Received: 16 October 2020 | Revised: 14 March 2021 | Accepted: 23 March 2021

DOI: 10.1111/cas.14919

ORIGINAL ARTICLE

Cancer Science WILEY

Characteristics of Li-Fraumeni syndrome in Japan: A review study by the special committee of JSHT

Michinori Funato[1] | Yukiko Tsunematsu[2] | Fumito Yamazaki[3] | Chieko Tamura[2,4] | Tadashi Kumamoto[5] | Masatoshi Takagi[6] | Shunsuke Kato[7] | Haruhiko Sugimura[8] | Kazuo Tamura[9] for the Li-Fraumeni syndrome special committee of the Japanese Society for Hereditary Tumors (JSHT)

[1]Department of Clinical Research, National Hospital Organization, Nagara Medical Center, Gifu, Japan

[2]Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan

[3]Department of Clinical Genomics, National Cancer Center Research Institute, Tokyo, Japan

[4]Medical Information & Genetic Counseling Division, FMC Tokyo Clinic, Tokyo, Japan

[5]Department of Pediatric Oncology, National Cancer Center Hospital, Tokyo, Japan

[6]Department of Pediatrics and Developmental Biology, Graduate School, Tokyo Medical and Dental University (TMDU), Tokyo, Japan

[7]Department of Clinical Oncology, Juntendo University Graduate School of Medicine, Tokyo, Japan

[8]Department of Tumor Pathology, Hamamatsu University School of Medicine, Shizuoka, Japan

[9]Division of Genetic Medicine, Master of Science, Graduate School of Science and Engineering Research, Kindai University, Higashiosaka, Japan

Correspondence
Kazuo Tamura, Division of Genetic Medicine, Master of Science, Graduate School of Science and Engineering Research, Kindai University, 3-4-1 Kowakae, Higashi-Osaka, Osaka 577-8502, Japan.
Email: tamura@life.kindai.ac.jp

Funding information
This study was supported in part by a grant from the Japanese Ministry of Education, Science, Sports and Culture (19K07763), the Health and Labor Sciences Research Grants of Research on Measures for Intractable Diseases (H23-nanchi-ippan-069), and Research on Cancer Control (H29-gantaisaku-ippan-002) from the Ministry of Health, Labor, and Welfare.

Abstract

Li-Fraumeni syndrome (LFS) is a hereditary cancer predisposition syndrome, and the majority of patients with LFS have been identified with germline variants in the *p53* tumor suppressor (*TP53*) gene. In the past three decades, considerable case reports of *TP53* germline variants have been published in Japan. To the best of our knowledge, there have been no large-scale studies of Japanese patients with LFS. In this study, we aimed to identify Japanese patients with *TP53* germline variants and to reveal the characteristics of LFS in Japan. We collected reported cases by reviewing the medical literature and cases diagnosed at the institutions of the authors. We identified 68 individuals from 48 families with *TP53* germline pathogenic or likely pathogenic variants. Of the 48 families, 35 (72.9%) had missense variants, most of which were located within the DNA-binding loop. A total of 128 tumors were identified in the 68 affected individuals. The 128 tumor sites were as follows: breast, 25; bones, 16; brain, 12; hematological, 11; soft tissues, 10; stomach, 10; lung, 10; colorectum, 10; adrenal gland, 9; liver, 4; and others, 11. Unique phenotype patterns of LFS were shown in Japan in comparison with those in a large national LFS cohort study in France. Above all, a higher frequency of patients with stomach cancer was observed in Japanese *TP53* germline variant carriers. These results may provide useful information for the clinical management of LFS in Japan.

KEYWORDS
Japan, Li-Fraumeni syndrome, phenocopy, stomach cancer, *TP53* germline pathogenic variant

1 | INTRODUCTION

Li-Fraumeni syndrome (LFS) is an autosomal dominant cancer predisposition syndrome with high penetrance, resulting in a high risk of developing various types of cancers from early childhood to adulthood. LFS was first proposed by Li and Fraumeni in 1969, and the causative gene was identified as the *p53* tumor suppressor (*TP53*) gene in 1990.[1-3] The *TP53* database of the International Agency for Research on Cancer (IARC) (http://p53.iarc.fr/) includes data on over 800 families worldwide.[4] Previously published literature review studies, cohort studies, and hospital-based follow-up studies have shown that tumors arising from LFS are increasingly diverse,[5-14] and the diagnostic criteria have changed over time[8,15-18] (Table S1). Recently, *TP53* germline variants were discovered through multigene cancer panel testing.[19-21] The interpretation of the pathological significance of *TP53* germline variants is sometimes difficult.[22,23] However, the detection and precise diagnosis of LFS is now considered more important because the usefulness of whole-body MRI as a cancer-screening technique for patients with LFS has been established.[24-26]

Since the first report in 1992 that identified *TP53* germline variants in two cases from a family survey of children with adrenocortical cancer (ACC) in Japan, a considerable number of studies on families with a *TP53* germline variant have been published.[27-54] However, no large-scale studies have been conducted on this syndrome in Japan, and the specific clinical and pathological features of cancers occurring in the Japanese population with *TP53* germline variants remain unknown. Genetic diagnosis of hereditary breast and ovarian cancers has frequently been conducted in Japan, and the search for *TP53* germline variants is considered in patients with breast cancer negative for *BRCA1* and *BRCA2*.[16]

In 2016, the Japanese Society for Hereditary Tumors (JSHT) established the LFS Special Committee. Its members, belonging to various specialized fields, came together to determine the characteristics of tumors that most commonly occur in Japanese families with LFS. Therefore, this study aimed to identify Japanese patients with *TP53* germline variants and identify the characteristics of LFS in Japan, in order to contribute to *TP53* genetic counseling, *TP53* germline testing, and healthcare management for LFS. We collected data on the affected *TP53* germline variant carriers and their pathological characteristics through a literature review. In addition, the characteristics of tumors occurring in the affected *TP53* germline variant carriers tested at our member institutions were examined. The pathogenicity of these identified *TP53* germline variants was assessed using widely accepted criteria for *TP53* variants.[55] Then, our Japanese study was compared with the French cohort study[17] because the French group had the world's largest series with *TP53* germline variants and reported the characteristics of the tumors that occurred in many of the individuals with *TP53* germline variants in almost the same period as that of our study.[17] Herein, we describe some findings of the LFS characteristics in Japan that were revealed in this study.

2 | MATERIALS AND METHODS

2.1 | Families and patients

Information on families with a *TP53* germline variant was obtained by searching PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Japan Medical Abstracts Society (http://search.jamas.or.jp), and the IARC *TP53* database R.18.[4] We used the keywords "Li-Fraumeni," "*TP53*," and "Japan" for our search and collected data on families carrying a *TP53* germline variant.[27-54] Data on sex, age at tumor onset, tumor sites, histopathological diagnosis, presence or absence of simultaneous or metachronous cancers, and *TP53* variant sites and types were obtained from the studies. Furthermore, unpublished data of the affected *TP53* germline variant carriers who underwent genetic testing at three institutions, namely the Nagara Medical Center, Hamamatsu University School of Medicine, and Kindai University, were added. Duplicated cases were excluded from the analysis. In addition, cases found using a next-generation DNA sequencer were excluded because exhaustive research had the possibility of causing confusion in our phenotype-conscious study. A compiled list of the families and patients in the order of publication year is presented in Table S2. This study was approved by the Ethics Board of the Japanese Society for Hereditary Tumors. The genetic studies described below were also approved by the ethics boards of the three institutions.

2.2 | *TP53* molecular analysis

For genetic analysis research in our facilities, written informed consent and patient agreement were obtained before the examination. DNA was collected from peripheral blood samples of patients using the QIAamp DNA Mini Kit (Qiagen), and DNA sequencing analysis of the *TP53* gene was performed using Big Dye Terminator Bidirectional Sequencing (Applied Biosystems), as previously reported.[31,41] The sequenced reads were aligned to the human reference genome (hg38), and primer sequences are available upon request.

2.3 | Interpretation of *TP53* germline variants

We assessed the pathogenicity of *TP53* germline variants based on the American College of Medical Genomics and Genetics/Association for Molecular Pathology (ACMG/AMP) guidelines for *TP53* variants.[55] The *TP53* germline variants were evaluated to determine *TP53* variant types and their known clinical significance using ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/); functional data based on the promoter-specific transcriptional activity measured in yeast assays[56]; a functional assay for loss of growth suppression and dominant-negative activities based on Z-scores[57]; population data of the Genome Aggregation Database (gnomAD) (https://gnomad.broadinstitute.org/), GEnome Medical Alliance Japan Whole Genome Aggregation (GEM-J WGA), ExAC (http://exac.broadinstitute.org/), human genetic variation database (HGVD) (http://www.hgvd.genome.med.kyoto-u.ac.jp/), and Tohoku Medical Megabank Organization (ToMMo) (https://www.megabank.tohoku.ac.jp/tommo); and in silico functional prediction algorithm of Align-GVGD (http://agvgd.hci.utah.edu/), BayesDel,[58] SIFT (http://provean.jcvi.org/index.php), Polyphen2 (http://genetics.bwh.harvard.edu/pph2/), and MutationTaster (http://www.mutationtaster.org/). The information was evaluated on December 10, 2020, and the results are summarized in Table S3. After annotation, the families and patients with pathogenic or likely pathogenic variants of the *TP53* germline were selected for further analysis.

2.4 | Genetic and phenotypic analysis

To analyze the characteristics of the tumor phenotypes, we counted all the tumors and sites affected in patients with the *TP53* germline pathogenic and likely pathogenic variants. For cases with multiple primary cancers, each cancer type was counted. Breast cancer also included those on the contralateral side. Based on this information, the effects and codon distribution of the *TP53* germline variants, the age at tumor onset, and the frequency distribution of the tumor were compared with data from 322 individuals affected with the *TP53* germline variants between 1993 and 2013, which was provided by the French LFS working group in 2015.[17]

2.5 | Statistical analysis

The statistical significance of the data on age at the first tumor onset in patients (female vs. male) and age at the first tumor onset according to the effect of *TP53* germline variants (missense variants vs. others than missense variants and dominant-negative missense variants vs. others than dominant-negative missense variants) was evaluated using the two-tailed Student's *t* test. Statistical significance was set at $P < .05$. A chi-square test of independence was performed by comparing the frequency of tumors associated with *TP53* germline variants (our study [n = 128] vs. the French LFS working group study [n = 548]). Statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | Japanese families and patients with LFS selected in this study

By reviewing the literature through 2016, we found a total of 128 Japanese families who met the diagnostic criteria for LFS or Li-Fraumeni like syndrome (LFL) and/or individuals with a *TP53* germline variant: 28 in PubMed, 62 in the Japan Medical Abstracts Society, 24 in the IARC *TP53* database, and 14 in our facility. After excluding duplicated cases, 88 Japanese families who met the criteria of LFS/LFL and/or carrying a *TP53* germline variant were identified. First, we excluded 29 families not verified for any *TP53* germline variants and one family with one Japanese-born Brazilian boy with p.Arg337His, whose parents were from the Brazilian state of Paraná (Figure 1). Among the remaining 58 families, we identified 38 distinct *TP53* germline variants (Table 1 and Table S3). We attempted to interpret each of these 38 variants of the 58 families based on the ACMG/AMP guidelines for *TP53* variants; 10 families with 12 individuals carrying p.Val31Ile, p.Asp49His, p.Ser106Arg, p.Ala189Val, p.Arg156His, and p.Glu285Gln were excluded (Table 1 and Table S3). Finally, among the 58 families with *TP53* germline variant carriers, 48 families with 68 affected individuals were found to have a germline pathogenic or likely pathogenic variant (Table 1 and Figure 1).

3.2 | Potency of the clinical criteria

Of the 48 families, six families (12.5%) met the classic LFS criteria, and 29 (60.4%) met the 2015 version of the Chompret criteria for *TP53* testing. Fifteen families (31.3%) had individuals with significant family history in the 2015 version of the Chompret criteria, seven (14.5%) had individuals with multiple primary cancers, 10 (20.8%) had individuals with ACC or choroid plexus cancer (CPC) without a significant family history, and eight (16.7%) had individuals with early diagnosis of breast cancer. Overall, 32 families (66.7%) tested positive for a *TP53* germline pathogenic or likely pathogenic variant meeting either classic diagnostic criteria or the 2015 version of the Chompret criteria for *TP53* testing (Table 1 and Table S2).

3.3 | Patterns of pathogenic or likely pathogenic variants

Among the 48 families with a *TP53* germline pathogenic or likely pathogenic variant, 32 distinct *TP53* germline variants were identified, corresponding to 23 missense variants, three nonsense variants, two splice variants, and four frameshift variants, including two deletions and two insertions (Figure S1). Among the 48 families, 35 (72.9%) had missense, six (12.5%) nonsense, four (8.3%) frameshift, and three (6.3%) splice variants. Among the 48 families with a *TP53* germline pathogenic or likely pathogenic variant, 41 families carried a single-base substitution of missense and nonsense variants.

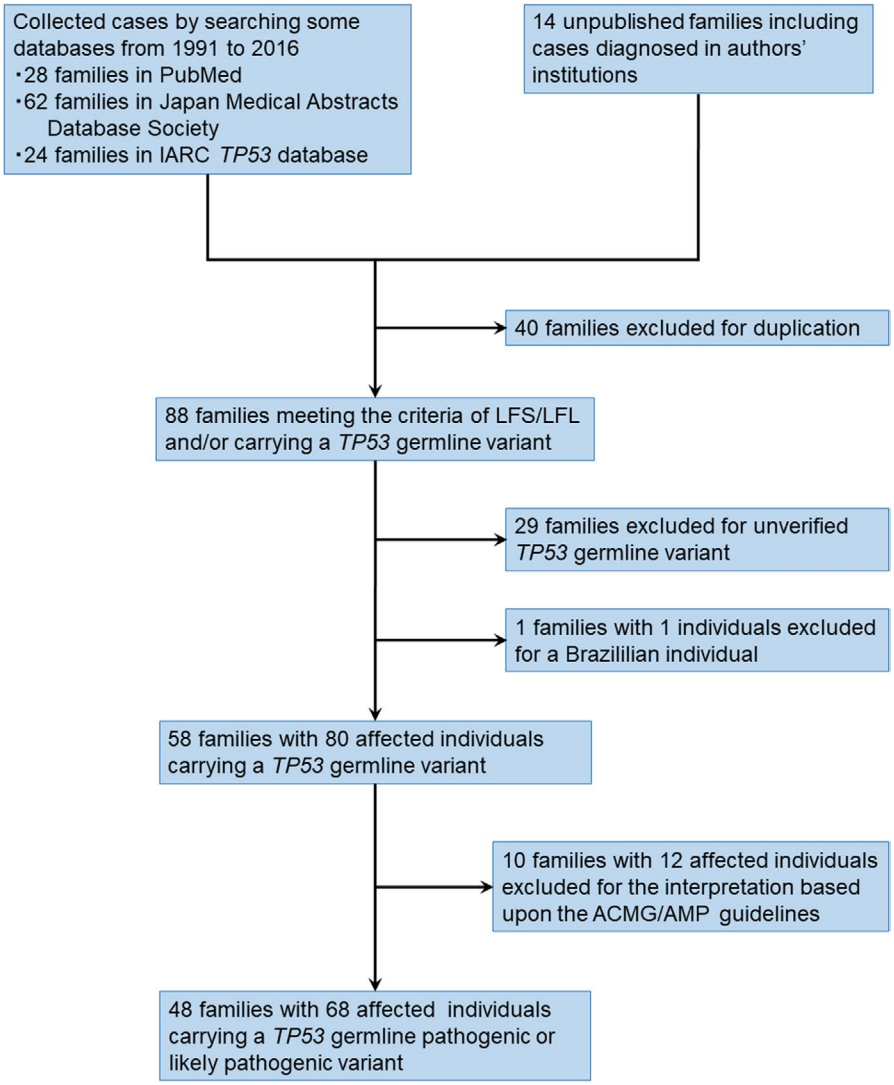

FIGURE 1 Flow diagram of this study population

Among the 41 families, sites of the variants in 39 families (95.1%), except two families with missense variants in codon 337, were located in the DNA-binding loop of *TP53* (Figure S2).

3.4 | LFS tumor onset in Japan

Among the 68 individuals affected with *TP53* germline variants (34 females and 34 males), a total of 128 tumors developed. The mean age at first tumor onset was 19.9 years (range: 8 months to 65 years), and the median age at first tumor onset was 16.5 years. Of the 68 affected individuals (both sexes), 14 (20.6%) firstly developed cancer by 5 years of age, and 50 (73.5%) and 67 (98.5%) individuals were aged by 30 and 60 years, respectively (Figure S3). Although we found a tendency for low cancer incidence in women during the first decade of life, no significant difference was observed between men and women according to the age at tumor onset ($P = .42$) (Figure 2).

Multiple primary cancers (n = 2-7) were observed in 32 of the 68 affected individuals (47.0%). Two individuals (2.9%) had simultaneous cancers at the onset, 30 (44.1%) had second primary cancers, and 14 (20.6%) had third or more primary cancers (Figure S4). The mean and median latency periods to the second tumor occurrence in 30 affected individuals were 6.8 and 5 years, respectively (range: 0-20 years) (Figure S5).

3.5 | LFS tumor distribution in Japan

The distribution of the 128 tumors is summarized in Table 2. The tumor sites were as follows: breast, 25; bones, 16; brain, 12; hematological, 11; soft tissues, 10; stomach, 10; lung, 10; colorectum, 10; adrenal gland, 9; liver, 4; and others, 11 (Table 2).

A total of 25 breast cancers were observed in 15 affected individuals, all female, with mean and median ages of 31.9 and 32 years (range: 19-47 years) at onset, respectively. Two of the 15 individuals with breast cancer had bilateral primary cancers at onset, and four had contralateral breast cancers during the clinical course. Seventeen out of 25 (68.0%) breast cancers were identified as second or more primary cancers. Four out of 15 (26.7%) individuals with breast cancer had phyllodes breast tumors. Limited histological

TABLE 1 Summary of each family and individual with TP53 germline pathogenic or likely pathogenic variant in this study

Family No.	Patient No.	Relationship	Sex	Cancer site	Age (y)	Clinical category	*TP53* variant	Clinvar	TA Class	PHANTM	gnomAD	GEM-J WGA	Align-GVGD	BayesDel
1	1	Proband	M	AC	5	Chompret	c.918_919insG, p.Ala307Hisfs	N/A	N/A	notDNE_LOF	N/A	N/A	N/A	-
2	2	Proband	M	CNS	41	Chompret	c.857A>C, p.Glu286Ala	LP	NF	DNE_LOF	N/A	N/A	C65	0.5335
	3	Son	M	TM	19									
3	4	Proband	F	OS	10	Chompret	c.844C>T, p.Arg282Trp	P/LP	NF	DNE_LOF	3.98E-06	N/A	C65	0.5418
	5	Father	M	ST	46									
4	6	Proband	F	OS-BR-ST	13	Classic LFS, Chompret	c.844C>T, p.Arg282Trp	P/LP	NF	DNE_LOF	3.98E-06	N/A	C65	0.5418
5	7	Proband	F	ST-LU	41	No	c.637C>T, p.Arg213X	P	N/A	notDNE_LOF	N/A	N/A	N/A	-
	8	Daughter	F	ST	20									
6	9	Proband	F	BR-BR-LU	26	Chompret	c.398T>G, p.Met133Arg	N/A	NF	DNE_LOF	N/A	N/A	C45	0.4966
	10	Sibling	M	HE-ST	37									
	11	Sibling	M	CNS	25									
	12	Sibling	F	BR(bilateral)	40									
7	13	Proband	M	ST	44	No	c.818G>A, p.Arg273His	P	NF	DNE_LOF	1.59E-05	6.60E-05	C25	0.5259
8	14	Proband	M	CNS-HE	28	Chompret	c.725G>A, p.Cys242Tyr	P	NF	DNE_LOF	N/A	N/A	C65	0.5405
9	15	Proband	F	SO	3	Classic LFS	c.839G>T, p.Arg280Ile	VUS	NF	DNE_LOF	N/A	N/A	C65	0.5969
	16	Mother	F	CNS	33									
	17	Sibling	M	CNS-OS	2									
10	18	Proband	M	ST	38	No	c.818G>A, p.Arg273His	P	NF	DNE_LOF	1.59E-05	6.60E-05	C25	0.5259
	19	Son	M	LI-HE	7									
11	20	Proband	F	OS-BR	12	Classic LFS, Chompret	c.524G>A, p.Arg175His	P	NF	DNE_LOF	3.98E-06	0.0002	C25	0.5462
12	21	Proband	F	AC-HE	3	Chompret	c.742C>T, p.Arg248Trp	P	NF	DNE_LOF	3.98E-06	N/A	C65	0.5336
13	22	Proband	F	OV-HE-SK	65	No	c.524G>A, p.Arg175His	P	NF	DNE_LOF	3.98E-06	0.0002	C25	0.5462
14	23	Proband	M	OS-LU	9	Chompret	c.16bp dup, p.Asn310X	N/A	N/A	notDNE_LOF	N/A	N/A	N/A	-
	24	Father	M	OS	26									
15	25	Proband	M	LU	30	No	c.277-278delCT, p.Leu93fsX224	N/A	N/A	N/A	N/A	N/A	N/A	-
16	26	Proband	M	KI-LU-ST-SK-CO-BL-TH	43	No	c.733G>A, p.Gly245Ser	C	NF	DNE_LOF	N/A	N/A	C55	0.5536
17	27	Proband	F	AC-LI-TH-BR&BR	2	Chompret	c.672+1G>T	P/LP	N/A	N/A	N/A	N/A	N/A	-
	28	Sibling	M	OS	13									

(Continues)

TABLE 1 (Continued)

Family No.	Patient No.	Relationship	Sex	Cancer site	Age (y)	Clinical category	*TP53* variant	Clinvar	TA Class	PHANTM	gnomAD	GEM-J WGA	Align-GVGD	BayesDel
18	29	Proband	F	SO-HE-HE	10	No	c.733G>A, p.Gly245Ser	C	NF	DNE_LOF	N/A	N/A	C55	0.5536
	30	Father	M	ST	44									
19	31	Proband	F	OS-BR-CO-SO-LU-BR(bilateral)-SO	15	Chompret	c.659A>G, p.Tyr220Cys	P	NF	DNE_LOF	7.96E-06	N/A	C65	0.5625
20	32	Proband	F	PA	12	No	c.733G>A, p.Gly245Ser	C	NF	DNE_LOF	N/A	N/A	C55	0.5536
21	33	Proband	M	CNS-CO	20	No	c.584T>C, p.Ile195Thr	VUS	NF	DNE_LOF	N/A	N/A	C55	0.5174
22	34	Proband	F	AC	20	Chompret	c.581T>C, p.Leu194Pro	VUS	NF	DNE_LOF	N/A	N/A	C65	0.6021
23	35	Proband	F	CNS	12	No	c.637C>T, p.Arg213X	P	N/A	notDNE_LOF	N/A	N/A	N/A	-
24	36	Proband	F	AC	31	Chompret	c.530C>G, p.Pro177Arg	C	NF	DNE_LOF	N/A	N/A	C65	0.4485
25	37	Proband	M	SO-SO	1	Chompret	c.818G>A, p.Arg273His	P	NF	DNE_LOF	1.59E-05	6.60E-05	C25	0.5259
26	38	Proband	M	OS	17	Classic LFS	c.818G>A, p.Arg273His	P	NF	DNE_LOF	1.59E-05	6.60E-05	C25	0.5259
	39	Sibling	F	HE	10									
27	40	Proband	F	LU-SO-SO	28	Classic LFS, Chompret	c.637C>T, p.Arg213X	P	N/A	notDNE_LOF	N/A	N/A	N/A	-
	41	Son	M	CO	11									
	42	Sibling	F	CO	28									
	43	Sibling	F	BR-BR	29									
28	44	Proband	F	OS&LI	8	No	c.722C>T, p.Ser241Phe	LP	NF	DNE_LOF	3.98E-06	N/A	C65	0.545
29	45	Proband	F	OS	15	Chompret	c.672+1G>T	P/LP	N/A	N/A	N/A	N/A	N/A	-
30	46	Proband	M	SO	2	Classic LFS	c.997delC, p.Arg333Valfs*12	N/A	N/A	N/A	N/A	N/A	N/A	-
	47	Mother	F	OS	11									
31	48	Proband	M	HE-CO-LI-CO-OS	12	No	c.742C>T, p.Arg248Trp	P	NF	DNE_LOF	3.98E-06	N/A	C65	0.5336
32	49	Proband	M	AC	8 M	Chompret	c.473G>A, p.Arg158His	P/LP	NF	DNE_LOF	3.98E-06	N/A	C25	0.5337
33	50	Proband	M	OS-UK	14	Chompret	c.711G>A, p.Met237Ile	C	NF	DNE_LOF	3.98E-06	N/A	C0	0.4419
	51	Son	M	CNS	9									
34	52	Proband	M	AC	3	Chompret	c.375+1G>A	LP	N/A	N/A	N/A	N/A	N/A	-
35	53	Proband	M	SO	2	Chompret	c.736A>G, p.Met246Val	P	NF	DNE_LOF	N/A	N/A	C15	0.371
	54	Sibling	M	AC	9									
36	55	Proband	F	BR-BR-LU	40	Chompret	c.743G>A, p.Arg248Gln	P	NF	DNE_LOF	1.19E-05	0.00013	C35	0.4738
37	56	Proband	F	OS-BR-CO	16	Chompret	c.743G>A, p.Arg248Gln	P	NF	DNE_LOF	1.19E-05	0.00013	C35	0.4738

(Continues)

TABLE 1 (Continued)

Family No.	Patient No.	Relationship	Sex	Cancer site	Age (y)	Clinical category	*TP53* variant	Clinvar	TA Class	PHANTM	gnomAD	GEM-J WGA	Align-GVGD	BayesDel
38	57	Proband	F	CO	17	No	c.1009C>T, p.Arg337Cys	P/LP	NF	notDNE_LOF	N/A	N/A	C45	0.3165
	58	Mother	F	OS-BR-CNS	39									
39	59	Proband	F	SO-BR	21	Chompret	c.1009C>T, p.Arg337Cys	P/LP	NF	notDNE_LOF	N/A	N/A	C45	0.3165
40	60	Proband	F	AC	2	Chompret	c.514G>T, p.Val172Phe	LP	NF	unclass	N/A	N/A	C45	0.5464
41	61	Proband	M	ST	42	No	c.541C>T, p.Arg181Cys	C	PF	notDNE_LOF	N/A	N/A	C65	0.4693
42	62	Proband	M	CNS	5	Chompret	c.817C>T, p.Arg273Cys	P/LP	PF	DNE_LOF	1.20E-05	N/A	C65	0.5537
43	63	Proband	M	CNS	1	Chompret	c.928_929ins14bp (GCATCCTCTCCCAG), p.Asn310Serfs*30	N/A	N/A	N/A	N/A	N/A	N/A	-
44	64	Proband	F	BR-BR	32	Chompret	c.743G>A, p.Arg248Gln	P	NF	DNE_LOF	1.19E-05	0.00013	C35	0.4738
45	65	Proband	M	CNS-TH-LU	21	Chompret	c.473G>A, p.Arg158His	P/LP	NF	DNE_LOF	3.98E-06	N/A	C25	0.5337
46	66	Proband	F	BR-BR-LU-CO	31	Chompret	c.586C>T, p.Arg196X	P	N/A	notDNE_LOF	3.98E-06	N/A	N/A	-
47	67	Proband	M	HE	1	No	c.637C>T, p.Arg213X	P	N/A	notDNE_LOF	N/A	N/A	N/A	-
48	68	Proband	F	BR-BR	32	No	c.749C>T, p.Pro250Leu	C	NF	DNE_LOF	N/A	N/A	C35	0.6029

Note: Age indicates age at first tumor onset. M in age indicates month.

Abbreviations: AC, adrenal cortex; BL, bladder; BR, breast; C, conflicting interpretations of pathogenicity; CNS, brain; CO, colorectum; F, female; GEM-J WGA, GEnome Medical Alliance Japan Whole Genome Aggregation; gnomAD, Genome Aggregation Database; HE, hematological; KI, kidney; LFS, Li-Fraumeni syndrome; LI, liver; LP, likely pathogenic; LU, lung; M, male; N/A, not available; NF, nonfunctional; OS, bones; OV, ovary; P, pathogenic; PA, pancreas; PF, partially functional; PHANTM, Phenotypic Annotation of *TP53* Mutations; SK, skin; SO, soft tissues; ST, stomach; TA, transactivation; TH, thyroid; TM, thymus; UK, unknown origin; VUS, variant of uncertain significance.

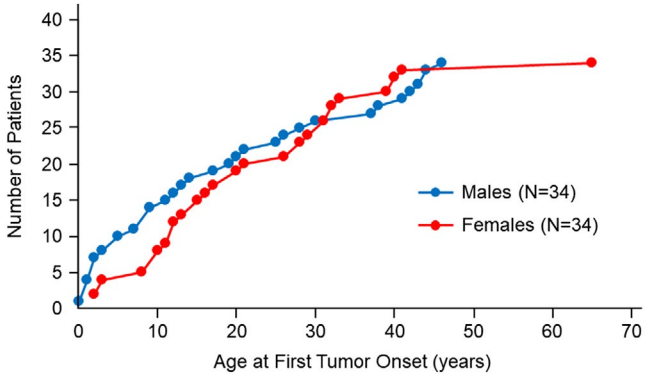

FIGURE 2 Age at first tumor onset in individuals affected with *TP53* germline pathogenic or likely pathogenic variants according to sex (women [n = 34] and men [n = 34]). The *X*-axis shows age in years at the first tumor onset. The *Y*-axis shows the cumulative number of patients

information, including hormone receptors and/or HER2-positive breast cancer, was available.

The mean and median ages of bone tumor onset were 16.3 and 14.5 years (range: 8-39 years), respectively, and all were histologically classified as osteosarcoma. Fourteen of the 16 (87.5%) individuals with bone tumors developed bone tumor as first primary cancer. In addition, three of them (18.8%) developed tumors at rare sites such as the cranial bone or maxillary sinus. A brain tumor was found in 12 individuals with mean and median ages of 20.7 and 20.5 years (range: 1-51 years) at onset, respectively, and 11 of 12 (91.7%) individuals with brain tumors developed brain tumor as first primary cancer. Five of 12 (41.7%) individuals with brain tumors had astrocytoma, three (25.0%) individuals had CPC, and none had medulloblastoma. Hematological malignancy was found in 10 individuals with mean and median ages at onset of 20.3 and 13 years (range: 1-70 years), respectively. Of the 10 individuals with hematological malignancies, five (50.0%) had acute leukemia, three (30.0%) had malignant lymphoma, and three (30.0%) had myelodysplastic syndrome. Six out of 10 (60.0%) individuals with hematological malignancies developed these malignancies as second or more primary cancers. No chromosomal findings were reported in two individuals who developed lymphocytic leukemia. Soft tissue sarcomas were observed in eight individuals at mean and median ages of 15.7 and 15.5 years (range: 1-36 years) at onset, respectively, and four out of 10 (40.0%) tumors in eight individuals indicated embryonal rhabdomyosarcoma. Intriguingly, a 10-year-old girl presented with primary ameloblastic fibrosarcoma, a rare malignant odontogenic tumor. All nine (100%) individuals indicated ACC as their first cancer, with mean and median ages at onset of 8.4 and 3 years (range: 8 months to 31 years), respectively.

Stomach, lung, and colorectal cancers that generally occur at older ages were observed in 10 individuals at a median age of 43 years (range: 20-46 years), 10 individuals at a median age of 38.5 years (range: 14-52 years), and nine individuals at a median age of 27.5 years (range: 11-52 years). The mean age of onset of these stomach, lung, and colorectal cancers was 38.8, 37.3, and 29.6 years, respectively. We found that eight out of 10 (80.0%) lung cancers in 10 individuals were identified as the second or more primary cancers. Liver cancer was also found in four individuals with mean and median ages of 13.8 years (range: 7-26 years), respectively, and two of four (50%) indicated liver sarcoma.

3.6 | Comparing the characteristics of the affected individuals in Japan and in France

To clarify the characteristics of individuals affected with *TP53* germline pathogenic or likely pathogenic variants in Japan, Japanese data were compared with data from the French LFS working group.[17] Both our study and the study of the French LFS working group showed some similarities regarding codon distribution and the effect of the *TP53* germline variants, age at the first tumor onset, frequency of patients with multiple primary tumors, and time of occurrence of second tumors. However, a comparison of the frequency distribution of the 128 tumors included in this study with that of the 548 tumors from the French LFS study group showed that the frequency of stomach cancer was significantly higher in Japan (7.8% vs. 1.3%; $P = .03$). Moreover, a high-frequency distribution was also observed for lung, colorectal, and liver cancers in Japan (7.8% vs. 3.3%; $P = .17$, 7.8% vs. 2.2%; $P = .08$, and 3.1% vs. 0%; $P = .08$, respectively) (Figure 3). Conversely, the frequency distribution of soft tissue sarcomas was lower in Japan than in France (7.8% vs. 19.0%; $P = .03$) (Figure 3). In addition, a low-frequency distribution of breast cancer in Japan was also found (19.5% vs. 31.4%; $P = .10$) (Figure 3).

Moreover, when comparing the mean and median ages at the onset of each tumor between the Japanese and French, the mean and median ages at tumor onset of soft tissue sarcoma, lung cancer, and colorectal cancer in Japan was earlier (16/16 vs. 29/31, 37/39 vs. 42/44, 30/28 vs. 40/40, respectively) than those in France (Table 2). In contrast, the mean and median ages at brain tumor onset in Japan were older (21/21 vs. 15/11) than those in France (Table 2).

3.7 | LFS genotype-phenotype correlations in Japan

Several genotype-phenotype correlations have been reported in families with *TP53* germline variants. One is the correlation between genotype and age at tumor onset. Missense variants have been reported to be associated with earlier tumor onset.[59,60] This study of 68 individuals affected with *TP53* germline pathogenic or likely pathogenic variants demonstrated that the average age at first tumor onset indicated no significant differences between missense variants (age 21.6 years [n = 48]) and nonsense or other types of variants (age 15.9 years [n = 20]) ($P = .15$) (Figure S6). In addition, a recent French report indicated that the average age at tumor onset in dominant-negative missense variants was 5 years earlier than in other types of alterations than the dominant-negative missense variants.[17] However, based on two systematic studies of dominant-negative

TABLE 2 Distribution of tumors in affected individuals with TP53 germline pathogenic or likely pathogenic variant

Site	Total no. of patients (N = 68)	No. of patients (females/males) (N = 34/34)	Total no. of tumors	No. of patients (0-18/>18 y)[a] (N = 36/32)	No. of patients (1st/>2nd)	Mean/median age at tumor onset, y (range)
Breast	15	15/0	25	0/25	8/17	31.9/32.0 (19-47)
Bones	16	9/7	16	13/3	14/2	16.3/14.5 (8-39)
Brain	12	3/9	12	5/7	11/1	20.7/20.5 (1-51)
Hematological	10	5/5	11	7/4	4/7	20.3/13.0 (1-70)
Soft tissues	8	5/3	10	5/5	6/4	15.7/15.5 (1-36)
Stomach	10	3/7	10	0/10	7/3	38.8/43.0 (20-46)
Lung	10	6/4	10	1/9	2/8	37.3/38.5 (14-52)
Colorectum	9	5/4	10	2/8	3/7	29.6/27.5 (11-52)
Adrenal cortex	9	5/4	9	7/2	9/0	8.4/3.0 (0-31)
Liver	4	2/2	4	3/1	2/2	13.8/13.75 (7-26)
Thyroid	3	1/2	3	1/2	0/3	38.0/35.0 (15-64)
Skin	2	1/1	2	0/2	0/2	58.0/58.0 (46-70)
Kidney	1	0/1	1	0/1	1/0	43/43
Pancreas	1	1/0	1	1/0	1/0	12/12
Ovary	1	1/0	1	0/1	1/0	65/65
Thymus	1	0/1	1	0/1	1/0	19/19
Bladder	1	0/1	1	0/1	0/1	64/64
Unknown origin	1	0/1	1	0/1	0/1	30/30
Total	114	62/52	128	45/83	70[b]/58	26.3/26.0 (0-70) (19.9[a]/16.5 (0-65))

[a]Age at first tumor onset was indicated.

[b]Two of 68 patients had simultaneous cancers at onset.

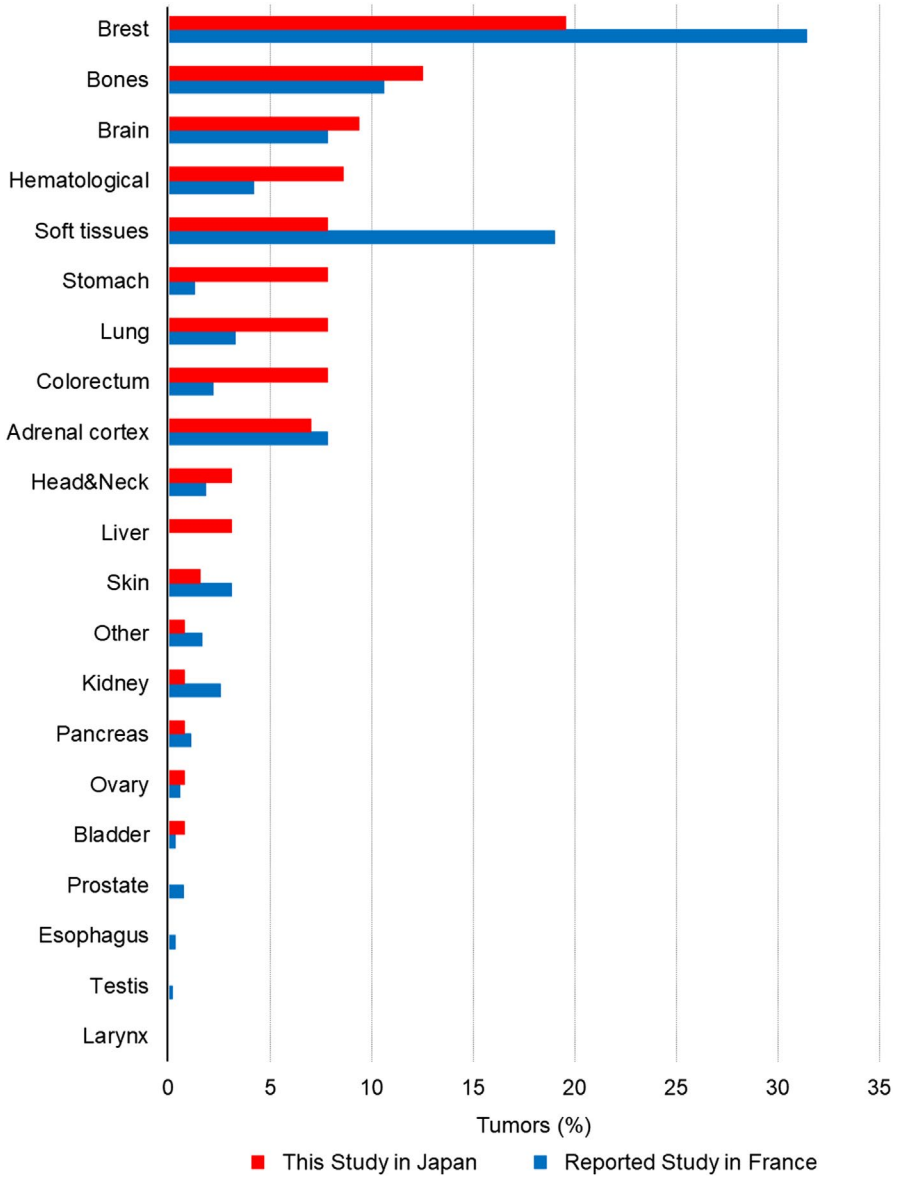

FIGURE 3 The frequency distribution of tumors associated with *TP53* germline variants in our study (n = 128) and the French LFS working group study (n = 548). The *X*-axis shows the tumor site. The *Y*-axis shows the frequency distribution of the tumor

effects,[61,62] this study indicated no significant differences between the dominant-negative missense variants (age 21.5 years [n = 31]) and types of alterations other than the dominant-negative missense variants (age 18.6 years [n = 37]) ($P = .42$) (Figure S7).

Moreover, correlations between cancer types and *TP53* germline variants at the DNA-binding site or dominant-negative missense variants have also been described.[17,63] In this study, the *TP53* germline pathogenic or likely pathogenic variants at the DNA-binding site were identified in all 10 (100%) individuals with hematological malignancies, all those (100%) with stomach cancer, and in eight out of nine (88.9%) individuals with colorectal cancer (Table S4). In addition, in Japan, we found that the dominant-negative missense variants were detected in seven of 10 (70.0%) individuals with hematological malignancies and seven of 10 (70.0%) individuals with stomach cancer (Table S4). In contrast, our study also indicated that seven of nine (77.8%) individuals with ACC and seven of 10 (70.0%) individuals with lung cancer showed other types of alterations than dominant-negative missense variants (Table S4).

4 | DISCUSSION

This study analyzed the characteristics of families with a *TP53* germline variant in Japan, which was examined by the LFS Special Committee of the Japanese Society for Hereditary Tumors (JSHT) through a literature review until 2016. Target families with LFS also included unpublished families tested at the authors' facilities. Of the Japanese families with LFS, 32 distinct *TP53* germline pathogenic or likely pathogenic variants were identified in 48 families with 68 patients. A total of 68 patients developed 128 tumors. Of the 68 patients, 32 (47.0%) had multiple primary cancers. We then compared the genetic and clinical characteristics of these Japanese families with LFS, mainly using data obtained from the French LFS working group study. Some similarities, such as genotype patterns and age at onset, were observed. In addition, our study indicated that the unique phenotypic patterns of LFS, the high frequency of stomach, colorectal, lung, and liver cancers, and the low frequency of breast cancer and soft tissue sarcoma, are observed in Japan.

In this study, we described that the LFS in Japan is mainly characterized by the frequent occurrence of stomach cancer in *TP53* germline variant carriers. Recently, Ikenoue et al reported a high incidence of stomach cancer in Lynch syndrome in Japan, with similar characteristics.[64] In addition, Ariffin et al reported the frequent occurrence of stomach cancer in Asian patients, particularly in Japanese patients, with a *TP53* germline variant based on the IARC *TP53* database R.16 in 2012, and reported that the frequent occurrence of stomach cancer in the general population might phenotypically determine the frequency of this cancer in Asian *TP53* germline variant carriers.[65] Ariffin et al suggested that the frequent occurrence of stomach cancer in Asian populations compared with Western populations is due to a combination of dietary (high-salt diet), environmental (chronic *Helicobacter pylori* infection), and genetic susceptibility risk factors.[65] Currently, the global frequency of cancer incidence in each population from 2003 to 2007 can be observed using the database managed by the IARC (http://ci5.iarc.fr/CI5-X/Pages/registry_summary.aspx).[66] The associated results are shown in Figures S8 and S9. We also speculate that the frequent occurrence of stomach cancer in the Japanese general population might partly explain the characteristic patterns in patients with *TP53* germline variants in Japan.

Similarly, when we consider the frequency of other cancer incidences, the frequent occurrence of colorectal and liver cancers in the Japanese general population may explain the high-frequency distribution of colorectal and liver cancers in patients with *TP53* germline variants in Japan. In addition, the low-frequency distribution of breast cancer and soft tissue sarcoma in patients with *TP53* germline variants in Japan may also be explained by the low frequency of breast cancer and soft tissue sarcoma in the general Japanese population in comparison with the general French population. In contrast, resolving the reason for the high frequency of lung cancer is difficult because no simple phenocopy was observed in the general population. In our study, eight of 10 patients with lung cancer in *TP53* germline variant carriers developed lung cancer as second or more primary cancers. Of the eight patients, three (patients 31, 55, and 66) of five patients with breast cancer had lung cancer after radiation therapy. Therefore, we speculate that the frequent occurrence of lung cancer in Japan may be due to treatment-related risk factors such as radiation (Table S2).

Children with CPC of the brain and ACC were reported to have a high likelihood of carrying a *TP53* germline variant, even in the absence of any family history.[17,67-70] Our analysis also showed that two children with CPC and six patients with ACC without any strong family history of cancer had *TP53* germline pathogenic or likely pathogenic variants (Table 1 and Table S2). Furthermore, phyllodes tumors in breast cancer and liver sarcoma in liver cancer were found to be the most frequent. Birch et al and Giacomazzi et al reported the greatest increase relative to the general population rates for phyllodes tumors.[9,10] Moreover, in liver sarcoma, one of 16 patients aged 1-21 years was a member of a family with LFS.[71] Therefore, we believe that at least patients in adolescence with phyllodes tumor and children with liver sarcoma in Japan may be considered for *TP53* germline variant testing even in the absence of a distinct family history.

The development of clinical surveillance programs for LFS is ongoing. As a leading study, Villani et al reported a survival rate of 88.8% in patients with *TP53* germline variants undergoing comprehensive screening compared with a 59.6% survival rate in those without surveillance.[26] They developed a practical surveillance protocol based on the available data, their own experience, and detection strategies for patients with sporadic LFS component tumors.[25] We speculate that there may be individual unusual LFS characteristics in different countries and regions, as they show different tumor characteristics in the general population of different countries and regions. Our study indicated the frequent occurrence of stomach, colorectal, and liver cancers, the frequent occurrence of lung cancer as second or more primary cancers, and the occurrence of distinctive tumor tissues, such as the phyllodes tumor and liver sarcoma, which may provide useful information for clinical LFS management in Japan. Furthermore, in our study, 6 of 15 (40.0%) patients with breast cancer showed simultaneous or metachronous bilateral primary cancers. This finding may also provide benefits for screening to reduce an elevated risk of contralateral breast cancer or considering the option of bilateral mastectomies, which are consistent with those of patients with breast cancer carrying *BRCA 1/2* germline pathogenic variants.[72]

The findings of this study have several limitations. First, this study must be interpreted based on the method of collection of study subjects. Although previous reports on the spectrum and frequency of cancers in patients with *TP53* germline variants have provided detailed information through registration or follow-up studies,[8,17] our analysis was mainly based on a heterogeneous group of collected cases through searching databases and self-analyzed cases. Thus, there is ascertainment bias in our study, and an old piece of information was not available in detail. However, we believe that most cases of *TP53* germline variants have been reported from inquiring about LFS experiences in Japan before the widespread use of next-generation DNA sequencing. In addition, the LFS Special Committee–related parties have been consulted for the majority of patients with LFS in Japan and have performed genetic testing. Next, in our study, the data of 128 cancers between 1992 and 2016 were compared with those of the French LFS working group comprising 548 cancers between 1993 and 2013. In this respect, we do not expect this limitation to have biased our results because both studies had some similarities, such as codon distribution and effect of *TP53* germline variants, age at the first tumor onset, frequency of patients with multiple primary tumors, and time of occurrence of second tumors. In the future, the variable phenotype, diverse tumor spectrum, diagnostic tumor tissue patterns, and other characteristics should be further investigated by accumulating many cases with *TP53* germline variants through patient registration, which will result in better LFS management.

In conclusion, we described *TP53* variant patterns and tumor characteristics in patients with *TP53* germline variants in Japan. Although we could recognize some unique findings of the LFS characteristics in Japan through this study, these need to be further investigated through clinical cohort studies and basic research on LFS. These findings will provide clues for clinical management measures, such as genetic counseling, genetic testing, and healthcare management.

ACKNOWLEDGMENTS

Professor Hiroshi Yagata (Saitama Medical University), who passed away before this paper was submitted, made a great contribution to the research on breast cancer occurring in Li-Fraumeni syndrome and its surveillance. We would like to express our deep appreciation for him. In addition, we greatly appreciate the patients and their families who cooperated with us for this study. We also thank Dr J. Toguchida (Kyoto University), Dr T. Oka (Asahikawa Medical University), Dr M. Tokunaga (Kagoshima Municipal Hospital), Dr T. Kawaguchi (Kumamoto University), Dr M. Tsurusawa (Aichi Medical University), Dr T. Yonemoto (Chiba Cancer Center), Dr M. Yano (Akita University), Dr H. Tsuchiya (Kanazawa University), Dr R. Fukano (Kyusyu Cancer Center), Dr M. Kouroki (Kumamoto University), Dr K. Ishiguro (Tottori University), Dr H. Ogi (Kumamoto University), Dr T. Matsubara (Mie University), Dr A. Matsumine (Mie University), Dr J. Yoshimura (Niigata University), Dr T. Iwai (Kagawa Children Hospital), Dr H. Maeda (Fukui University), Dr N. Kagawa (Osaka University), Dr H. Uchida (Kagoshima University), Dr T. Yoshikawa (Fujita Medical University), Dr S. Sugihara (Shikoku Cancer Center), Dr. S. Nakamura (Showa University), Dr. H. Yamagami (Sapporo-Kosei General Hospital), Dr. M. Yanagimachi (Yokohama City University), Dr. M. Yamauchi (St. Luke's International Hospital) for providing the clinical information and Dr S. Kojima (Nagoya University), Dr S. Mizutani (Tokyo Medical Dental University), Dr M. Tsurusawa (Aichi Medical University), Dr K. Osafune (Kyoto University), and Dr H. Kaneko (Nagara Medical Center) for providing advice on this study. We also thank the Japanese Society of Hereditary Tumors (JSHT) for their strong support as the backbone of our Li-Fraumeni Working Group. We would like to thank Editage (www.editage.com) for English language editing.

DISCLOSURE

The authors declare to have no potential conflict of interest to disclose.

ORCID

Michinori Funato https://orcid.org/0000-0001-8836-8333
Yukiko Tsunematsu https://orcid.org/0000-0002-3278-2911
Fumito Yamazaki https://orcid.org/0000-0002-3579-634X
Chieko Tamura https://orcid.org/0000-0002-7496-4289
Tadashi Kumamoto https://orcid.org/0000-0001-7325-5950
Masatoshi Takagi https://orcid.org/0000-0002-7580-9184
Shunsuke Kato https://orcid.org/0000-0002-4860-1687
Haruhiko Sugimura https://orcid.org/0000-0002-0779-3088
Kazuo Tamura https://orcid.org/0000-0002-1087-9851

REFERENCES

1. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? *Ann Intern Med*. 1969;71:747-752.
2. Li FP, Fraumeni JF Jr, Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res*. 1988;48:5358-5362.
3. Malkin D, Li FP, Strong LC, et al. Germ line *p53* mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science*. 1990;250:1233-1238.
4. Bouaoun L, Sonkin D, Ardin M, et al. *TP53* variations in human cancers: new lessons from the IARC *TP53* database and genomics data. *Hum Mutat*. 2016;37:865-876.
5. Masciari S, Dewanwala A, Stoffel EM, et al. Gastric cancer in individuals with Li-Fraumeni syndrome. *Genet Med*. 2011;13:651-657.
6. Wong P, Verselis SJ, Garber JE, et al. Prevalence of early onset colorectal cancer in 397 patients with classic Li-Fraumeni syndrome. *Gastroenterology*. 2006;130:73-79.
7. Ruijs MW, Verhoef S, Rookus MA, et al. *TP53* germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. *J Med Genet*. 2010;47:421-428.
8. Nichols KE, Malkin D, Garber JE, Fraumeni JF Jr, Li FP. Germ-line *p53* mutations predispose to a wide spectrum of early-onset cancers. *Cancer Epidemiol Biomarkers Prev*. 2001;10:83-87.
9. Masciari S, Dillon DA, Rath M, et al. Breast cancer phenotype in women with *TP53* germline mutations: a Li-Fraumeni syndrome consortium effort. *Breast Cancer Res Treat*. 2012;133:1125-1130.
10. Birch JM, Alston RD, McNally RJ, et al. Relative frequency and morphology of cancers in carriers of germline *TP53* mutations. *Oncogene*. 2001;20:4621-4628.
11. Giacomazzi J, Koehler-Santos P, Palmero EI, et al. A *TP53* founder mutation, p.R337H, is associated with phyllodes breast tumors in Brazil. *Virchows Arch*. 2013;463:17-22.
12. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet*. 2013;45:242-252.
13. Hettmer S, Archer NM, Somers GR, et al. Anaplastic rhabdomyosarcoma in *TP53* germline mutation carriers. *Cancer*. 2014;120:1068-1075.
14. Zhukova N, Ramaswamy V, Remke M, et al. Subgroup-specific prognostic implications of *TP53* mutation in medulloblastoma. *J Clin Oncol*. 2013;31:2927-2935.
15. Chompret A, Abel A, Stoppa-Lyonnet D, et al. Sensitivity and predictive value of criteria for *p53* germline mutation screening. *J Med Genet*. 2001;38:43-47.
16. Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni syndrome: clinical characteristics of families with *p53* germline mutations. *J Clin Oncol*. 2009;27:1250-1256.
17. Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from *TP53* mutation carriers. *J Clin Oncol*. 2015;33:2345-2352.
18. Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among *TP53* mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer*. 2016;122:3673-3681.
19. Susswein LR, Marshall ML, Nusbaum R, et al. Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. *Genet Med*. 2016;18:823-832.
20. LaDuca H, Polley EC, Yussuf A, et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. *Genet Med*. 2020;22:407-415.
21. Coffee B, Cox HC, Kidd J, et al. Detection of somatic variants in peripheral blood lymphocytes using a next generation sequencing multigene pan cancer panel. *Cancer Genet*. 2017;211:5-8.
22. Yang S, Lincoln SE, Kobayashi Y, Nykamp K, Nussbaum RL, Topper S. Sources of discordance among germ-line variant classifications in ClinVar. *Genet Med*. 2017;19:1118-1126.
23. Bittar CM, Vieira IA, Sabato CS, et al. TP53 variants of uncertain significance: increasing challenges in variant interpretation and genetic counseling. *Fam Cancer*. 2019;18:451-456.
24. Ballinger ML, Best A, Mai PL, et al. Baseline surveillance in Li-Fraumeni syndrome using whole-body magnetic resonance imaging: a meta-analysis. *JAMA Oncol*. 2017;3:1634-1639.

25. Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: a prospective observational study. *Lancet Oncol*. 2011;12:559-567.
26. Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol*. 2016;17:1295-1305.
27. Sameshima Y, Tsunematsu Y, Watanabe S, et al. Detection of novel germ-line *p53* mutations in diverse-cancer-prone families identified by selecting patients with childhood adrenocortical carcinoma. *J Natl Cancer Inst*. 1992;84:703-707.
28. Toguchida J, Yamaguchi T, Dayton SH, et al. Prevalence and spectrum of germline mutations of the *p53* gene among patients with sarcoma. *N Engl J Med*. 1992;326:1301-1308.
29. Shiseki M, Nishikawa R, Yamamoto H, et al. Germ-line *p53* mutation is uncommon in patients with triple primary cancers. *Cancer Lett*. 1993;73:51-57.
30. Horio Y, Suzuki H, Ueda R, et al. Predominantly tumor-limited expression of a mutant allele in a Japanese family carrying a germline *p53* mutation. *Oncogene*. 1994;9:1231-1235.
31. Saeki Y, Tamura K, Yamamoto Y, Hatada T, Furuyama J, Utsunomiya J. Germline *p53* mutation at codon 133 in a cancer-prone family. *J Mol Med*. 1997;75:50-56.
32. Murakawa Y, Yokoyama A, Kato S, et al. Astrocytoma and B-cell lymphoma development in a man with a *p53* germline mutation. *Jpn J Clin Oncol*. 1998;28:631-637.
33. Konno K, Iwata N, Agata H, Hirota T, Tsurusawa M, Fujimoto T. A Li-Fraumeni syndrome family. *Jpn J Pediatr Soc*. 1999;103:563-566.
34. Sugano K, Taniguchi T, Saeki M, Tsunematsu Y, Tomaru U, Shimoda T. Germline *p53* mutation in a case of Li-Fraumeni syndrome presenting gastric cancer. *Jpn J Clin Oncol*. 1999;29:513-516.
35. Kimura K, Shinmura K, Hasegawa T, Beppu Y, Yokoyama R, Yokota J. Germline *p53* mutation in a patient with multiple primary cancers. *Jpn J Clin Oncol*. 2001;31:349-351.
36. Miyaki M, Iijima T, Ohue M, et al. A novel case with germline *p53* gene mutation having concurrent multiple primary colon tumours. *Gut*. 2003;52:304-306.
37. Yonemoto T, Tatezaki S, Ishii T, Hagiwara Y, Inoue M. Multiple primary cancers in patients with osteosarcoma: influence of anticancer drugs and genetic factors. *Am J Clin Oncol*. 2004;27:220-224.
38. Nagasaki K, Horikawa R, Nagaishi J, et al. Virilizing adrenocortical carcinoma invading the right atrium with histological high-grade malignancy and *p53* mutation in a 3-year-old child: indication of post operative adjuvant chemotherapy. *Clin Pediatr Endocrinol*. 2004;13:25-32.
39. Kuribayashi K, Matsunaga T, Sakai T, et al. A patient with *TP53* germline mutation developed Bowen's disease and myelodysplastic syndrome with myelofibrosis after chemotherapy against ovarian cancer. *Intern Med*. 2005;44:490-495.
40. Tamura K, Sakagami T, Tsuda S, et al. A case of multiple primary malignant tumors with germline mutation of the *TP53* gene. *J Fam Tumor*. 2006;6:53-57.
41. Yamada H, Shinmura K, Okudela K, et al. Identification and characterization of a novel germ line *p53* mutation in familial gastric cancer in the Japanese population. *Carcinogenesis*. 2007;28:2013-2018.
42. Izawa N, Matsumoto S, Manabe J, et al. A Japanese patient with Li-Fraumeni syndrome who had nine primary malignancies associated with a germline mutation of the *p53* tumor-suppressor gene. *Int J Clin Oncol*. 2008;13:78-82.
43. Yamada H, Shinmura K, Yamamura Y, et al. Identification and characterization of a novel germline *p53* mutation in a patient with glioblastoma and colon cancer. *Int J Cancer*. 2009;125:973-976.
44. Momota H, Narita Y, Miyakita Y, Hosono A, Makimoto A, Shibui S. Acute lymphoblastic leukemia after temozolomide treatment for anaplastic astrocytoma in a child with a germline *TP53* mutation. *Pediatr Blood Cancer*. 2010;55:577-579.
45. Ide H, Terado Y, Tokiwa S, et al. Novel germ line mutation *p53*–P177R in adult adrenocortical carcinoma producing neuron-specific enolase as a possible marker. *Jpn J Clin Oncol*. 2010;40:815-818.
46. Sugawara W, Arai Y, Kasai F, et al. Association of germline or somatic *TP53* missense mutation with oncogene amplification in tumors developed in patients with Li-Fraumeni or Li-Fraumeni-like syndrome. *Genes Chromosomes Cancer*. 2011;50:535-545.
47. Kato T, Ishikawa K, Satoh M, Kondo S, Kaji M. Pleomorphic carcinoma of the lung arising in a patient with Li-Fraumeni syndrome: report of a case. *Surg Today*. 2011;41:841-845.
48. Osumi T, Miharu M, Fuchimoto Y, Morioka H, Kosaki K, Shimada H. The germline *TP53* mutation c.722 C>T promotes bone and liver tumorigenesis at a young age. *Pediatr Blood Cancer*. 2012;59:1332-1333.
49. Piao J, Sakurai N, Iwamoto S, et al. Functional studies of a novel germline *p53* splicing mutation identified in a patient with Li-Fraumeni-like syndrome. *Mol Carcinog*. 2013;52:770-776.
50. Yoshimura J, Natsumeda M, Nishihira Y, et al. Radiation-induced intracranial osteosarcoma after radiation for acute lymphocytic leukemia associated with Li-Fraumeni syndrome. *No Shinkei Geka*. 2013;41:499-505.
51. Tanaka S, Ohsumi S, Kiyotou S, et al. A case of early lung cancer detected by surveillance PET/CT for Li-Fraumeni syndrome. *J Fam Tumor*. 2017;1:22-25.
52. Fujisawa Y, Sakaguchi K, Ono H, et al. Combined steroidogenic characters of fetal adrenal and Leydig cells in childhood adrenocortical carcinoma. *J Steroid Biochem Mol Biol*. 2016;159:86-93.
53. Matsuoka T, Shinozaki H, Ozawa H, et al. Juvenile rectal cancer in a family with Li-Fraumeni syndrome. *Jpn J Gastroenterol Surg*. 2016;49:1170-1178.
54. Yamazaki F, Shima H, Osumi T, Narumi S, Kuroda T, Shimada H. Nodular Lymphocyte-predominant Hodgkin Lymphoma in a 15-year-old boy with Li-Fraumeni syndrome having a germline *TP53* D49H mutation. *J Pediatr Hematol Oncol*. 2018;40:e195-e197.
55. Fortuno C, Lee K, Olivier M, et al. ClinGen TP53 variant curation expert panel. Specifications of the ACMG/AMP variant interpretation guidelines for germline TP53 variants. *Hum Mutat*. 2020; Epub ahead of print.
56. Kato S, Han SY, Liu W, et al. Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. *Proc Natl Acad Sci USA*. 2003;100:8424-8429.
57. Giacomelli AO, Yang X, Lintner RE, et al. Mutational processes shape the landscape of TP53 mutations in human cancer. *Nat Genet*. 2018;50:1381-1387.
58. Fortuno C, Cipponi A, Ballinger ML, et al. A quantitative model to predict pathogenicity of missense variants in the TP53 gene. *Hum Mutat*. 2019;40:788-800.
59. Bougeard G, Sesboüé R, Baert-Desurmont S, et al. Molecular basis of the Li-Fraumeni syndrome: an update from the French LFS families. *J Med Genet*. 2008;45:535-538.
60. Palmero EI, Schüler-Faccini L, Caleffi M, et al. Detection of R337H, a germline *TP53* mutation predisposing to multiple cancers, in asymptomatic women participating in a breast cancer screening program in Southern Brazil. *Cancer Lett*. 2008;261:21-25.
61. Dearth LR, Qian H, Wang T, et al. Inactive full-length p53 mutants lacking dominant wild-type p53 inhibition highlight loss of heterozygosity as an important aspect of p53 status in human cancers. *Carcinogenesis*. 2007;28:289-298.
62. Monti P, Perfumo C, Bisio A, et al. Dominant-negative features of mutant TP53 in germline carriers have limited impact on cancer outcomes. *Mol Cancer Res*. 2011;9:271-279.
63. Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and *TP53* genotype. *Cancer Res*. 2003;63:6643-6650.

64. Ikenoue T, Arai M, Ishioka C, et al. Importance of gastric cancer for the diagnosis and surveillance of Japanese Lynch syndrome patients. *J Hum Genet*. 2019;64:1187-1194.
65. Ariffin H, Chan AS, Oh L, et al. Frequent occurrence of gastric cancer in Asian kindreds with Li-Fraumeni syndrome. *Clin Genet*. 2015;88:450-455.
66. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends–an update. *Cancer Epidemiol Biomarkers Prev*. 2016;25:16-27.
67. Varley JM, McGown G, Thorncroft M, et al. Are there low-penetrance *TP53* Alleles? Evidence from childhood adrenocortical tumors. *Am J Hum Genet*. 1999;65:995-1006.
68. Libé R, Bertherat J. Molecular genetics of adrenocortical tumours, from familial to sporadic diseases. *Eur J Endocrinol*. 2005;153:477-487.
69. Raymond VM, Else T, Everett JN, Long JM, Gruber SB, Hammer GD. Prevalence of germline *TP53* mutations in a prospective series of unselected patients with adrenocortical carcinoma. *J Clin Endocrinol Metab*. 2013;98:E119-125.
70. Gozali AE, Britt B, Shane L, et al. Choroid plexus tumors; management, outcome, and association with the Li-Fraumeni syndrome: the Children's Hospital Los Angeles (CHLA) experience, 1991–2010. *Pediatr Blood Cancer*. 2012;58:905-909.
71. Lack EE, Schloo BL, Azumi N, Travis WD, Grier HE, Kozakewich HP. Undifferentiated (embryonal) sarcoma of the liver. Clinical and pathologic study of 16 cases with emphasis on immunohistochemical features. *Am J Surg Pathol*. 1991;15:1-16.
72. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*. 2017;317:2402-2416.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Funato M, Tsunematsu Y, Yamazaki F, et al. Characteristics of Li-Fraumeni syndrome in Japan: A review study by the special committee of JSHT. *Cancer Sci*. 2021;112:2821–2834. https://doi.org/10.1111/cas.14919