 82-2-2228-8460, Fax: 82-2-2227-7732, E-mail: shl1106@yuhs.ac and
Dr. Ji Hyun Lee, Department of Clinical Pharmacology and Therapeutics, College of Medicine, Kyung Hee University, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul, 02447, Korea.
Tel: 82-2-961-9564, Fax: 82-2-958-9559, E-mail: hyunihyuni@khu.ac.kr

•The authors have no financial conflicts of interest.

controlled diabetes mellitus (HbA1c ≥8%), excessive alcohol consumption (>15 drinks/week for men or >8 drinks/week for women), hypothyroidism, proteinuria, pregnancy, or corticosteroids or oral estrogen were excluded. All participants gave their written informed consent and Institutional Review Board of Severance Hospital approved the study (4-2001-0039).

Five target genes were sequenced: *LPL* (MIM 609708), *APOC2* (MIM 608083), *GPIHBP1* (MIM 612757), *APOA5* (MIM 606368), and *LMF1* (MIM 611761). Genomic DNA from blood was extracted with the Qiagen DNeasy kit (Qiagen, Valencia, CA, USA). For mutation analysis, a panel for targeted DNA capture and sequencing by selecting five genes associated with lipolysis was developed by Celemics, Inc. (Seoul, Korea). For targeted sequencing, DNA fragments containing all coding exons and exon-intron junctions were enriched by solution-based hybridization capture, followed by sequencing with an Illumina Hiseq2000 platform (Illumina, San Diego, CA, USA). Analysis of next-generation sequencing data was performed using an in-house analysis pipeline. Variants were called using the GATK v3.3.0 Unified Genotyper algorithm (Broad Institute, Cambridge, MA, USA) for loci with sequencing depth greater than or equal to 20X. Functional annotation of genetic variants was performed by ANNOVAR (ver. 2014-11-12).

Functional effect predictions for single nucleotide variants were performed using SIFT, PolyPhen-2, and MutationTaster, and were matched against Korean population exome data (n=476) and public databases of variants (dbSNP 138, Exome Variant Server and 1000 Genome project SNP from both Asian and all-population databases). Analyses comprise evolutionary conservation, splice-site changes, loss of protein features, and changes that might affect the amount of mRNA. Test results are then evaluated by a naïve Bayes classifier, which predicts disease potential. We then prioritized variants according to the following criteria: 1) variants that were reported to be disease-causing in the Human Gene Mutation Database; 2) disruptive variants (nonsense, splice-site, and frameshift) that were novel or rare (minor allele frequency <1% in public databases); and 3) novel or rare missense variants that were predicted to be deleterious by SIFT, Polyphen-2 (HumVar), or MutationTaster. Variants that met these criteria were validated by bidirectional Sanger sequencing of PCR amplicons.

Clinical characteristics of the study patients are described in Table 1. They were younger than the total population, and more likely to be male (85%). Among 26 subjects, five (19%) had a history of coronary artery disease, whereas one (4%) had a history of pancreatitis. The median TG level was 1213 mg/dL, while the mean high-density lipoprotein-cholesterol was 32.9 mg/dL.

Ten rare variants of three candidate genes were found in nine (34.6%) patients (three in *LPL*, four in *APOA5*, and three in *LMF1*) (Tables 2 and 3). Six were novel and all variants were suspected of being disease-causing. Nine of them were heterozygous, and one (3.8%) subject had homozygous form of a rare variant in *LPL*. Six common variants of four genes were observed in 25 (96.2%) patients (one in *LPL*, one in *GPIHBP1*, two in *APOA5*, and two in *LMF1*) and have been previously reported. Among common variants, c.G41T (p.C14F) of *GPIHBP1* and c.G533T (p.G185C) of *APOA5* were most frequent, and were found in 15 (57.7%) and 14 (53.8%) patients, respectively. One (3.8%) patient did not show any rare or common variant. In addition, no variant was found in *APOC2* (Fig. 1).

Three rare variants of *LPL*, c.G872A (p.C291Y), c.T913C (p.C305R), and c.T985G (p.Y329D), were identified in three subjects. The c.G872A and c.T985C variants were novel and were predicted to be damaging by *in silico* analysis, while c.T913C variant has been known to be associated with LPL deficiency.[5] Only the c.T985G variant was homozygous. One common variant that has been reported as a stopgain single nucleotide variant,[6] c.C1421G (p.S474X), was found in two patients.

One common variant of *GPIHBP1*, c.G41T (p.C14F), was found in 15 patients and seven of them were homozygous. This variant has been reported previously, but its influence on pro-

Table 1. Clinical Characteristics of Study Patients

	Total population (n=13545)	Patients with very high TG (n=26)	*p* value
Age (yr)	60.4±10.6	46.8±8.6	<0.001
Male	6722 (50)	22 (85)	<0.001
Medical history			
Hypertension	7234 (53)	11 (42)	0.25
Diabetes mellitus	2293 (17)	5 (19)	0.77
Smoking	2004 (15)	11 (42)	0.01
Coronary artery disease	4747 (35)	5 (19)	0.04
Body mass index (kg/m^2)	24.8±3.1	26.7±4.4	0.04
Laboratory values (mg/dL)			
Total cholesterol	189±43	282±54	<0.001
TG	117 (83)	1213 (459)	<0.001
HDL-C	48.8±14.7	32.9±11.1	<0.001

TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; SD, standard deviation; IQR, interquartile range.
Values are presented as mean±SD, n (%), or median (IQR).

Table 2. Genetic Variants Iidentified in Candidate Genes in Study Patients

Gene	Genomic coordinate	Nucleotide change	Mutation type	Amino acid change (rs number)	Affected patients (frequency)	Korean reference allele frequency	Frequency in public database	Affected patients (homo/hetero)	Reported	Effect	SIFT/Polyphen/Mutation Taster prediction
LPL	chr8: 19,813,448	c.G872A	Nonsynonymous SNV	p.C291Y	1 (0.038)	NA	NA	0/1	No	Unknown	-/damaging/disease_causing
	chr8: 19,813,489	c.T913C	Nonsynonymous SNV	p.C305R	1 (0.038)	NA	NA	0/1	Yes	*LPL* deficiency	-/damaging/disease_causing
	chr8: 19,813,561	c.T985G	Nonsynonymous SNV	p.Y329D	1 (0.038)	NA	NA	1/0	No	Unknown	-/damaging/disease_causing
	chr8: 19,819,724	c.C1421G	Stopgain SNV	p.S474X (rs328)	2 (0.077)	0.127	0.085–0.122	0/2	Yes	Gain-of-function	
GPIHBP1	chr8: 144,295,183	c.G41T	Nonsynonymous SNV	p.C14F (rs11538389)	15 (0.577)	0.329	0.089–0.295	7/8	Yes	Unknown	Tolerated/benign/polymorphism_automatic
APOA5	chr11: 116,662,531	c.46delT	Frameshift deletion	p.S16Qfs X40	1 (0.038)	NA	NA	0/1	No	Unknown	
	chr11: 116,661,488	c.G457A	Nonsynonymous SNV	p.V153M (rs3135507)	6 (0.231)	0.215	0.048–0.119	0/6	Yes	Unknown	Tolerated/benign/polymorphism_automatic
	chr11: 116,661,394	c.C551G	Nonsynonymous SNV	p.T184S (rs201229911)	1 (0.038)	0.011	≤0.002	0/1	Yes	Unknown	Tolerated/possibly damiging/disease_causing
	chr11: 116,661,393	c.552delC	Frameshift deletion	p.T184T fs X15	1 (0.038)	NA	NA	0/1	No	Unknown	Tolerated/possibly damiging/disease_causing
	chr11: 116,661,392	c.G553T	Nonsynonymous SNV	p.G185C (rs2075291)	14 (0.538)	0.078	0.001–0.05	4/10	Yes	Hyper-triglyceridemia	Deleterious/damaging/polymorphism
	chr11: 116,661,358	c.586_587insC	Frameshift insertion	p.E196A fs X71	1 (0.038)	NA	NA	0/1	No	Unknown	
LMF1	chr16: 1,020,874	c.G107A	Nonsynonymous SNV	p.G36D (rs111980103)	2 (0.077)	0.031	0.037–0.177	0/2	Yes	Unknown	Tolerated/benign/polymorphism_automatic
	chr16: 921,203	c.A1036G	Nonsynonymous SNV	p.M346V (rs201767825)	1 (0.038)	0.009	≤0.003	0/1	Yes	Unknown	Tolerated/benign/disease_causing
	chr16: 920,733	c.G1228A	Nonsynonymous SNV	p.G410R (rs199713950)	1 (0.038)	0.007	≤0.002	0/1	Yes	Unknown	Deleterious/damaging/disease_causing
	chr16: 904,615	c.G1621A	Nonsynonymous SNV	p.G541R (rs377058908)	1 (0.038)	NA	≤0.001	0/1	Yes	Unknown	Tolerated damaging/disease_causing
	chr16: 904,551	c.C1685G	Nonsynonymous SNV	p.P562R (rs4984948)	9 (0.346)	0.122	0.008–0.129	0/9	Yes	Polymorphism	Tolerated/benign/disease_causing

SNV, single nucleotide variant; NA, not available.

https://doi.org/10.3349/ymj.2018.59.1.148

Table 3. Genetic Variants of Target Genes Identified in Each Individual

Patients	Sex	Age	TC	TG	HDL-C	Genes and variants: [nucleotide change], amino acid change			
						LPL	*GPIHBP1*	*APOA5*	*LMF1*
1	M	32	257	948	45	[c.C1421G], p.S474X		[c.G553T], p.G185C	[c.C1685G], p.P562R
2	M	31	366	1305	24			[c.G553T], p.G185C	[c.C1685G], p.P562R
3	M	40	240	992	30		[c.G41T], p.C14F*		[c.C1685G], p.P562R
4	M	34	348	1590	77	[c.C1421G], p.S474X	[c.G41T], p.C14F*	[c.G553T], p.G185C	[c.C1685G], p.P562R
5	F	57	278	1163	36		[c.G41T], p.C14F		[c.G107A], p.G36D
6	F	52	209	1001	28		[c.G41T], p.C14F	[c.G553T], p.G185C	
7	F	58	327	1659	29		[c.G41T], p.C14F*	**[c.C551G], p.T184S** [c.G553T], p.G185C	**[c.A1036G], p.M346V**
8	M	52	280	1040	34		[c.G41T], p.C14F		**[c.G1621A], p.G541R**
9	M	42	226	1020	39			**[c.46delT], p.S16Q fs X40**† [c.G553T], p.G185C	
10	M	38	209	943	37				
11	M	47	224	2080	31			[c.G457A], p.V153M	
12	M	56	271	1280	33		[c.G41T], p.C14F	[c.G553T], p.G185C	[c.C1685G], p.P562R
13	M	39	184	1022	32			[c.G553T], p.G185C	
14	M	42	253	1370	28		[c.G41T], p.C14F		
15	M	48	292	1230	20		[c.G41T], p.C14F	**[c.552delC], p.T184T fs X15**† [c.G553T], p.G185C*	
16	M	61	326	1489	22			**[c.586_587insC], p.E196A fs X71**†	[c.G107A], p.G36D
17	M	38	323	1196	31		[c.G41T], p.C14F*	[c.G553T], p.G185C [c.G457A], p.V153M	
18	M	40	257	1104	32			[c.G553T], p.G185C*	
19	F	56	305	1089	28		[c.G41T], p.C14F*		
20	M	51	243	926	44			[c.G457A], p.V153M	**[c.G1228A], p.G410R**
21	M	45	340	1250	34		[c.G41T], p.C14F*		[c.C1685G], p.P562R
22	M	51	302	1902	37			[c.G553T], p.G185C*	
23	M	53	257	1440	33		[c.G41T], p.C14F*	[c.G457A], p.V153M	[c.C1685G], p.P562R
24	M	54	258	910	29	**[c.G872A], p.C291Y**†	[c.G41T], p.C14F	[c.G553T], p.G185C*	[c.C1685G], p.P562R
25	M	52	363	3348	19	**[c.T985G], p.Y329D***,†	[c.G41T], p.C14F	[c.G457A], p.V153M	
26	M	55	313	1479	23	**[c.T913C], p.C305R**		[c.G457A], p.V153M [c.G553T], p.G185C	[c.C1685G], p.P562R

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol.
Rare variants in bold character.
*Homozygous, †Novel variants.

tein function has been only partially shown.[7,8] *In silico* algorithms indicated that this variant could be benign.

Four rare variants of *APOA5*, c.46delT (p.S16Q fs X40), c.C551G (p.T184S), c.C552celC (p.T184T fs X15), and c.586_587insC (p.E196fs), were discovered in four subjects. Patients possessing these variants were all heterozygous, and three of four variants have not been reported before. The c.46delT and c.552delC were frameshift deletions; c.586_587insC was a frameshift insertion; and c.C551G was a single nucleotide variant. These four rare variants were assumed to be disease-causing in prediction algorithms. Two common variants of *APOA5*, c.G457A (p.V153M) and c.G553T (p.G185C), were found in six and 14 people, respectively. These two variants have been previously reported. c.G553T has been known to be associated with hypertriglyceridemia,[3,9] while c.G457A has been reported to be benign.[10]

Three rare variants of *LMF1*, c.A1036G (p.M346V), c.G1228A (p.G410R), and c.G1621A (p.G541R), were identified in three patients. They were all heterozygous and already have been reported. *In silico* analysis indicated that these three variants may be disease-causing. Two common variants, c.G107A (p.G36D) and c.C1685G (p.P562R), were discovered in two and nine individuals, respectively. Both of these single nucleotide variants were suspected of being benign in prediction algorithms.

The major findings of our study are: 1) 10 rare variants of three genes were found in nine (34.6%) patients (three in *LPL*, four in *APOA5*, and three in *LMF1*). Among them, five were novel and nine were heterozygous. All rare variants were suspected of being disease-causing by *in silico* analysis. 2) Only

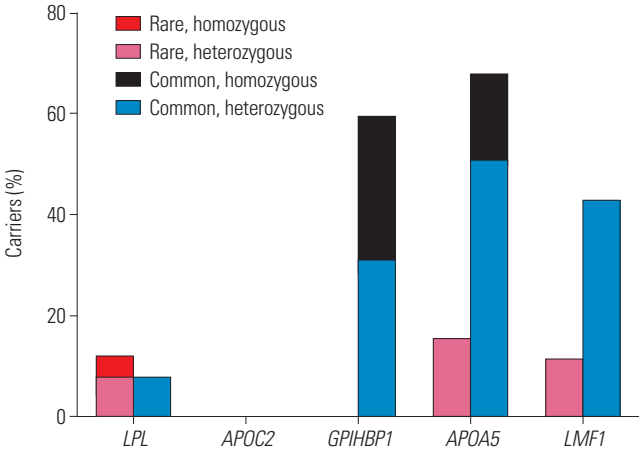

Fig. 1. Proportion of carriers who have variants of each gene identified in the study population.

one (3.8%) subject had the homozygous form of a rare variant of *LPL*. 3) Six common variants of four genes were identified in 25 (96.2%) patients (one in *LPL*, one in *GPIHBP1*, two in *APOA5*, and two in *LMF1*). 4) c.G41T of *GPIHBP1* and c.G553T of *APOA5* were the most frequent common variants, found in 15 (57.7%) and 14 (53.8%) patients, respectively. We showed, for the first time, the prevalence and characteristics of rare and common variants of five lipolysis-related genes in Koreans with very high TG.

To date, more than a hundred homozygous or compound heterozygous mutations have been identified and shown to cause LPL deficiency. Additional heterozygous mutations have also been found to reduce *LPL* activity.[2,11] In our results, one rare variant (3.8%), c.T985C, was homozygous, and two rare variants (7.7%), c.G872A and c.T913C, were heterozygous. Analyses by multiple algorithms predicted that these variants may be disease-causing. In patients with severe hypertriglyceridemia of other ethnicities, homozygous or compound heterozygous rare variants of *LPL* were in 1% in Thai study,[4] 20% in Dutch study,[12] and 23% in Italian study.[13] Conversely, heterozygous rare variants were 6% in Canadian and Dutch studies,[12,14] 10% in Italian study,[13] and 11% in Thai study.[4] The prevalence of such variants in our study was lower than in those studies; nonetheless, homozygous variants appear scarce in Asian studies, including ours. It is worth mentioning that loci of rare variants of *LPL* are quite diverse. Only one common variant of *LPL*, c.C1421G, was discovered in two of our subjects. However, it is uncertain whether this variant is associated with hypertriglyceridemia, because these patients had other common functional variants, such as c.G553T. In addition, the relationship between the variant and phenotype was not consistent in prior studies.[4,15]

Although rare variants of *GPIHBP1* are steadily being discovered,[12,16] only one form of the common variant was identified in our study. The biological impact of our variant, c.G41T, is only partially known. This variant was identified in 11% of French patients with severe hypertriglyceridemia, in association with a mutation in another site of *GPIHBP1*. In that study, the c.G41T variant was shown to be associated with mildly reduced protein levels, and was assumed to influence phenotype.[7] This variant was also identified in 26% of Spanish patients with the same lipid trait. However, most patients with this variant simultaneously had other variants related to TG levels, thus the impact of this variant was not sufficiently clear.[17] This is in accordance with findings in our subjects who had both the c.G41T variant and other rare and common variants of *LPL*, *APOA5*, and *LMF1*.

Our study identified four (15.4%) patients with four rare variants of *APOA5* that were all heterozygous. Three of them were novel and all variants were assumed to be disease-causing in prediction algorithms. Several rare variants of *APOA5* have been reported in prior studies, and have been diverse in multiple ethnicities. The prevalence was 1.1% in a study of patients with European ancestry and severe hypertriglyceridemia,[18] 2.3% in a Dutch study,[12] and 9.2% in a German study.[10] The prevalence of rare *APOA5* variants in our population was relatively higher that of other studies. It is also noteworthy that three of four variants in our study were frameshift substitutions or insertions. However, it is difficult to tell how much of an effect these rare variants had on phenotype. A high prevalence (53.8%) of the common c.G553T variant of *APOA5* was another characteristic in our subjects. A previous study showed that heterozygous patients of Asian ancestry with this variant have 2.7 times higher TG levels than controls.[9] It is interesting that this variant has also been reported in Chinese, Pacific Islander,[9] and Taiwanese populations.[3]

We identified three rare variants of *LMF1*, and two (7.7%) of them were predicted to be disease-causing. *LMF1* has recently been reported to have a role in lipoprotein lipase maturation.[19] To date, although only a few rare variants have been discovered and shown to be relevant to TG levels,[16] novel variants of *LMF1* are being explored. Rare variants were found in 3.4% of Spanish patients with severe hypertriglyceridemia. In Dutch patients, 9.3% revealed these kinds of variants, although only 3.5% were linked to the phenotype.[12] Taken together, the prevalence of rare variants of *LMF1* in severe hypertriglyceridemia was largely similar between different ethnicities.

Our study has potential limitations. First, several clinical characteristics of the study population selected for re-sequencing were different from those of the total population. For instance, the mean body mass index and the rate of alcohol intake (data not shown) were slightly higher in the study subjects. We cannot completely rule out the fact that these factors might have induced secondary elevation of TG. However, we tried to minimize these effects by excluding patients with high body mass index, uncontrolled diabetes mellitus, or heavy alcohol intake. Second, it was difficult to include and examine variants in family members of the probands. Because the pathogenicity of variants is occasionally clarified by this process, we could have obtained more concrete information on the

https://doi.org/10.3349/ymj.2018.59.1.148

variants if it has been performed.

In conclusion, we comprehensively analyzed and reported the prevalence and characteristics of variants of *LPL*, *APOC2*, *GPIHBP1*, *APOA5*, and *LMF1* in Korean patients with very high TG. Rare homozygous variants were very uncommon. According to our data, most study subjects may be manifesting the combined effects of rare heterozygous variants and common variants of these genes.

ACKNOWLEDGEMENTS

This research was financially supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science, and Technology (2012R1A4A1029061 and 2014R1A1A2056104) (SH Lee), the Bio & Medical Technology Development Program of the NRF funded by the Korean government, MSIP (2015M3A9B6029138) (SH Lee), the National Research Council of Science & Technology (NST) grant by the Korean government (MSIP) (No. CAP-12-2-KBSI) (SH Lee), and Basic Science Research Program through the NRF funded by the Ministry of Science, ICT and future Planning (No: NRF-2015R1A2A2A03 006577 (JH Lee), and a grant from Kyung Hee University in 2016 (KHU-20160543) (JH Lee).

ORCID

Chan Joo Lee https://orcid.org/0000-0002-8756-409X
Sang-Hak Lee https://orcid.org/0000-0002-4535-3745
Ji Hyun Lee https://orcid.org/0000-0003-3640-2928

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