



Original Article

Clinical Features of Li-Fraumeni Syndrome in Korea

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Purpose Li-Fraumeni syndrome (LFS) is a hereditary disorder caused by germline mutation in *TP53*. Owing to the rarity of LFS, data on its clinical features are limited. This study aimed to evaluate the clinical characteristics and prognosis of Korean patients with LFS.

Materials and Methods Patients who underwent genetic counseling and confirmed with germline *TP53* mutation in the National Cancer Center in Korea between 2011 and 2022 were retrospectively reviewed. Data on family history with pedigree, types of mutation, clinical features, and prognosis were collected.

Results Fourteen patients with LFS were included in this study. The median age at diagnosis of the first tumor was 32 years. Missense and nonsense mutations were observed in 13 and one patients, respectively. The repeated mutations were p.Arg273His, p.Ala138Val, and p.Pro190Leu. The sister with breast cancer harbored the same mutation of p.Ala138Val. Seven patients had multiple primary cancers. Breast cancer was most frequently observed, and other types of tumor included sarcoma, thyroid cancer, pancreatic cancer, brain tumor, adrenocortical carcinoma, ovarian cancer, endometrial cancer, colon cancer, vaginal cancer, skin cancer, and leukemia. The median follow-up period was 51.5 months. Two and four patients showed local recurrence and distant metastasis, respectively. Two patients died of leukemia and pancreatic cancer 3 and 23 months after diagnosis, respectively.

Conclusion This study provides information on different characteristics of patients with LFS, including types of mutation, types of cancer, and prognostic outcomes. For more appropriate management of these patients, proper genetic screening and multidisciplinary discussion are required.

Key words Li-Fraumeni syndrome, *TP53*, Germ-line mutation, Hereditary disease

Introduction

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant hereditary disorder caused by a germline mutation in *TP53* [1,2]. *TP53* gene is a tumor suppressor gene that provides instruction for making a protein called p53 and plays a key role in apoptosis, cell cycle regulation, and DNA repair [3,4]. Therefore, LFS is associated with a high risk of early-onset malignancies, such as breast cancer, bone and soft tissue sarcoma, brain tumor, adrenocortical carcinoma, leukemia, gastric cancer, and colorectal cancer. Its lifetime risks of malignancy are $\geq 70\%$ for male and $\geq 90\%$ for female patients [1,5,6].

Owing to the high cancer risk of LFS, several efforts have been made to identify its phenotype and genotype. Although previous studies have reported the mutational characteristics of LFS based on locus-specific databases, including the International Agency for Research on Cancer (IARC) *TP53*

database (<http://p53.iarc.fr/>) [6,7] and Universal Mutation Database (UMD) (<http://p53.fr/>) [8], most of the data originate from Western populations.

In Korea, studies have analyzed 14 patients with nine different types of *TP53* mutations [9] and 12 patients with LFS with breast cancer [10]. Other case reports also have described patients with LFS with various types of malignancies [11-13].

However, because of the rarity of LFS, data on its types of mutation, clinical features, and treatment outcomes in Korean patients are limited. This study aimed to evaluate the clinical characteristics and prognosis of Korean patients with germline *TP53* mutation.

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Materials and Methods

Patients who met the LFS criteria clinically, including the classic LFS criteria and Chompret criteria, or had a suspicious personal or family history underwent genetic counseling. All patients with confirmed germline *TP53* mutation at the National Cancer Center, Korea, between 2011 and 2022 were included and retrospectively reviewed. Genetic testing was performed by direct sequencing of 11 exons of *TP53* gene or by next-generation sequencing (NGS) of > 22 genes. Data on the age at diagnosis of the tumor, sex, personal history, family history with pedigree (Fig. 1), types of mutation, clinical features, and prognosis were collected.

Results

Fourteen patients with germline *TP53* mutation were included in this study. Clinical and *TP53* mutation data are summarized in Table 1.

1. Demographic data

Among the total patients, there was only one male patient and the rest were female (male:female ratio, 0.1:1). The median age at diagnosis of the first tumor was 32 years (range, 1 to 67 years). A family history of primary cancer was observed in 12 patients, and family members of eight patients had LFS-related tumors, including osteosarcoma, breast cancer, brain tumor, and lung cancer. Three patients,

including two patients who were sisters, had a sibling diagnosed with LFS.

2. Types of germline *TP53* mutation

Half of the patients underwent genetic testing using direct sequencing, and the other half underwent multigene panel NGS. Eleven different types of mutation were identified in the 14 Korean patients. Missense and nonsense mutations were observed in 13 and one patients, respectively. The repeated mutations were located at codons 273 (p.Arg273His, n=2), 138 (p.Ala138Val, n=2), and 190 (p.Pro190Leu, n=2) (Fig. 2), and the sister with breast cancer harbored the same mutation of p.Ala138Val. All mutations were heterozygous, including one case of mosaicism (patient 10) with a variant allele frequency of 11.4%.

3. Clinical characteristics

Twelve patients had suspicious clinical features, two of whom met the classic LFS criteria and eight met the Chompret criteria. A patient with early-onset breast cancer and a negative BRCA test (patient 7) and a patient with multiple primary tumors (patient 12) also underwent genetic testing. Two patients diagnosed with pancreatic cancer did not have a significant family history in pedigrees, but *TP53* mutations were found during screening.

Various primary malignancies were identified. "Core" cancers, including breast cancer, sarcoma, brain tumor, and adrenocortical carcinoma, were observed in 12 patients (85.7%). Breast cancer was most frequently observed (n=9),

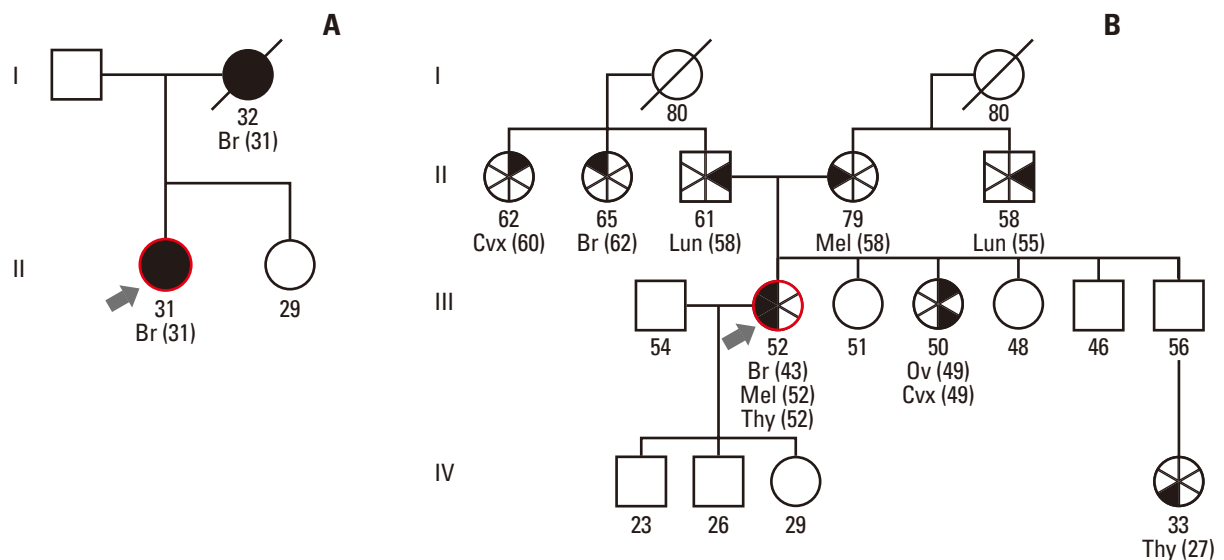


Fig. 1. Comparison of pedigrees between patients with Li-Fraumeni syndrome. (A) A pedigree of patient 7 with only a family history of breast cancer. (B) A pedigree of patient 11 with a family history of various malignancies in first- or second-degree relatives and who met the Chompret criteria. Br, breast cancer; Cvx, cervical cancer; Lun, lung cancer; Mel, melanoma; Ov, ovarian cancer; Thy, thyroid cancer.

Table 1. Clinical and mutation data of 14 Korean patients with LFS

Patient	Age ^{a)} (yr)	Sex	Indication	Testing method	Testing result	Nucleotide alteration	Amino acid alteration	Mutation type	Tumor type (age at diagnosis, yr)	Local/systemic recurrence	Death	Follow-up ^{b)} (mo)
1	1	M	Classic LFS criteria	Direct sequencing	LPV	c.817C>T	p.Arg273Cys	Missense	Rhabdomyosarcoma (1)	Yes	No	25
2	4	F	Chompret criteria	Direct sequencing	LPV	c.569C>T	p.Pro190Leu	Missense	Adrenal cortical carcinoma (4), thyroid cancer (10), osteosarcoma (11), osteoblastoma (12)	Yes	No	188
3	7	F	Chompret criteria	Direct sequencing	PV	c.524G>A	p.Arg175His	Missense	Brain tumor (7), breast cancer (24, 35), dermatofibrosarcoma (35), leukemia (38)	Yes	Yes	375
4	13	F	Classic LFS criteria	Direct sequencing	PV	c.818G>A	p.Arg273His	Missense	Mesenchymal chondrosarcoma (13)	No	No	11
5	28	F	Chompret criteria	Multigene panel NGS	LPV	c.569C>T	p.Pro190Leu	Missense	Breast cancer (28), colon cancer (28)	No	No	8
6 ^{c)}	29	F	Chompret criteria	Direct sequencing	LPV	c.413C>T	p-Ala138Val	Missense	Breast cancer (29)	No	No	134
7	31	F	Young age breast cancer with negative BRCA gene test	Direct sequencing	PV	c.733G>A	p.Gly245Ser	Missense	Breast cancer (31, 34)	No	No	110
8	33	F	Chompret criteria	Multigene panel NGS	PV	c.844C>T	p.Arg282Irp	Missense	Breast cancer (33), sarcoma (35), basal cell carcinoma (35)	No	No	26
9	38	F	Chompret criteria	Multigene panel NGS	PV	c.742C>T	p.Arg248Irp	Missense	Breast cancer (38, 38), thyroid cancer (38), endometrial cancer (39)	No	No	26
10 ^{d)}	40	F	Chompret criteria	Direct sequencing	LPV	c.413C>T	p-Ala138Val	Missense	Breast cancer (40)	No	No	57
11	43	F	Chompret criteria	Multigene panel NGS	LPV	c.517G>T	p.Val173Leu	Missense	Breast cancer (43), vaginal melanoma (52), thyroid cancer (52)	Yes	No	123
12	47	F	Multiple primary tumors	Multigene panel NGS	PV	c.517G>A	p.Val173Met	Missense	Breast cancer (47), ovarian cancer (55)	Yes	No	100
13	64	F	N/A	Multigene panel NGS	PV	c.637C>T	p.Arg213*	Nonsense	Pancreatic cancer (64)	No	No	17
14	67	F	N/A	Multigene panel NGS	PV	c.818G>A	p.Arg273His	Missense	Pancreatic cancer (67)	Yes	Yes	24

F, female; LFS, Li-Fraumeni syndrome; LPV, likely pathogenic variant; M, male; N/A, not applicable; NGS, next-generation sequencing; PV, pathogenic variant. ^{a)}Age at diagnosis of the first tumor, ^{b)}Follow-up periods after the diagnosis of the first tumor, ^{c)}Patients in the same family.

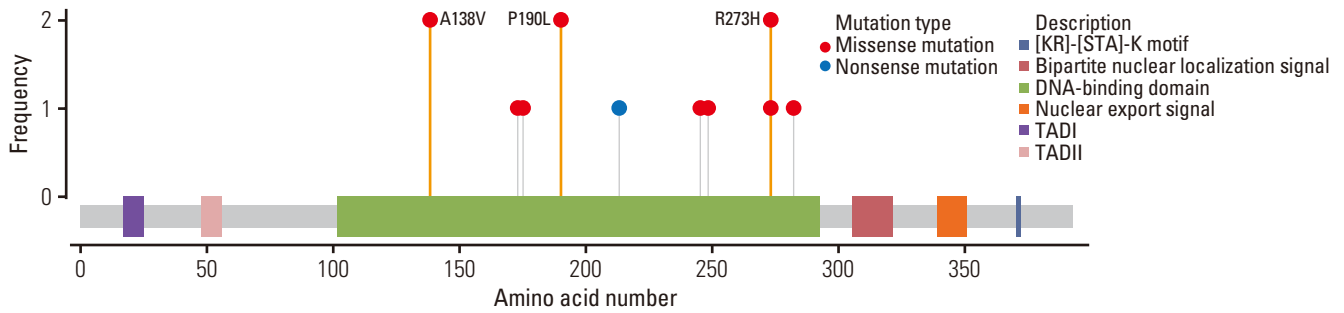


Fig. 2. Lollipop mutation diagram of the study population. All mutations shown in this study were at DNA-binding domain. Except for one patient with nonsense mutation in codon 213, other 13 patients showed missense mutations. A138V (n=2), P190L (n=2), and R273H (n=2) were repeated, and two patients with A138V mutation were sisters. A, alanine; H, histidine; L, leucine; P, proline; R, arginine; T, tryptophan; V, valine.

Table 2. Comparison of characteristics between the present study and two main references

	Present study	Park et al. (2016) [9]	Alyami et al. (2021) [10]
Patient selection	Patients with germline <i>TP53</i> mutation (2011-2022)	Patients with germline <i>TP53</i> mutation (2003-2015)	Patients with breast cancer with germline <i>TP53</i> mutation (2005-2019)
No. of patients	14	14	12
F:M	13:1	11:3	12:0
Age at first diagnosis (yr), median (range)	32 (1-67)	25	33.5 (20-52)
Multiple primary cancer, n (%)	7 (50.0)	11 (78.6)	9 (75.0)
Breast cancer	9 (64.3)	6 (42.9)	12 (100)
Sarcoma	5 (35.7)	5 (35.7)	1 (8.3)
Thyroid cancer	3 (21.4)	2 (14.3)	2 (16.7)
Pancreatic cancer	2 (14.3)	0	1 (8.3)
Brain tumor	1 (7.1)	4 (28.6)	0
Adrenocortical carcinoma	1 (7.1)	1 (7.1)	0
Ovarian cancer	1 (7.1)	0	0
Endometrial cancer	1 (7.1)	0	0
Colon cancer	1 (7.1)	0	1 (8.3)
Vaginal cancer	1 (7.1)	0	0
Skin cancer	1 (7.1)	2 (14.3)	1 (8.3)
Leukemia	1 (7.1)	2 (14.3)	0
Lung cancer	0	2 (14.3)	4 (33.3)
Stomach cancer	0	2 (14.3)	1 (8.3)
Nasal cavity cancer	0	1 (7.1)	1 (8.3)
Lymphoma	0	0	3 (25.0)

F, female; M, male.

and other types of tumor included sarcoma (n=5), thyroid cancer (n=3), pancreatic cancer (n=2), brain tumor (n=1), adrenocortical carcinoma (n=1), ovarian cancer (n=1), endometrial cancer (n=1), colon cancer (n=1), vaginal cancer (n=1), skin cancer (n=1), and leukemia (n=1). Seven (50%) patients had multiple primary cancers (range, 2 to 4). Leukemia found in one patient was induced by treatment of the

preceding breast cancer (patient 3).

In some malignancies, biomarker testing was performed on cancer specimens for the selection of drug regimens. Except for patients without data, one *BRAF*-mutated thyroid cancer and one *BRCA1*-mutated ovarian cancer were identified (S1 Table).

Table 3. Clinicopathologic features, treatment, and follow-up data in patients with breast cancer with Li-Fraumeni syndrome

Patient	Age (yr)	Side	Histological type	Grade	Stage	ER	PR	HER2	Surgery	CTX	HTX	RTX	Anti-HER2 therapy
3	24	Right	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Mastectomy	Adjuvant	No	Yes	No
	35	Left	IDC	3	cT2N2 ^{a)}	Neg	Neg	Pos	Mastectomy	Neoadjuvant	No	Yes	Yes
5	28	Left	DCIS	1	pT1sN0	Pos	Pos	Neg	Mastectomy	No	Yes	No	No
6	29	Right	Mucinous carcinoma	2	pT1N0	Pos	Pos	Neg	Mastectomy	Adjuvant	Yes	No	No
7	31	Right	IDC	3	cT2N3 ^{a)}	Neg	Neg	Pos	BCS	Neoadjuvant	No	Yes	Yes
	34	Left	IDC	2	pT1N0	Pos	Pos	Neg	BCS	No	Yes	Yes	No
8	33	Left	IDC	Unknown	cT1N1 ^{a)}	Pos	Neg	Pos	Mastectomy	Neoadjuvant	Yes	No	Yes
9	38	Right	IDC	3	cT3N0 ^{a)}	Pos	Neg	Pos	Mastectomy	Neoadjuvant	Yes	No	Yes
	38	Left	IDC	2	cT2N0 ^{a)}	Pos	Neg	Neg	Mastectomy	Neoadjuvant	Yes	No	Yes
10	40	Right	DCIS	3	pT1sN0	Neg	Neg	Pos	Mastectomy	No	No	No	No
11	43	Left	IDC	Unknown	Unknown	Unknown	Unknown	Unknown	BCS	No	No	Yes	Unknown
12	47	Right	IDC	3	pT2N2	Pos	Pos	Pos	Mastectomy	Adjuvant	Yes	Unknown	Unknown

BCS, breast-conserving surgery; CTX, chemotherapy; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HTX, hormone therapy; IDC, invasive ductal carcinoma; Neg, negative; Pos, positive; PR, progesterone receptor; RTX, radiation therapy. ^{a)}Clinical stage before neoadjuvant chemotherapy.

4. Prognostic outcomes

The median follow-up period from the diagnosis of the first tumor was 51.5 months (range, 6 to 188 months). After the diagnosis of LFS with genetic testing, one patient with breast cancer was diagnosed with colon cancer during the work-up for other malignancies (patient 5), and additional new-onset malignancies were found in three other patients during the follow-up. There were two and four cases of local recurrences and systemic recurrences, respectively. Two patients died of leukemia and pancreatic cancer 3 and 23 months after diagnosis, respectively.

Discussion

In this study, we reviewed Korean patients with LFS to evaluate their types of mutation and clinical features. There were 11 different types of mutation in 14 patients, and various spectra of malignancies were found.

Studies based on the IARC p53 database showed that most *TP53* mutations were missense mutations, accounting for 74%, and nonsense and splice mutations accounted for approximately 9% and 8%, respectively [6,7]. Except for one patient with nonsense mutation, all patients in this study had missense mutation. Park et al. [9] investigated the mutations and tumor spectra of LFS in Korean patients and identified two novel frameshift mutations in codons 98 and 27. Other studies on Korean patients have reported other types of mutation, such as frameshift or silent mutation (S2 Table) [9-18]. Based on the IARC database, the most common hot-spot mutations were found in codons 175, 245, 248, 273, and 282 (<http://p53.iarc.fr/>). In this study, six different mutations were identified in these hotspots in seven unrelated patients. Other mutations were located in codons 138, 173, 190, and 213. Mutations in codons 173 (p.Val173Leu, p.Val173Met) and 213 (p.Arg213*) have not been reported in the Korean Reference Genome Database (KRGDB) or Genome Aggregation database (gnomAD).

In addition to the types of mutation, the age at onset of the first tumor varied in this study. Studies have reported that age and sex are associated with cancer risk in patients with LFS. Cancer risk is highest after the age of 20 years in female patients, whereas it is higher in childhood and later adulthood in male patients [5]. It is difficult to compare because there was only one male patient in the present study, but compared with the 1-year-old male patient, all female patients, except for two teenagers, were adults. A previous study reported a positive relationship between the age of onset of the first tumor and development of secondary tumors [19]. In this study, secondary malignancies were observed in two of four patients (50%), four of seven patients

(57.1%), and one of three patients (33.3%) aged 0-19, 20-44 years, and ≥ 45 years, respectively. This result is due to the relatively small number of patient aged 0-19 years, and two of them had short follow-up periods of 11 and 25 months.

Among the tumors identified in this study, core cancers, such as breast cancer and sarcoma, were frequently observed (85.7%), as reported previously [6,20,21]. Notably, two out of 14 patients were diagnosed with pancreatic cancer. According to the IARC database, the relative risk of pancreatic cancer in patients with LFS is 7.3, with an incidence rate of 1.2% [22]. However, our study showed a higher incidence of pancreatic cancer, even compared to other Korean studies (Table 2). This is because, in our institution, genetic testing was performed for screening all patients with any risk of hereditary pancreatic cancer syndrome. Another difference from previous studies is that no patients with gastric cancer were included, although this study was conducted on Korean patients. A study reported that gastric cancer occurred more frequently in Asian populations than in similar Caucasian cohorts [23]. Other Korean studies have reported the incidence of stomach cancer (Table 2).

As is already well known [20], breast cancer was most frequently identified in this study, with a rate of 64.3%. Three patients had bilateral breast cancer, two of whom had metachronous and one had synchronous breast cancer. In the 12 cases of breast cancer in 9 different patients, the median age at diagnosis was 33.5 years (range, 23 to 47 years). Except for two cases with no pathological information, seven (70%) were endocrine receptor (ER)-positive and six (60%), including three with ER co-expression, were human epidermal growth factor receptor 2 (HER2)-positive, showing a higher rate of HER2 expression than the general population [24]. Breast-conserving surgery with adjuvant radiation therapy was performed in three (25%) cases, and the other nine (75%) cases underwent mastectomy (Table 3).

These results are similar to those of previous studies investigating the clinicopathological features of breast cancer in patients with LFS [25,26]. Breast cancer showed early onset with a median age of 32-34 years, and in immunohistochemistry staining, the proportion of receptor expression was similar with 84%-90.5% ER positivity, 39.5%-63% HER2 positivity, and 32.8%-53% ER and HER2 co-expression. However, a Korean study by Alyami et al. [10] showed differences in histological features and treatment outcomes. This study reported a lower rate of ER expression and a higher rate of triple-negative breast cancer. The recurrence rate was also higher than that in our study, which may be due to differences in subtypes.

A patient (patient 3) of the present study diagnosed with bilateral breast cancer died of acute myeloid leukemia induced by breast cancer treatment. Similar with this case, several

reports demonstrated that therapeutic interventions, such as chemotherapy and radiation therapy, caused therapy-induced secondary malignancies, including breast cancer [27,28], sarcoma [29], thyroid cancer [28,29], central nervous system tumor [28], and leukemia [9,28,30]. Despite clinical suspicion, there have been no large-scale comparative studies supporting the tumorigenesis of therapeutic interventions. Further multicenter studies with larger populations are required to evaluate which treatments can increase the risk of malignancy or which tissues are particularly vulnerable. Clinicians should be aware of the possibility of secondary cancer and should be careful when making treatment decisions.

This study is one of the largest case series performed in Korean patients with LFS and includes prognostic data. However, this study has some limitations. This was a retrospective study, and the data were obtained from medical records. Therefore, clinical information, such as indications for genetic testing or environmental factors, including lifestyle, was insufficient. In addition, this study was conducted in a single institution, and the number of included patients was small; therefore, it is difficult to define the characteristics and prognosis of patients with the disease. Finally, because this study included patients lost to follow-up or recently diagnosed patients, the prognostic outcomes were inaccurate.

This study provides information regarding the mutational features and clinical characteristics of patients with LFS in South Korea. Similar to other countries, several Korean patients with LFS also have early onset and multiple primary tumors. The clinical features and prognosis vary according to the type of mutation, type of cancer, and time of diagnosis.

This study emphasizes that genetic counseling and screening are required not only for patients but also for their family members. And for proper management, clinicians should assess genetic testing results and conduct multidisciplinary discussion before making treatment decisions. Further multicenter, large-cohort studies are required for the proper screening and management of Korean patients with LFS.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).




Ethical Statement

This study was approved by the Institutional Review Board of the National Cancer Center, Korea (IRB No. NCC2022-0268). The requirement for informed consent was waived owing to the retrospective nature of this study.

Author Contributions

Conceived and designed the analysis: Song R, Kong SY, Jung SY.
 Collected the data: Song R.
 Contributed data or analysis tools: Song R.
 Performed the analysis: Song R.
 Wrote the paper: Song R.
 Interpretation of data, critical revision of manuscript, final approval of the version: Song R, Kong SY, Choi W, Jung SY.
 Interpretation of data: Lee EG, Woo J, Han JH, Lee S, Kang HS.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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