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Li-Fraumeni Syndrome

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Summary

Clinical characteristics

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with high risks for a broad spectrum of cancers including early-onset cancers. Five cancer types account for the majority of LFS tumors: adrenocortical carcinomas, breast cancer, central nervous system tumors, osteosarcomas, and soft-tissue sarcomas. Other cancers associated with LFS include leukemia, colorectal cancer, stomach cancer, lung cancer, melanoma, pediatric head and neck cancers, pancreatic cancer, and prostate cancer. Cancer survivors are at increased risk for developing additional primary cancers and treatment-related secondary cancers. The lifetime risks of cancer for women and men with classic LFS are 90% and 70%, respectively, and 50% of cancers occur prior to age 40 years.

Diagnosis/testing

The clinical diagnosis of LFS can be established in a proband who meets clinical diagnostic criteria, or the molecular diagnosis is established in a proband with a germline pathogenic variant in *TP53* identified by molecular genetic testing.

Management

Treatment of manifestations: Bilateral mastectomy rather than lumpectomy is often recommended for LFS-related breast cancer to reduce the risk of a second primary breast cancer and to avoid radiation therapy. Radiation therapy should be avoided if possible with treatment of other cancers, to reduce the risk of secondary malignancies. Conventional cytotoxic chemotherapy may also pose an increased secondary cancer risk; however, treatment efficacy should be prioritized above concerns about late effects. Otherwise, standard oncologic management is recommended.

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Prevention of primary manifestations: Risk-reducing bilateral mastectomy to reduce the risk for breast cancer is an option for women with LFS; colonoscopy may be considered as surveillance as well as primary prevention of colorectal cancer; dermatologic surveillance can be used to detect and remove premalignant lesions.

Surveillance: Comprehensive physical examination and ultrasound of abdomen and pelvis every three to four months from birth to age 18 years; comprehensive physical examination every six months in those older than age 18 years; annual whole-body MRI; females should have a clinical breast examination every six to 12 months beginning at age 20-25 years, annual breast MRI starting between age 20-30 years, and annual mammogram alternating with breast MRI from age 30 to 75 years; annual brain MRI; upper endoscopy and colonoscopy every two to five years beginning at age 25 years; annual dermatologic exam beginning at age 18 years; annual ultrasound of the abdomen and pelvis beginning at age 18 years; consider additional screening for lung, pancreatic, prostate, and thyroid cancer depending on family history and additional risk factors; assess social work and genetic counseling needs at each visit.

Agents/circumstances to avoid: Minimize exposure to diagnostic and therapeutic radiation; avoid known carcinogens including unprotected sun exposure, tobacco use, occupational exposures, and excessive alcohol use.

Evaluation of relatives at risk: If a molecular diagnosis of LFS has been established in the proband, offer *TP53* molecular genetic testing to all first-degree relatives (including children) and other relatives in order to identify individuals with LFS who would benefit from increased cancer monitoring, with attention to symptoms or signs of cancer and early intervention when a cancer or precancer is identified. If a clinical diagnosis of LFS has been established in the proband but the proband does not have an identified *TP53* pathogenic variant, all at-risk family members should be counseled regarding their potential increased risks for LFS-related cancers and options for surveillance and risk reduction.

Genetic counseling

LFS is inherited in an autosomal dominant manner. Most individuals diagnosed with LFS inherited a *TP53* pathogenic variant from a parent. Some individuals diagnosed with LFS have the disorder as the result of a *de novo* germline pathogenic variant. The frequency of *de novo* pathogenic variants is estimated at between 7% and 20%. Each child of an individual with a molecular diagnosis of LFS has a 50% risk of inheriting the *TP53* pathogenic variant; each child of an individual with a clinical diagnosis of LFS (in whom a *TP53* pathogenic variant has not been identified) is presumed to have an increased risk for LFS. If a *TP53* pathogenic variant has been identified in an affected family member, predictive testing for at-risk family members and prenatal/preimplantation genetic testing are possible.

Diagnosis

Consensus clinical diagnostic criteria for Li-Fraumeni syndrome (LFS) have been published [Li & Fraumeni 1969].

Suggestive Findings

LFS **should be suspected** in probands who meet modified Chompret criteria or have any additional suggestive findings.

Modified Chompret criteria [Bougeard et al 2015]:

- A proband with a tumor belonging to the classic LFS tumor spectrum (e.g., premenopausal breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system [CNS] tumor, adrenocortical carcinoma

[ACC]) before age 46 years **AND** at least one first- or second-degree relative with a classic LFS tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors; **OR**
- A proband with multiple tumors (except multiple breast tumors), two of which belong to the classic LFS tumor spectrum and the first of which occurred before age 46 years; **OR**
- A proband with ACC, choroid plexus tumor, or rhabdomyosarcoma (embryonal anaplastic subtype), irrespective of family history; **OR**
- A proband with breast cancer before age 31 years

Additional suggestive findings:

- Human epidermal growth factor receptor 2 (HER2)-positive breast cancer before age 40 years [Fortuno et al 2020]
- Pediatric low-hypodiploid acute lymphoblastic leukemia (ALL) [Holmfeldt et al 2013, Frebourg et al 2020]
- Pediatric unexplained sonic hedgehog-activated medulloblastoma or jaw osteosarcoma that is not explained by another tumor predisposition syndrome, such as nevoid basal cell carcinoma syndrome [Waszak et al 2018, Frebourg et al 2020].
- Second primary tumor occurring within the radiation field following treatment of a classic LFS tumor, with the initial tumor diagnosed before age 46 years [Frebourg et al 2020]
- Any pediatric cancer in an individual of southern or southeastern Brazilian ancestry (See Establishing the Diagnosis, **Single-gene testing**.)
- The identification of a *TP53* pathogenic variant in the tumor tissue of an adult with cancer who also has family history suggestive of LFS or in a child with cancer regardless of family history [MacFarland et al 2019b, Frebourg et al 2020]

Establishing the Diagnosis

Clinical diagnosis. A clinical diagnosis of LFS **can be established** in a proband who meets ALL THREE classic LFS criteria [Li & Fraumeni 1969]:

- A proband with a sarcoma diagnosed before age 45 years;
- A first-degree relative with any cancer diagnosed before age 45 years;
- A first- or second-degree relative with any cancer diagnosed before age 45 years or a sarcoma diagnosed at any age.

Molecular diagnosis. The molecular diagnosis of LFS **is established** in a proband with a heterozygous germline pathogenic (or likely pathogenic) variant in *TP53* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *TP53* variant of uncertain significance does not establish or rule out the diagnosis. (3) Identification of low-level mosaicism for a *TP53* pathogenic variant in leukocytes is suggestive of a postzygotic (acquired) pathogenic variant. Variants at allele frequencies in the heterozygous range may also be acquired, and clinical evaluation should guide further testing to determine if a pathogenic variant is constitutional or somatic [Coffee et al 2020, Schwartz et al 2021, Castillo et al 2022] (see also www.nccn.org; subscription required).

Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Molecular analysis of *TP53* includes sequence analysis to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions and gene-targeted deletion/duplication analysis.

Note: Targeted testing for the *TP53* p.Arg337His founder variant can be considered first in individuals of southern and southeastern Brazilian ancestry [Frebourg et al 2020].

- **A multigene panel** that includes *TP53* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Hereditary cancer multigene panels typically include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Li-Fraumeni Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
TP53	Sequence analysis [3]	89% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	1% [7]
Unknown [8]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Guha & Malkin [2017]
5. Sequence analysis of the entire *TP53* coding region (exons 2-11) detects about 95% of *TP53* pathogenic variants, most of which are missense variants.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. LFS can be caused by a deletion involving the coding region of *TP53* or the promoter and noncoding exon [Guha & Malkin 2017].
8. To date, *TP53* is the only gene known to be associated with LFS. However, a germline pathogenic variant is detected in only 90% of individuals who meet classic LFS criteria and 50% of individuals who meet modified Chompret criteria [Bougeard et al 2015, Guha & Malkin 2017].

Clinical Characteristics

Clinical Description

Li-Fraumeni syndrome (LFS) is associated with a high risk for a broad spectrum of cancers. The five core LFS-related cancers are adrenocortical carcinomas (ACC), breast cancer, central nervous system (CNS) tumors, osteosarcomas, and soft-tissue sarcomas [Evans & Woodward 2021]. The risk of any type of cancer by age 50 years in an international study of 4,028 individuals with LFS was 92.4% in women and 59.7% in men [Fortuno et al 2024]. In one study, the most frequent first cancer was breast cancer for women and CNS and soft-tissue sarcoma for men [de Andrade et al 2021]. The most frequent cancers by age group include the following [Amadou et al 2018, Shin et al 2020]:

- Childhood (age 0-15 years): ACC, choroid plexus carcinoma, rhabdomyosarcoma, and medulloblastoma

- Adolescent to adulthood (16-50 years): breast cancer, osteosarcoma, soft-tissue sarcoma, leukemia, astrocytoma, glioblastoma, colorectal cancer, and lung cancer
- Late adulthood (51-80 years): pancreatic cancer and prostate cancer

ACC develops in 6%-13% of individuals with LFS most often as a pediatric cancer [Bougeard et al 2015]. ACC can also occur in adulthood, typically before age 40 years [Mai et al 2016]. The southern Brazilian *TP53* founder variant p.Arg337His is associated with a very high risk of pediatric ACC. In one series of individuals with *TP53* pathogenic variant p.Arg337His, ACC accounted for 55% of childhood cancers and 23% of adult-onset cancers [Ferreira et al 2019].

Breast cancer risk for females with LFS is 80%-90%, which is higher than the lifetime risk associated with *BRCA1*- and *BRCA2*-related hereditary breast cancer [Mai et al 2016, Blondeaux et al 2023]. Breast cancer risk is based on assigned sex at birth but may also be influenced by gender-affirming treatment. LFS-related breast cancers occur at a younger age, with almost all breast cancers in women with LFS occurring prior to menopause [Bougeard et al 2015]. LFS-related breast cancers are more likely to be ductal, estrogen receptor and progesterone receptor positive, and show human epidermal growth factor receptor 2 (HER2) amplification [Melhem-Bertrandt et al 2012, Kuba et al 2021, Sandoval et al 2022]. Studies have indicated significantly higher rates of ipsilateral breast cancer with breast-conserving surgery, higher rates of contralateral breast cancer, and lower rates of relapse-free survival in individuals with LFS-related breast cancer compared to other individuals with breast cancer [Hyder et al 2020, Sheng et al 2020, Evans & Woodward 2021, Guo et al 2022]. Men with LFS do not appear to have an increased risk of breast cancer, though male breast cancer has been reported [Mai et al 2016, Shin et al 2020]. In women, malignant phyllodes breast tumors are associated with LFS [Villani et al 2016].

CNS tumors account for 9%-14% of LFS cancers [Bougeard et al 2015]. In one series, the cumulative incidence of CNS tumors by age 70 years was 6% for women and 19% for men [Mai et al 2016]. The age of onset of CNS tumors is biphasic with both childhood and adult onset, often before age 40 years (median age: 16 years) [Valdez et al 2017]. Glioblastomas and astrocytomas are the most common CNS tumor types in individuals with LFS, although many other CNS tumor types have been reported, including ependymomas, choroid plexus carcinomas, supratentorial primitive neuroectodermal tumors, and medulloblastomas [Bougeard et al 2015, Valdez et al 2017]. LFS-related medulloblastomas are more likely to be of the sonic hedgehog-activated subtypes [Waszak et al 2018].

Osteosarcomas account for up to 16% of LFS cancers. Occurrence of osteosarcoma is highest in childhood and adolescence; however, osteosarcoma diagnosis in adulthood is also reported [Bougeard et al 2015]. In one series, the cumulative incidence of bone cancers by age 70 years was 5% for women and 11% for men [Mai et al 2016].

Soft-tissue sarcomas, especially rhabdomyosarcoma, are the most common LFS cancers in children and account for 17%-27% of the total cancers occurring in individuals with LFS [Bougeard et al 2015]. In one series, the cumulative incidence of soft-tissue sarcoma was 15% for women and 22% for men [Mai et al 2016]. The highest risk of rhabdomyosarcoma is between ages 0-15 years; however, rhabdomyosarcoma can also occur at older ages.

Leukemia occurs in about 4% of individuals with LFS [Bougeard et al 2015]. The risk of leukemia seems highest from ages 0 to 15 years but can occur at any age. Low-hypodiploid acute lymphoblastic leukemia (ALL), in which leukemic blasts have 32-39 chromosomes, is the most common hematologic malignancy in individuals with LFS; B-cell ALL is also common [Qian et al 2018, Swaminathan et al 2019, Winter et al 2021]. Other forms of leukemia include acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), which can occur as primary cancers or secondary treatment-related cancers. Adults may also develop treatment-related chronic myeloid leukemia (CML). There is an increased risk of therapy-related leukemia and MDS with the use of cytotoxic agents and/or radiation therapy. Individuals with LFS-related leukemia may have shorter clinical responses and poorer outcomes compared to other individuals with leukemia [Swaminathan et al 2019].

Gastrointestinal (GI) cancers account for about 5.1% of malignancies in individuals with LFS; 2.8% of individuals have colorectal cancer and 1.3% have esophageal or gastric cancer [Hatton et al 2024]. Gastroesophageal junction (GEJ) cancer has also been reported in individuals with LFS [Tjandra & Boussioutas 2024]. GI cancers in individuals with LFS tend to occur at a younger age than in those without LFS [Yurgelun et al 2015, Rengifo-Cam et al 2018, Hatton et al 2024]. The risk of LFS-related gastric cancer is higher in individuals of Japanese and other Asian ancestry, likely due to dietary risk factors and higher incidence of *H pylori* infection [Ariffin et al 2015, Funato et al 2021]. There also appears to be an increased risk of pancreatic cancer in individuals with LFS [Amadou et al 2018].

Other cancers. Individuals with LFS are reported to have an increased risk of early-onset lung cancer, often with increased frequency of somatic *EGFR* pathogenic variants [Benusiglio et al 2021, Kerrigan et al 2021]. An increased risk of melanoma [Hatton et al 2022, Sandru et al 2022], lymphoma [Bougeard et al 2015], and prostate cancer have been reported [Maxwell et al 2022] There may also be an increased risk of kidney, larynx, non-melanoma skin, ovary, testis, and thyroid cancer [Mai et al 2016, Valdez et al 2017].

Gestational choriocarcinoma. Gestational choriocarcinoma or other gestational trophoblastic disease has been reported in women with LFS and in women (without LFS) carrying a fetus with a paternally inherited *TP53* pathogenic variant [Brehin et al 2018, Cotter et al 2018].

Excess of early-onset cancers. In one series, the average onset of first cancer for men with LFS was age 17 years; the average onset of first cancer for women was age 28 years when including breast cancer and age 13 years when excluding breast cancer [Bougeard et al 2015]. In another series, it was estimated that 50% of LFS-related cancers occurred by age 30-31 years in women and age 46 in men [Mai et al 2016].

Excess of multiple primary cancers. Individuals with LFS have up to 50% risk of developing a second cancer (median onset: 10 years after the first cancer diagnosis). Radiation and chemotherapy treatment of an LFS-related cancer may increase the risk of a second malignancy [Mai et al 2016, Schon & Tischkowitz 2018, Swaminathan et al 2019].

Prognosis. In one study, LFS-related breast cancer was associated with lower rates of recurrence-free survival and overall survival compared to other individuals with breast cancer [Sheng et al 2020]. There may also be poorer outcomes in LFS-related leukemia compared to leukemia in other individuals [Swaminathan et al 2019].

Genotype-Phenotype Correlations

There continues to be debate regarding genotype-phenotype correlations in LFS.

Nonsense, frameshift, and missense pathogenic variants that cause complete loss of p53 function or a dominant-negative effect are associated with a more severe phenotype compared to pathogenic variants that cause partial loss of p53 function [Rana et al 2019, de Andrade et al 2021, Rocca et al 2022]. The more severe phenotype is associated with an earlier onset of first cancer, higher incidence of breast cancer and other cancers, and a greater likelihood of meeting classic or modified Chompret criteria [Fortuno et al 2019, Rana et al 2019]. The six most common *TP53* pathogenic variants that cause complete loss of function or a dominant-negative effect lie in the DNA-binding domain and include p.Arg175His, p.Gly245Ser, p.Arg248Gln, p.Arg248Trp, p.Arg273His, and p.Arg282Trp [Wasserman et al 2015, Fortuno et al 2019]. In a report from the German LFS registry, the incidence of childhood cancers was significantly lower in individuals with *TP53* pathogenic variants that resulted in partial loss of p53 function [Penkert et al 2022].

TP53 pathogenic variant p.Arg337His, a founder variant in southern and southeastern Brazil, is associated with a high risk of childhood-onset ACC. Additional LFS-associated cancers have been reported in individuals with p.Arg337His; however, these cancers tend to occur at an older age and with decreased frequency compared to individuals with other *TP53* pathogenic variants [Ferreira et al 2019]. Maternal inheritance of p.Arg337His was

identified in 72% of individuals, suggesting preferential selection. One individual who was homozygous for p.Arg337His had a clinical phenotype that did not appear to differ from p.Arg337His heterozygotes [Ferreira et al 2019, Seidinger et al 2020].

Additional missense pathogenic variants are associated with lower risk of cancer and older age of onset compared to other *TP53* pathogenic variants [Fortuno et al 2019, de Andrade et al 2021], including the following variants: p.Pro47Ser, p.Gly334Arg, p.Asp49His, Arg181Cys, p.Arg181His, and c.*1175A>C [Fischer et al 2023, Arnon et al 2024].

One study suggested that p.Pro152Leu is a reduced-penetrance variant [Evans et al 2023].

Penetrance

Penetrance in LFS is variable and is partially due to the type of pathogenic variant (see Genotype-Phenotype Correlations). For classic LFS, there is an 80% risk of cancer by age 70, with 22% of the cancers occurring between ages 0 and 15 years, 51% between ages 16 and 50 years, and 27% between ages 51 and 80 years [Amadou et al 2018]. However, low-penetrance *TP53* pathogenic variants have been identified (see Genotype-Phenotype Correlations) [Ferreira et al 2019, de Andrade et al 2021, Penkert et al 2022]. Some *TP53* variants that are suspected to be associated with low penetrance may have discordant variant classifications among different laboratories [Kratz et al 2021]. A study of 140 families with LFS found that affected individuals from 11% of families had a *TP53* variant with clinically significant discordant classifications (e.g., variant of uncertain significance vs likely pathogenic variant) [Frone et al 2021]. Management recommendations for individuals with low-penetrance variants is evolving.

Genetic Modifiers

Genetic modifiers of LFS-associated cancer risk include the following:

- ***TP53* p.Arg72Pro polymorphism.** The p.Arg72Pro (c.215G>C) (rs1042522) polymorphism causes increased affinity toward MDM2, resulting in higher levels of p53 degradation and earlier onset of first cancer [Guha & Malkin 2017].
- ***MDM2* c.14+309T>G variant.** The presence of the NM_002392.2:c.14+309G>T (rs2279744) variant in the *MDM2* promoter region leads to increased MDM2 expression, resulting in higher levels of p53 degradation and earlier onset of first cancer [Guha & Malkin 2017, Amadou et al 2018].
- ***MIR605* n.74T>C variant.** The presence of NM_030336.1:n.74T>C variant in *MIR605*, which regulates the p53-MDM2 loop, has resulted in a ten-year accelerated mean age of tumor onset [Guha & Malkin 2017, Amadou et al 2018, Bandeira et al 2020].
- **16-base pair duplication polymorphism in intron 3 of *TP53* (PIN3; rs17878362).** The presence of the 16-base pair duplication appears to be protective, with older ages of first cancer compared to individuals who do not have this duplication [Guha & Malkin 2017, Amadou et al 2018].
- ***XAF1* p.Glu134Ter variant.** Individuals who are double heterozygotes for the *XAF1* NP_059993.2:p.Glu134Ter variant and the *TP53* p.Arg337His pathogenic variant have a more aggressive phenotype with higher cancer risks [Pinto et al 2020].
- **Shortened telomere length.** Shortened telomere length over subsequent generations has been associated with accelerated tumor development (anticipation) in families with LFS [Guha & Malkin 2017]. The association between telomere erosion and earlier cancer onset continues to be studied.

Additional epigenetic modifiers are being investigated, including variants in the WNT signaling pathway, which appear to decrease cancer risk, and inherited epimutations in *ASXL1*, *ETV6*, and *LEF1*, which appear to increase cancer risk in individuals with germline *TP53* pathogenic variants [Subasri et al 2023].

Nomenclature

As the clinical and molecular definitions of LFS have expanded, alternate terms have been proposed, including "Li-Fraumeni spectrum" and "heritable *TP53*-related cancer (hTP53rc) syndrome" [Frebourg et al 2020, Kratz et al 2021]. Historically, LFS was referred to as SBLA (*s*arcoma, *b*reast, *l*eukemia, and *a*drenal gland) syndrome.

Attenuated LFS. Individuals with a germline *TP53* pathogenic variant who do not meet classic LFS or modified Chompret criteria may be categorized as attenuated LFS. Individuals with attenuated LFS have been shown to have an increased risk for developing LFS-related cancers, albeit with lower overall cancer risk and later age of onset compared to individuals with classic LFS. However, individuals categorized as attenuated LFS may be later determined to have classic LFS as personal and family history evolves over time [Rana et al 2018, Kratz et al 2021]. At this time, classification of LFS as attenuated may not change recommended surveillance.

Prevalence

The prevalence of germline *TP53* pathogenic variants in the general population is estimated to be between 1:3,000 and 1:10,000 [de Andrade et al 2024].

The *TP53* p.Arg337His founder pathogenic variant in southern and southeastern Brazil has a prevalence between 0.21% and 0.3% [Achatz & Zambetti 2016, Seidinger et al 2020]. This has led to population newborn screening for *TP53* pathogenic variant p.Arg337His in Brazil [Achatz & Zambetti 2016].

Genetically Related (Allelic) Disorders

Sporadic tumors occurring as single tumors in the absence of any other findings of Li-Fraumeni syndrome (LFS) frequently contain a somatic variant in *TP53* that is **not** present in the germline. Somatic *TP53* pathogenic variants are found in approximately 50% of all tumors, making it one of the most frequently mutated genes in human cancers.

Low-level somatic mosaicism for a *TP53* pathogenic variant in leukocytes is a common finding and is suggestive of a postzygotic (acquired) pathogenic variant associated with clonal hematopoiesis of indeterminate potential (CHIP), an underlying hematologic malignancy or premalignancy, or circulating tumor cells [Batalini et al 2019, Coffee et al 2020, Mester et al 2020, Schwartz et al 2021, Castillo et al 2022]. Individuals with a *TP53* pathogenic variant that is not present in non-hematopoietic tissue and is confirmed through ancillary evaluation to be the result of CHIP or other forms of aberrant clonal expansion in hematopoietic cells do not have LFS [Batalini et al 2019].

Ancillary evaluation to determine constitutional or somatic status of a *TP53* pathogenic variant may include *TP53* molecular genetic testing on non-hematopoietic tissue such as cultured skin fibroblasts and *TP53* testing of the proband's parents and offspring; for detailed information see Table 1: Workup and Management Depending on Etiology of *TP53* Mutation Found on Genetic Testing in the 2024 NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Guidelines (www.nccn.org; subscription required). Of note, the variant allele frequency [VAF] of a somatic mosaic *TP53* pathogenic variant may overlap the heterozygous range [Coffee et al 2020, Mester et al 2020], and some studies suggest that the possibility of somatic mosaicism should be a consideration in all individuals with a *TP53* pathogenic variant who do not have features suggestive of LFS regardless of the VAF [Schwartz et al 2021, Castillo et al 2022].

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TP53*.

Differential Diagnosis

Table 2. Other Genes of Interest in the Differential Diagnosis of Li-Fraumeni Syndrome

Gene(s)	Disorder	MOI	Core Cancer(s)	Typical Age at Cancer Onset	Comments
BRCA1 *BRCA2*	*BRCA1*- & *BRCA2*-assoc hereditary breast & ovarian cancer	AD	Breast, ovary, pancreas, prostate, melanoma	Adulthood	Pathogenic variants in *BRCA1* & *BRCA2* are more likely to be identified in persons w/personal & family histories that include ER/PR/HER2-negative breast cancers, male breast cancer, ovarian cancer, advanced prostate cancer, & Ashkenazi Jewish ancestry, & do not include childhood cancers.
CHEK2	*CHEK2* cancer susceptibility (OMIM 609265)	AD	Breast, colorectal, prostate	Adulthood	Pathogenic variants in *CHEK2* are more likely to be identified in persons w/ personal & family histories of predominantly breast, colon, & prostate cancers. Note: Although *CHEK2* cancer susceptibility has been referred to as "Li-Fraumeni syndrome 2," *CHEK2* pathogenic variants are not assoc w/ACC, CNS tumors, or osteosarcoma, & *CHEK2* should not be considered an LFS-related gene. [1]
MLH1 *MSH2* *MSH6* *PMS2*	Constitutional mismatch repair deficiency (CMMRD; a variant of Lynch syndrome)	AR	Colorectal, small bowel, hematologic, brain	Childhood	CMMRD should be considered in persons w/childhood-onset GI cancer or polyps, malignant brain tumor, hematologic cancer, &/or café au lait macules.
POT1	*POT1* tumor predisposition	AD	Melanoma, CLL, glioma, angiosarcoma (esp cardiac angiosarcoma)	Adulthood	*POT1* tumor predisposition should be considered in persons w/personal or family history of melanoma, CLL, glioma, &/or angiosarcoma.

ACC = adrenocortical carcinoma; AD = autosomal dominant; AR = autosomal recessive; CLL = chronic lymphocytic leukemia; CNS = central nervous system; ER = estrogen receptor; GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2; LFS = Li-Fraumeni syndrome; MOI = mode of inheritance; PR = progesterone receptor

1. Fortuno et al [2023]

Management

Clinical practice guidelines for Li-Fraumeni syndrome (LFS) have been published [Villani et al 2016, Kratz et al 2017, Kumamoto et al 2021].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with LFS, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Li-Fraumeni Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment [1]
All cancers	• Complete physical exam w/high index of suspicion for cancer (incl blood pressure, full neurologic exam, & assessment of growth, sudden weight gain or loss, cushingoid appearance, or signs of virilization in a child) [2] • Whole-body MRI w/o contrast [3]	At diagnosis (all ages)
Breast cancer	• Clinical breast exam • Breast MRI w/& w/o contrast	Beginning at age 20 yrs
CNS tumors	• Neurologic exam • Brain MRI w/contrast	At diagnosis (all ages); 1st brain MRI is done w/ contrast
GI cancers	Upper endoscopy & colonoscopy	Beginning at age 25 yrs
Melanoma	Dermatologic exam	Beginning at age 18 yrs
Sarcomas	Ultrasound of abdomen & pelvis	
Genetic counseling	By genetics professionals [4] w/experience in cancer genetics counseling	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of LFS to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations [5]	Assessment of family & social structure to determine need for: • Community or online resources • Social work involvement for parental support

CNS = central nervous system; GI = gastrointestinal; LFS = Li-Fraumeni syndrome; MOI = mode of inheritance

1. Individuals with a family history of LFS should begin surveillance at the ages listed in this table or 5-10 years before the onset of the cancer in the family, whichever comes first.

2. Kumamoto et al [2021]

3. Evidence supports the use of whole-body MRI for surveillance in individuals with LFS [Ahlawat et al 2023]. Benefits include significantly increased detection of a variety of tumor types, which is important in a population at risk for diverse cancers. The risks of whole-body MRI include expense, difficulty with access, high false positive rate (especially with the baseline whole-body MRI), and the need for sedation in young children [Consul et al 2021, Kumamoto et al 2021, Ahlawat et al 2023, Kagami et al 2023].

4. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

5. Individuals with LFS may need mental health support and resources due to the burden of intensive surveillance protocols and their personal and family cancer experiences [Forbes Shepherd et al 2021, Barnett et al 2022].

Treatment of Manifestations

Breast cancer. Bilateral mastectomy rather than lumpectomy is often recommended in those with LFS-related breast cancer to reduce the risk of a second primary breast cancer and to avoid radiation therapy [Siegel et al 2022].

Other cancers

- Radiation therapy should be avoided if possible to reduce the risk of secondary malignancies [Kumamoto et al 2021]. Radiation-induced tumors and leukemias have been reported among individuals with LFS [Swaminathan et al 2019]. However, one small study found that four of 14 individuals with LFS treated with radiation who developed a malignancy within the radiation treatment field had local recurrence rather than a new primary cancer [Hendrickson et al 2020]. If clinically indicated, radiation therapy

should be considered for individuals with LFS; close surveillance for the development of new cancers in the radiation field post-treatment is recommended.
- The use of conventional cytotoxic chemotherapy may also pose an increased secondary cancer risk [Kumamoto et al 2021]. However, most experts recommend that after careful analysis of the risks and benefits, treatment efficacy should be prioritized above concerns about late effects.
- Otherwise, standard oncologic management is recommended.

Note: In some hereditary cancer syndromes, tumor tissue testing for loss of heterozygosity (LOH) and other features in the tumor can be informative; however, this is not usually the case in LFS. Thus, molecular analysis of tumor tissue to identify LOH of *TP53* is not recommended.

Prevention of Primary Manifestations

Breast cancer. Women with LFS have the option of risk-reducing bilateral mastectomy to decrease the risk of breast cancer [Siegel et al 2022].

Colorectal cancer. Adults with LFS should have screening colonoscopy examinations, which can be considered surveillance as well as primary prevention of colorectal cancer [MacFarland et al 2019a].

Skin cancer. Dermatologic surveillance can be used to detect and remove premalignant lesions [Hatton et al 2022].

Surveillance

Surveillance guidelines for adults and children with LFS have been developed and modified from the Toronto protocol [Villani et al 2016, Kratz et al 2017, Kumamoto et al 2021]. Other published guidelines (e.g., American Association for Cancer Research and National Institute for Health and Care Excellence guidelines) may differ slightly from the recommendations in Table 4 due to the lack of definitive data on the efficacy of these strategies.

Table 4. Li-Fraumeni Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency [1]
All cancers	Comprehensive physical exam w/high index of suspicion for cancer (incl blood pressure, full neurologic exam, & assessment of growth, sudden weight gain or loss, cushingoid appearance, &/or signs of virilization in a child) [2]	• Every 3-4 mos from birth to age 18 yrs • Every 6 mos from age ≥18 yrs
	Whole-body MRI [3]	Annually at all ages
ACC	Ultrasound of abdomen & pelvis	Every 3-4 mos from birth to age 18 yrs (not on same visit as whole-body MRI)
	Serum total testosterone, dehydroepiandrosterone sulfate, & androstenedione	If ultrasound is unsatisfactory
Breast cancer	Clinical breast exam	Every 6-12 mos starting between age 20-25 yrs
	Breast MRI w/& w/o contrast	Annually starting between age 20-30 yrs
	Mammogram & breast MRI w/& w/o contrast	Annually, alternating mammogram & breast MRI every 6 mos, in those age 30-75 yrs
CNS tumors	Brain MRI w/o contrast (initial brain MRI at diagnosis w/contrast) [4]	Annually
GI cancers	Upper endoscopy & colonoscopy	Every 2-5 yrs from age ≥25 yrs

Table 4. continued from previous page.

System/Concern	Evaluation	Frequency [1]
Leukemia/ Lymphoma	None recommended [5]	NA
Melanoma	Dermatologic exam	Annually from age ≥18 yrs
Sarcomas	Whole-body MRI	Annually at all ages
	Ultrasound of abdomen & pelvis	Annually from age ≥18 yrs
Lung cancer	Consider low-dose spiral CT	Consider screening adults (need, frequency, & age to begin screening depends on family history of lung cancer &/or history of smoking).
Pancreatic cancer	Consider contrast-enhanced MRI/MRCP &/or EUS in a research setting to better delineate risks & benefits of pancreatic cancer surveillance.	Consider annually from age ≥50 yrs. [6]
Prostate cancer	Consider PSA blood test.	Consider annually from age ≥40 yrs.
Thyroid cancer	Consider thyroid ultrasound.	Consider screening children & adults (need, frequency, & age to begin screening depends on family history &/or other risk factors).
Family/Community	Assess family need for social work support or follow-up genetic counseling if new questions arise (e.g., family planning). [7]	At each visit

ACC = adrenocortical carcinomas; CNS = central nervous system; EUS = endoscopic ultrasound; MRCP = magnetic resonance cholangiopancreatography; GI = gastrointestinal; NA = not applicable; PSA = prostate-specific antigen

1. Individuals with a family history of LFS should begin surveillance at the ages listed in this table or 5-10 years before the onset of the cancer in the family, whichever comes first.

2. Kumamoto et al [2021]

3. Evidence supports the role of whole-body MRI in individuals with LFS [Ahlawat et al 2023]. Benefits of whole-body MRI include significantly increased ability to detect a variety of tumor types, which is important in a population at risk for diverse cancers. The risks of whole-body MRI include expense, difficulty with access, high false positive rate (especially with baseline whole-body MRI), and the need for sedation in young children [Consul et al 2021, Kumamoto et al 2021, Ahlawat et al 2023, Kagami et al 2023].

4. The first brain MRI should be done with contrast, and subsequent brain MRIs may be done without contrast if the previous MRI was normal and there are no new clinical manifestations [Kratz et al 2017, Kumamoto et al 2021].

5. Interim blood counts and inflammatory biomarkers have not been shown to have independent benefit for cancer detection [Oba et al 2022].

6. National Comprehensive Cancer Network (NCCN) guidelines suggest pancreatic cancer surveillance only if the individual has ≥1 first- or second-degree relative with exocrine pancreatic cancer (www.nccn.org; subscription required); however, others suggest that pancreatic cancer surveillance should be considered in all individuals with LFS [Abe et al 2021].

7. Individuals with LFS recognize the value of surveillance but may need additional mental health support and resources due to the burden of intensive surveillance protocols and their personal and family cancer experiences. More research is needed in this area [Forbes Shepherd et al 2021, Barnett et al 2022].

Agents/Circumstances to Avoid

Individuals with LFS are encouraged to avoid or minimize exposures to known or suspected carcinogens, including ionizing radiation, unprotected sun exposure, tobacco use, occupational exposures, and excessive alcohol use, because the effects of carcinogenic exposures and germline *TP53* pathogenic variants may be cumulative.

Evaluation of Relatives at Risk

If a molecular diagnosis of LFS has been established in the proband, it is recommended that *TP53* molecular genetic testing be offered to all first-degree relatives (including children) as well as to more distant relatives (e.g., aunts, uncles, and cousins) in order to identify individuals with LFS who would benefit from increased cancer monitoring, with attention to symptoms or signs of cancer and early intervention when a cancer or precancer is identified. If the proband is a child, then cascade testing would typically begin with the child's sibs and parents.

Since the risks of LFS-related cancers are increased at all ages, including infancy and childhood, it is recommended that *TP53* testing be offered to individuals at birth (via cord blood analysis) or soon after birth. In families who are not ready to test very young children, the issues in initiating intensive surveillance should be discussed.

If a clinical diagnosis of LFS has been established in the proband but the proband does not have an identified *TP53* pathogenic variant, all at-risk family members should be counseled regarding their potential increased risks for LFS-related cancers and options for surveillance and risk reduction.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Female with LFS. Women with LFS who are pregnant should report any signs or symptoms of cancer to their physicians. Women with LFS who are pregnant can continue to have clinical breast exams and/or breast imaging studies if indicated.

Heterozygous fetus. There are no specific recommendations for surveillance of a fetus identified as having a germline *TP53* pathogenic variant. Following delivery, the infant should begin recommended cancer screening (see Surveillance).

Rare risk of gestational choriocarcinoma. Gestational choriocarcinoma and other gestational trophoblastic disease has been reported in women with LFS and in women carrying a fetus heterozygous for a paternally inherited *TP53* pathogenic variant [Brehin et al 2018, Cotter et al 2018]. There are no established guidelines for beta-human chorionic gonadotropin blood level screening; however, this screening can be considered as clinically appropriate.

Therapies Under Investigation

There are efforts to identify medications that can reduce the risk of cancer in individuals with LFS. One medication that looks promising is metformin; additional clinical trials investigating metformin are planned by groups in the United States, Canada, Germany, and the United Kingdom [Pantziarka & Blagden 2022, Rocca et al 2022].

There are also studies evaluating the clinical application and utility of cell-free DNA for early cancer detection in individuals with LFS. One study looked at the efficacy of a multimodal liquid biopsy assay in a longitudinal cohort of 89 individuals with LFS. The results showed that cancer-associated signal(s) were detected in individuals with LFS prior to identification of cancer by conventional screening (positive predictive value = 67.6%; negative predictive value = 96.5%) [Wong et al 2024].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

Additional resources include the Li-Fraumeni Exploration (LiFE) Research Consortium, Li-Fraumeni syndrome association (LFSA), Living LFS, and the LiFT Up study.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Li-Fraumeni syndrome (LFS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with LFS inherited a *TP53* pathogenic variant from a parent.
- Some individuals diagnosed with LFS have the disorder as the result of a *de novo* germline pathogenic variant. The frequency of *de novo* pathogenic variants is estimated at between 7% and 20%. A 14% *de novo* rate was reported in one series; about one fifth of the *de novo* pathogenic variants in this series were mosaic [Renaux-Petel et al 2018].
- If a *TP53* pathogenic variant has been identified in a proband and a diagnosis of LFS has not already been established in one of the parents, molecular genetic testing is recommended for the parents of the proband. If one parent has a significant personal and/or family history of cancer, that parent should be tested first. Otherwise, the parents can be tested simultaneously.
- If a *TP53* pathogenic variant is identified in a parent, the parent should be followed by appropriate medical surveillance (see Surveillance).
- If a *TP53* pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with gonadal mosaicism [Khincha et al 2019, Donovan et al 2020]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the gonadal cells only.
- The family history of some individuals diagnosed with LFS may appear to be negative because of failure to recognize the disorder in family members, a small family size, variable expressivity, early death of the parent before the onset of symptoms, or late onset of cancer in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless a molecular diagnosis has been established in the proband and molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.
- If a *TP53* pathogenic variant has not been identified in a proband who meets classic criteria for LFS and a diagnosis of LFS has not already been established in one of the parents, both parents should be counseled regarding their potential increased risks for LFS-related cancers and the options for surveillance and risk reduction.

Sibs of a proband. The risk to sibs of the proband depends on the status of the proband's parents:

- If a molecular diagnosis of LFS has been established in the proband (i.e., the proband has a known germline *TP53* pathogenic variant) and:
  - A parent of the proband is heterozygous for the *TP53* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
  - The *TP53* pathogenic variant is not identified in leukocyte DNA from either parent, the pathogenic variant most likely occurred *de novo* in the proband and the recurrence risk to sibs is low. However, because of the possibility of undetected parental somatic and/or gonadal mosaicism it is recommended that sibs be tested for the *TP53* pathogenic variant.
- If a clinical diagnosis of LFS has been established in the proband but a *TP53* pathogenic variant has not been identified in the proband, sibs should be counseled regarding their potential increased risks for LFS-related cancers and the options for surveillance and risk reduction.

Offspring of a proband

- Each child of an individual with a molecular diagnosis of LFS has a 50% risk of inheriting the *TP53* pathogenic variant.
- Each child of an individual with a clinical diagnosis of LFS (in whom a *TP53* pathogenic variant has not been identified) is presumed to have an increased risk for LFS.

Other family members

- The risk to other family members (e.g., aunts, uncles, cousins) depends on the genetic status of the proband's parents: if a parent has the *TP53* pathogenic variant, the heterozygous parent's family members may be at risk. Family history and molecular genetic testing can help determine whether maternal or paternal relatives are at increased risk.
- If the *TP53* pathogenic variant occurred as a postzygotic *de novo* event in the proband, it is presumed that neither parent of the proband has the *TP53* pathogenic variant and other family members are not at increased risk for LFS.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic individuals. Consideration of molecular genetic testing of young, at-risk family members is appropriate for guiding medical management (see Management, Evaluation of Relatives at Risk).

Molecular genetic testing can be used with certainty to clarify the genetic status of at-risk family members if a clinically diagnosed relative has undergone molecular genetic testing and is found to have a pathogenic variant in *TP53*.

The use of molecular genetic testing for determining the genetic status of at-risk relatives when a *TP53* pathogenic variant has not been identified in a clinically diagnosed relative is problematic, and test results need to be interpreted with caution. A positive test result in the at-risk family member indicates the presence of a *TP53* pathogenic variant and that the same molecular genetic testing method can be used to assess the genetic status of other, at-risk family members. In contrast, a "negative" molecular genetic test result in an at-risk family member is uninformative (i.e., the result does exclude the possibility that the family member has LFS).

Because cancer screening for individuals with LFS begins in infancy, molecular genetic testing is offered to at-risk children and adolescents.

Parents are motivated to arrange testing for their offspring to clarify their child's cancer risk status and the need for enhanced surveillance. Special consideration should be given to education of the children and their parents prior to genetic testing, and older children and adolescents should be given the option of assenting to the test.

The method of results disclosure should be discussed and agreed upon by the provider, parent(s), and older child/adolescent.

Living with a diagnosis of LFS can take an emotional toll on individuals, especially those in the adolescent / young adult age group. Individuals in this age group describe the burden of coping with one or more cancer diagnoses and/or living with the anticipation and fear of cancer as well as a range of family communication challenges [Rising et al 2022, Werner-Lin et al 2023].

Obtaining a family history in a proband suspected of having LFS includes obtaining information on all childhood- and adult-onset malignancies (e.g., age of onset, type of malignancy) among first-, second-, and third-degree relatives. Family history may be incorrect or incomplete for a variety of reasons (e.g., the topic of cancer may be avoided or a death in the family may have led to estrangement). In addition, obtaining a cancer history for a proband with suspected LFS is often emotionally charged because of the number of cancer-related illnesses and deaths among close relatives.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/ preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

If a *TP53* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Li-Fraumeni Syndrome Association**
  Phone: 833-469-5372
  lfsassociation.org
- **Living LFS**
  Phone: 844-537-2255
  livinglfs.org

- **MedlinePlus**
  Li-Fraumeni syndrome
- **National Cancer Institute (NCI)**
  Phone: 800-422-6237 (toll-free)
  Email: cancergovstaff@mail.nih.gov
  Genetics of Breast and Gynecologic Cancers (PDQ®): Li-Fraumeni Syndrome
- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  cancercare.org
- **National Cancer Institute (NCI)**
  Phone: 800-422-6237
  Email: NCIinfo@nih.gov
  cancer.gov
- **National Coalition for Cancer Survivorship (NCCS)**
  Phone: 877-NCCS-YES
  Email: info@canceradvocacy.org
  canceradvocacy.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Li-Fraumeni Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TP53	17p13.1	Cellular tumor antigen p53	p53 Mutations and Cancer IARC TP53 Mutation Database TP53 @ LOVD Database of Germline p53 Mutations	TP53	TP53

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Li-Fraumeni Syndrome (View All in OMIM)

151623	LI-FRAUMENI SYNDROME; LFS
191170	TUMOR PROTEIN p53; TP53

Molecular Pathogenesis

TP53 encodes p53, which has been termed the guardian of the genome and has many important cellular functions, especially in response to stress (e.g., DNA damage, oncogene activation, nutrient deprivation, oxidative stress). Cellular stress induces the activation, stabilization, and accumulation of p53, which can initiate

various responses including cell cycle arrest, apoptosis, senescence, DNA repair, and cell differentiation [Rocca et al 2022].

It has been proposed that p53 is a central driver in creating a cellular microenvironment that is conducive to tumor formation and growth. This theory, termed the precancerous niche hypothesis, may eventually lead to possible treatment options [Pantziarka & Blagden 2022].

Mechanism of disease causation. Germline *TP53* pathogenic variants result in loss of function by creating a constitutive defect of p53 DNA binding and decreased transcriptional response to DNA damage. Some *TP53* pathogenic variants have a dominant-negative effect, reducing the function of the normal allele in cells that have not acquired a secondary somatic pathogenic variant.

***TP53*-specific laboratory technical considerations.** *TP53* missense variants are commonly identified in tumor tissue. An alternate tissue that is free from cancerous cells (e.g., leukocytes from blood [except in those with leukemia], saliva, skin) is necessary to identify a germline *TP53* pathogenic variant.

Identification of a *TP53* pathogenic variant with low allele frequency (e.g., significantly less than 50%) may be indicative of mosaicism, clonal hematopoiesis of indeterminate potential (CHIP), hematologic malignancy or premalignancy, or circulating tumor cells [Batalini et al 2019, Coffee et al 2020, Mester et al 2020, Schwartz et al 2021, Castillo et al 2022]. Individuals with constitutional or early postzygotic *TP53* mosaicism have an increased risk of LFS-related cancers; individuals with CHIP do not [Batalini et al 2019].

Table 5. *TP53* Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000546.6 NP_000537.3	c.139C>T	p.Pro47Ser	See Genotype-Phenotype Correlations.
	c.145G>C	p.Asp49His	
	c.215G>C	p.Arg72Pro	See Genetic Modifiers.
	c.455C>T	p.Pro152Leu	See Genotype-Phenotype Correlations.
	c.524G>A	p.Arg175His	
	c.541C>T	p.Arg181Cys	
	c.542G>A	p.Arg181His	
	c.733G>A	p.Gly245Ser	
	c.743G>A	p.Arg248Gln	
	c.742C>T	p.Arg248Trp	
	c.818G>A	p.Arg273His	
	c.844C>T	p.Arg282Trp	
	c.1000G>C	p.Gly334Arg	
	c.1010G>A	p.Arg337His	High risk of ACC; low-penetrance allele for other LFS cancers; founder variant in southern Brazil [Ferreira et al 2019]
NM_000546.6	c.*1175A>C (rs78378222)	--	See Genotype-Phenotype Correlations.

Table 5. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NG_017013.2	16-bp duplication in intron 3 [1] (rs17878362)	--	See Genetic Modifiers.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
ACC = adrenocortical carcinoma; LFS = Li-Fraumeni syndrome
1. Variant designation that does not conform to current naming conventions

Chapter Notes

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References

Literature Cited

Abe K, Kitago M, Kitagawa Y, Hirasawa A. Hereditary pancreatic cancer. Int J Clin Oncol. 2021;26:1784-92. PubMed PMID: 34476650.

Achatz MI, Zambetti GP. The inherited p53 mutation in the Brazilian population. Cold Spring Harb Perspect Med. 2016;6:a026195. PubMed PMID: 27663983.

Ahlawat S, Debs P, Amini B, Lecouvet FE, Omoumi P, Wessell DE. Clinical applications and controversies of whole-body MRI: AJR Expert Panel Narrative Review. AJR Am J Roentgenol. 2023;220:463-75. PubMed PMID: 36169545.

Amadou A, Achatz MIW, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol. 2018;30:23–9. PubMed PMID: 29076966.

Ariffin H, Chan AS, Oh L, Abd-Ghafar S, Ong GB, Mohamed M, Razali H, Juraida E, Teo SH, Karsa M, Shamsani J, Hainaut P. Frequent occurrence of gastric cancer in Asian kindreds with Li-Fraumeni syndrome. Clin Genet. 2015;88:450–5. PubMed PMID: 25318593.

Arnon J, Zick A, Maoz M, Salaymeh N, Gugenheim A, Marouani M, Mor E, Hamburger T, Saadi N, Elia A, Ganz G, Fahham D, Meirovitz A, Kadouri L, Meiner V, Yablonski-Peretz T, Shkedi-Rafid S. Clinical and genetic characteristics of carriers of the TP53 c.541C > T, p.Arg181Cys pathogenic variant causing hereditary cancer in patients of Arab-Muslim descent. Fam Cancer. 2024. Epub ahead of print. PubMed PMID: 38743206.

Bandeira IC, Vieira IA, Andreis TF, Brussa Reis L, Macedo GS, Vianna FSL, Santos-Silva P, Palmero EI, Galvão HCR, Ramos CRN, Santiago KM, Achatz MI, da Costa AABA, Ashton-Prolla P. MIR605 rs2043556 is associated with the occurrence of multiple primary tumors in TP53 p.(Arg337His) mutation carriers. Cancer Genet. 2020;240:54-8. PubMed PMID: 31778928.

Barnett M, Breen KE, Kennedy JA, Hernandez M, Matsoukas K, MacGregor M. Psychosocial interventions and needs among individuals and families with Li-Fraumeni syndrome: a scoping review. Clin Genet. 2022;101:161-82 PubMed PMID: 34355387.

Batalini F, Peacock EG, Stobie L, Robertson A, Garber J, Weitzel JN, Tung NM. Li-Fraumeni syndrome: not a straightforward diagnosis anymore-the interpretation of pathogenic variants of low allele frequency and the differences between germline PVs, mosaicism, and clonal hematopoiesis. Breast Cancer Res. 2019;21:107. PubMed PMID: 31533767.

Benusiglio PR, Fallet V, Sanchis-Borja M, Coulet F, Cadranel J. Lung cancer is also a hereditary disease. Eur Respir Rev. 2021;30:210045. PubMed PMID: 34670806.

Blondeaux E, Arecco L, Punie K, Graffeo R, Toss A, De Angelis C, Trevisan L, Buzzatti G, Linn SC, Dubsky P, Cruellas M, Partridge AH, Balmaña J, Paluch-Shimon S, Lambertini M. Germline TP53 pathogenic variants and breast cancer: A narrative review. Cancer Treat Rev. 2023;114:102522. PubMed PMID: 36739824.

Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, Gauthier-Villars M, Stoppa-Lyonnet D, Consolino E, Brugieres L, Caron O, Benusiglio PR, Bressac-de-Paillerets B, Bonadona V, Bonaiti-Pellie C, Tinat J, Baert-Desurmont S, Frebourg T. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol. 2015;33:2345–52. PubMed PMID: 26014290.

Brehin AC, Patrier-Sallebert S, Bougeard G, Side-Pfennig G, Llamas Gutierrez F, Lamy A, Colasse E, Kandel-Aznar C, Delnatte C, Vuillemin E, Sadot-Lebouvier S, Odent S, Sabourin JC, Golfier F, Frebourg T. Gestational choriocarcinoma associated with a germline TP53 mutation. Fam Cancer. 2018;17:113-7. PubMed PMID: 28477316.

Castillo D, Yuan TA, Nehoray B, Cervantes A, Tsang KK, Yang K, Sand SR, Mokhnatkin J, Herzog J, Slavin TP, Hyman S, Schwartz A, Ebert BL, Amos CI, Garber JE, Weitzel JN. Clonal hematopoiesis and mosaicism revealed by a multi-tissue analysis of constitutional TP53 status. Cancer Epidemiol Biomarkers Prev. 2022;31:1621-9. PubMed PMID: 35654360.

Coffee B, Cox HC, Bernhisel R, Manley S, Bowles K, Roa BB, Mancini-DiNardo D. A substantial proportion of apparently heterozygous TP53 pathogenic variants detected with a next-generation sequencing hereditary pan-cancer panel are acquired somatically. Hum Mutat. 2020;41:203-11. PubMed PMID: 31490007.

Consul N, Amini B, Ibarra-Rovira JJ, Blair KJ, Moseley TW, Taher A, Shah KB, Elsayes KM. Li-Fraumeni syndrome and whole-body MRI screening: screening guidelines, imaging features, and impact on patient management. AJR Am J Roentgenol. 2021;216:252-63. PubMed PMID: 33151095.

Cotter JA, Szymanski L, Karimov C, Boghossian L, Margol A, Dhall G, Tamrazi B, Varaprasathan GI, Parham DM, Judkins AR, Biegel JA. Transmission of a TP53 germline mutation from unaffected male carrier associated with pediatric glioblastoma in his child and gestational choriocarcinoma in his female partner. Cold Spring Harb Mol Case Stud. 2018;4:a002576. PubMed PMID: 29581140.

de Andrade KC, Khincha PP, Hatton JN, Frone MN, Wegman-Ostrosky T, Mai PL, Best AF, Savage SA. Cancer incidence, patterns, and genotype-phenotype associations in individuals with pathogenic or likely pathogenic germline TP53 variants: an observational cohort study. Lancet Oncol. 2021;22:1787-98. PubMed PMID: 34780712.

de Andrade KC, Strande NT, Kim J, Haley JS, Hatton JN, Frone MN, Khincha PP, Thone GM, Mirshahi UL, Schneider C, Desai H, Dove JT, Smelser DT; Penn Medicine BioBank; Regeneron Genetics Center; Levine AJ, Maxwell KN, Stewart DR, Carey DJ, Savage SA. Genome-first approach of the prevalence and cancer phenotypes of pathogenic or likely pathogenic germline TP53 variants. HGG Adv. 2024;5:100242. . PubMed PMID: 37777824.

Donovan LN, Kohlmann W, Snow AK, Neklason DW, Schiffman JD, Maese L. Germ cell mosaicism: a rare cause of Li-Fraumeni recurrence among siblings. JCO Precis Oncol. 2020;4:PO.20.00064.

Evans DG, Harkness EF, Woodward ER. TP53 c.455C>T p.(Pro152Leu) pathogenic variant is a lower risk allele with attenuated risks of breast cancer and sarcoma. J Med Genet. 2023;60:1057-60. PubMed PMID: 37076289.

Evans DG, Woodward ER. New surveillance guidelines for Li-Fraumeni and hereditary TP53 related cancer syndrome: implications for germline TP53 testing in breast cancer. Fam Cancer. 2021;20:1-7. PubMed PMID: 32984917.

Ferreira AM, Brondani VB, Helena VP, Charchar HLS, Zerbini MCN, Leite LAS, Hoff AO, Latronico AC, Mendonca BB, Diz MDPE, de Almeida MQ, Fragoso MCBV. Clinical spectrum of Li-Fraumeni syndrome/Li-Fraumeni-like syndrome in Brazilian individuals with the TP53 p.R337H mutation. J Steroid Biochem Mol Biol. 2019;190:250–5. PubMed PMID: 30974190.

Fischer NW, Ma YV, Gariépy J. Emerging insights into ethnic-specific TP53 germline variants. J Natl Cancer Inst. 2023;115:1145-56. PubMed PMID: 37352403.

Forbes Shepherd R, Keogh LA, Werner-Lin A, Delatycki MB, Forrest LE. Benefits and burdens of risk management for young people with inherited cancer: A focus on Li-Fraumeni syndrome. Aust J Gen Pract. 2021;50:538-44. PubMed PMID: 34333565.

Fortuno C, Feng BJ, Carroll C, Innella G, Kohlmann W, Lázaro C, Brunet J, Feliubadaló L, Iglesias S, Menéndez M, Teulé A, Ballinger ML, Thomas DM, Campbell A, Field M, Harris M, Kirk J, Pachter N, Poplawski N,

Susman R, Tucker K, Wallis M, Williams R, Cops E, Goldgar D; kConFab Investigators; James PA, Spurdle AB. Cancer risks associated with TP53 pathogenic variants: maximum likelihood analysis of extended pedigrees for diagnosis of first cancers beyond the Li-Fraumeni syndrome spectrum. JCO Precis Oncol. 2024;8:e2300453. PubMed PMID: 38412388.

Fortuno C, Mester J, Pesaran T, Weitzel JN, Dolinsky J, Yussuf A, McGoldrick K, Garber JE, Savage SA, Khincha PP, Gareth Evans D, Achatz MI, Nichols KE, Maxwell KN, Schiffman JD, Sandoval R; Li-Fraumeni Exploration (LIFE) Consortium; James PA, Spurdle AB. Suggested application of HER2+ breast tumor phenotype for germline TP53 variant classification within ACMG/AMP guidelines. Hum Mutat. 2020;41:1555-62. PubMed PMID: 32485079.

Fortuno C, Pesaran T, Dolinsky J, Yussuf A, McGoldrick K, Kho PF, James PA, Spurdle AB. p53 major hotspot variants are associated with poorer prognostic features in hereditary cancer patients. Cancer Genet. 2019;235-236:21-7. PubMed PMID: 31296311.

Fortuno C, Richardson M, Pesaran T, Yussuf A, Horton C, James PA, Spurdle AB. CHEK2 is not a Li-Fraumeni syndrome gene: time to update public resources. J Med Genet. 2023;60:1215-7. PubMed PMID: 37536919.

Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DG; European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet. 2020;28:1379-86. PubMed PMID: 32457520.

Frone MN, Stewart DR, Savage SA, Khincha PP. Quantification of discordant variant interpretations in a large family-based study of Li-Fraumeni syndrome. JCO Precis Oncol. 2021;5:PO.21.00320.

Funato M, Tsunematsu Y, Yamazaki F, Tamura C, Kumamoto T, Takagi M, Kato S, Sugimura H, Tamura K. Characteristics of Li-Fraumeni syndrome in Japan; a review study by the Special Committee of JSHT. Cancer Sci. 2021;112:2821–34. PubMed PMID: 33932062.

Guha T, Malkin D. Inherited TP53 mutations and the Li-Fraumeni syndrome. Cold Spring Harb Perspect Med. 2017;7:a026187. PubMed PMID: 28270529.

Guo Y, Wan Q, Ouyang T, Li J, Wang T, Fan Z, Xie Y. Risk of ipsilateral breast tumor recurrence and contralateral breast cancer in patients with and without TP53 variant in a large series of breast cancer patients. Breast. 2022;65:55-60. PubMed PMID: 35820297.

Hatton JN, de Andrade KC, Frone MN, Savage SA, Khincha PP. Spectrum and excess risk of gastrointestinal tumors in Li-Fraumeni syndrome. Clin Gastroenterol Hepatol. 2024;22:662-5.e1. PubMed PMID: 37714395.

Hatton JN, Sargen MR, Frone MN, de Andrade KC, Savage SA, Khincha PP. Spectrum and incidence of skin cancer among individuals with Li-Fraumeni syndrome. J Invest Dermatol. 2022;142:2534-37.e1. PubMed PMID: 35183552.

Hendrickson PG, Luo Y, Kohlmann W, Schiffman J, Maese L, Bishop AJ, Lloyd S, Kokeny KE, Hitchcock YJ, Poppe MM, Gaffney DK, Tao R. Radiation therapy and secondary malignancy in Li-Fraumeni syndrome: A hereditary cancer registry study. Cancer Med. 2020;9:7954-63. PubMed PMID: 32931654.

Holmfeldt L, Wei L, Diaz-Flores E, Walsh M, Zhang J, Ding L, Payne-Turner D, Churchman M, Andersson A, Chen SC, McCastlain K, Becksfort J, Ma J, Wu G, Patel SN, Heatley SL, Phillips LA, Song G, Easton J, Parker M, Chen X, Rusch M, Boggs K, Vadodaria B, Hedlund E, Drenberg C, Baker S, Pei D, Cheng C, Huether R, Lu C, Fulton RS, Fulton LL, Tabib Y, Dooling DJ, Ochoa K, Minden M, Lewis ID, To LB, Marlton P, Roberts AW, Raca G, Stock W, Neale G, Drexler HG, Dickins RA, Ellison DW, Shurtleff SA, Pui CH, Ribeiro RC, Devidas M, Carroll AJ, Heerema NA, Wood B, Borowitz MJ, Gastier-Foster JM, Raimondi SC, Mardis ER, Wilson RK, Downing JR, Hunger SP, Loh ML, Mullighan CG. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet. 2013;45:242–52 PubMed PMID: 23334668.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Hyder Z, Harkness EF, Woodward ER, Bowers NL, Pereira M, Wallace AJ, Howell SJ, Howell A, Lalloo F, Newman WG, Smith MJ, Evans DG. Risk of contralateral breast cancer in women with and without pathogenic variants in BRCA1, BRCA2, and TP53 genes in women with very early-onset (<36 years) breast cancer. Cancers (Basel). 2020;12:378 PubMed PMID: 32045981.

Kagami LAT, Du YK, Fernandes CJ, Le AN, Good M, Duvall MM, Baldino SE, Powers J, Zelley K, States LJ, Mathew MC, Katona BW, MacFarland SP, Maxwell KN. Rates of intervention and cancer detection on initial versus subsequent whole-body MRI screening in Li-Fraumeni syndrome. Cancer Prev Res (Phila). 2023;16:507-12. PubMed PMID: 37428016.

Kerrigan K, Chan J, Vagher J, Kohlmann W, Naumer A, Anson J, Low S, Schiffman J, Maese L. Lung cancer in Li-Fraumeni syndrome. JCO Precis Oncol. 2021;5:PO.20.00468.

Khincha PP, Jones K, Teshome K, Hicks B, Mai PL, Savage SA. Gonadal mosaicism in a family with TP53-associated Li-Fraumeni syndrome [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2019 Mar 29-Apr 3; Atlanta, GA. Cancer Res. 2019;79:4159A.

Kratz CP, Achatz MI, Brugieres L, Frebourg T, Garber J, Greer MLC, Hansford JR, Janeway KA, Kohlmann WK, McGee R, Mullighan CG, Onel K, Pajtler KW, Pfister SM, Savage SA, Schiffman JD, Schneider KA, Strong LC, Evans DGR, Wasserman JD, Villani A, Malkin D. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. Clin Cancer Res. 2017;23:e38–45. PubMed PMID: 28572266.

Kratz CP, Freycon C, Maxwell KN, Nichols KE, Schiffman JD, Evans DG, Achatz MI, Savage SA, Weitzel JN, Garber JE, Hainaut P, Malkin D. Analysis of the Li-Fraumeni spectrum based on an international germline TP53 variant data set: an International Agency for Research on Cancer TP53 database analysis. JAMA Oncol. 2021;7:1800-5. PubMed PMID: 34709361.

Kuba MG, Lester SC, Bowman T, Stokes SM, Taneja KL, Garber JE, Dillon DA. Histopathologic features of breast cancer in Li-Fraumeni syndrome. Mod Pathol. 2021;34:542-8. PubMed PMID: 32636452.

Kumamoto T, Yamazaki F, Nakano Y, Tamura C, Tashiro S, Hattori H, Nakagawara A, Tsunematsu Y. Medical guidelines for Li-Fraumeni syndrome 2019, version 1.1. Int J Clin Oncol. 2021;26:2161-78. PubMed PMID: 34633580.

Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med. 1969;71:747-52. PubMed PMID: 5360287.

MacFarland SP, Zelley K, Long JM, McKenna D, Mamula P, Domchek SM, Nathanson KL, Brodeur GM, Rustgi AK, Katona BW, Maxwell KN. Earlier colorectal cancer screening may be necessary in patients with Li-Fraumeni syndrome. Gastroenterology. 2019a;156:273–4. PubMed PMID: 30243621.

MacFarland SP, Zelley K, Surrey LF, Gallo D, Luo M, Raman P, Wertheim G, Hunger SP, Li MM, Brodeur GM. Pediatric somatic tumor sequencing identifies underlying cancer predisposition. JCO Precis Oncol. 2019b;3:PO.19.00062.

Mai PL, Best AF, Peters JA, DeCastro R, Khincha PP, Loud JT, Bremer RC, Rosenberg PS, Savage SA. Risks of first and subsequent cancers among TP53 mutation-carriers in the NCI LFS cohort. Cancer. 2016;122:3673–81. PubMed PMID: 27496084.

Maxwell KN, Cheng HH, Powers J, Gulati R, Ledet EM, Morrison C, Le A, Hausler R, Stopfer J, Hyman S, Kohlmann W, Naumer A, Vagher J, Greenberg SE, Naylor L, Laurino M, Konnick EQ, Shirts BH, AlDubayan SH, Van Allen EM, Nguyen B, Vijai J, Abida W, Carlo MI, Dubard-Gault M, Lee DJ, Maese LD, Mandelker D, Montgomery B, Morris MJ, Nicolosi P, Nussbaum RL, Schwartz LE, Stadler Z, Garber JE, Offit K, Schiffman JD, Nelson PS, Sartor O, Walsh MF, Pritchard CC. Inherited TP53 variants and risk of prostate cancer. Eur Urol. 2022;81:243-50 PubMed PMID: 34863587.

Melhem-Bertrandt A, Bojadzieva J, Ready KJ, Obeid E, Liu DD, Gutierrez-Barrera AM, Litton JK, Olopade OI, Hortobagyi GN, Strong LC, Arun BK. Early onset HER2-positive breast cancer is associated with germline TP53 mutations. Cancer. 2012;118:908-13. PubMed PMID: 21761402.

Mester JL, Jackson SA, Postula K, Stettner A, Solomon S, Bissonnette J, Murphy PD, Klein RT, Hruska KS. Apparently heterozygous TP53 pathogenic variants may be blood limited in patients undergoing hereditary cancer panel testing. J Mol Diagn. 2020;22:396-404. PubMed PMID: 31881331.

Oba L, Best AF, Mai PL, Achatz MI, Albert PS, Savage SA, Khincha PP. Utility of interim blood tests for cancer screening in Li-Fraumeni syndrome. Fam Cancer. 2022;21:333-6. PubMed PMID: 34076823.

Pantziarka P, Blagden S. Inhibiting the priming for cancer in Li-Fraumeni syndrome. Cancers (Basel). 2022;14:1621. PubMed PMID: 35406393.

Penkert J, Strüwe FJ, Dutzmann CM, Doergeloh BB, Montellier E, Freycon C, Keymling M, Schlemmer HP, Sänger B, Hoffmann B, Gerasimov T, Blattmann C, Fetscher S, Frühwald M, Hettmer S, Kordes U, Ridola V, Kroiss Benninger S, Mastronuzzi A, Schott S, Nees J, Prokop A, Redlich A, Seidel MG, Zimmermann S, Pajtler KW, Pfister SM, Hainaut P, Kratz CP. Genotype-phenotype associations within the Li-Fraumeni spectrum: a report from the German Registry. J Hematol Oncol. 2022;15:107. PubMed PMID: 35974385.

Pinto EM, Figueiredo BC, Chen W, Galvao HCR, Formiga MN, Fragoso MCBV, Ashton-Prolla P, Ribeiro EMSF, Felix G, Costa TEB, Savage SA, Yeager M, Palmero EI, Volc S, Salvador H, Fuster-Soler JL, Lavarino C, Chantada G, Vaur D, Odone-Filho V, Brugières L, Else T, Stoffel EM, Maxwell KN, Achatz MI, Kowalski L, de Andrade KC, Pappo A, Letouze E, Latronico AC, Mendonca BB, Almeida MQ, Brondani VB, Bittar CM, Soares EWS, Mathias C, Ramos CRN, Machado M, Zhou W, Jones K, Vogt A, Klincha PP, Santiago KM, Komechen H, Paraizo MM, Parise IZS, Hamilton KV, Wang J, Rampersaud E, Clay MR, Murphy AJ, Lalli E, Nichols KE, Ribeiro RC, Rodriguez-Galindo C, Korbonits M, Zhang J, Thomas MG, Connelly JP, Pruett-Miller S, Diekmann Y, Neale G, Wu G, Zambetti GP. XAF1 as a modifier of p53 function and cancer susceptibility. Sci Adv. 2020;6:eaba3231. PubMed PMID: 32637605.

Qian M, Cao X, Devidas M, Yang W, Cheng C, Dai Y, Carroll A, Heerema NA, Zhang H, Moriyama T, Gastier-Foster JM, Xu H, Raetz E, Larsen E, Winick N, Bowman P, Martin PI, Mardis ER, Fulton R, Zambetti G, Borowitz M, Wood B, Nichols KE, Carroll WL, Pui CH, Mullighan CG, Evans WE, Hunger SP, Relling MV, Loh ML, Yang JJ. TP53 germline variations influence the predisposition and prognosis of B-cell acute lymphoblastic leukemia in children. J Clin Oncol. 2018;36:591–9. PubMed PMID: 29300620.

Rana HQ, Clifford J, Hoang L, LaDuca H, Black MH, Li S, McGoldrick K, Speare V, Dolinsky JS, Gau CL, Garber JE. Genotype-phenotype associations among panel-based TP53+ subjects. Genet Med. 2019;21:2478–84. PubMed PMID: 31105275.

Rana HQ, Gelman R, LaDuca H, McFarland R, Dalton E, Thompson J, Speare V, Dolinsky JS, Chao EC, Garber JE. Differences in TP53 mutation carrier phenotypes emerge from panel-based testing. J Natl Cancer Inst. 2018;110:863–70. PubMed PMID: 29529297.

Renaux-Petel M, Charbonnier F, Thery JC, Fermey P, Lienard G, Bou J, Coutant S, Vezain M, Kasper E, Fourneaux S, Manase S, Blanluet M, Leheup B, Mansuy L, Champigneulle J, Chappe C, Longy M, Sevenet N, Bressac-de Paillerets B, Guerrini-Rousseau L, Brugieres L, Caron O, Sabourin JC, Tournier I, Baert-Desurmont S, Frebourg T, Bougeard G. Contribution of de novo and mosaic TP53 mutations to Li-Fraumeni syndrome. J Med Genet. 2018;55:173–80. PubMed PMID: 29070607.

Rengifo-Cam W, Shepherd HM, Jasperson KW, Samadder NJ, Samowitz W, Tripp SR, Schiffman JD, Kohlmann W. Colon pathology characteristics in Li-Fraumeni syndrome. Clin Gastroenterol Hepatol. 2018;16:140–1. PubMed PMID: 28624650.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rising CJ, Wilsnack C, Boyd P, Sleight AG, Hutson SP, Khincha PP, Werner-Lin A. Family communication challenges of adolescents and young adults with Li-Fraumeni syndrome: implications for psychosocial care. Patient Educ Couns. 2022;105:3259-66. PubMed PMID: 35918231.

Rocca V, Blandino G, D'Antona L, Iuliano R, Di Agostino S. Li-Fraumeni syndrome: mutation of TP53 is a biomarker of hereditary predisposition to tumor: new insights and advances in the treatment. Cancers (Basel). 2022;14:3664. PubMed PMID: 35954327.

Sandoval RL, Polidorio N, Leite ACR, Cartaxo M, Pisani JP, Quirino CV, Cezana L, Pereira NG, Pereira AAL, Rossi BM, Achatz MI. Breast cancer phenotype associated with Li-Fraumeni syndrome: a Brazilian cohort enriched by TP53 p.R337H carriers. Front Oncol. 2022;12:836937. PubMed PMID: 35371985.

Sandru F, Dumitrascu MC, Petca A, Carsote M, Petca RC, Ghemigian A. Melanoma in patients with Li-Fraumeni syndrome (review). Exp Ther Med. 2022;23:75. PubMed PMID: 34934446.

Schon K, Tischkowitz M. Clinical implications of germline mutations in breast cancer: TP53. Breast Cancer Res Treat. 2018;167:417–23. PubMed PMID: 29039119.

Schwartz AN, Hyman SR, Stokes SM, Castillo D, Tung NM, Weitzel JN, Rana HQ, Garber JE. Evaluation of TP53 variants detected on peripheral blood or saliva testing: discerning germline from somatic TP53 variants. JCO Precis Oncol. 2021;5:1677-86. PubMed PMID: 34994652.

Seidinger AL, Caminha IP, Mastellaro MJ, Gabetta CS, Nowill AE, Pinheiro VRP, Yunes JA. TP53 p.Arg337His geographic distribution correlates with adrenocortical tumor occurrence. Mol Genet Genomic Med. 2020;8:e1168. PubMed PMID: 32592449.

Sheng S, Xu Y, Guo Y, Yao L, Hu L, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, Xie Y. Prevalence and clinical impact of TP53 germline mutations in Chinese women with breast cancer. Int J Cancer. 2020;146:487-95. PubMed PMID: 31119730.

Shin SJ, Dodd-Eaton EB, Peng G, Bojadzieva J, Chen J, Amos CI, Frone MN, Khincha PP, Mai PL, Savage SA, Ballinger ML, Thomas DM, Yuan Y, Strong LC, Wang W. Penetrance of different cancer types in families with Li-Fraumeni syndrome: a validation study using multicenter cohorts. Cancer Res. 2020;80:354-60. PubMed PMID: 31719101.

Siegel A, Bremer RC, Klein WMP, Savage SA, Loud JT, Khincha PP. Uptake and timing of bilateral and contralateral risk-reducing mastectomy in women with Li-Fraumeni syndrome. Breast Cancer Res Treat. 2022;191:159-67. PubMed PMID: 34652547.

Subasri V, Light N, Kanwar N, Brzezinski J, Luo P, Hansford JR, Cairney E, Portwine C, Elser C, Finlay JL, Nichols KE, Alon N, Brunga L, Anson J, Kohlmann W, de Andrade KC, Khincha PP, Savage SA, Schiffman JD, Weksberg R, Pugh TJ, Villani A, Shlien A, Goldenberg A, Malkin D. Multiple germline events contribute to cancer development in patients with Li-Fraumeni syndrome. Cancer Res Commun. 2023;3:738-54. PubMed PMID: 37377903.

Swaminathan M, Bannon SA, Routbort M, Naqvi K, Kadia TM, Takahashi K, Alvarado Y, Ravandi-Kashani F, Patel KP, Champlin R, Kantarjian H, Strong L, DiNardo CD. Hematologic malignancies and Li-Fraumeni syndrome. Cold Spring Harb Mol Case Stud. 2019;5:a003210. PubMed PMID: 30709875.

Tjandra D, Boussioutas A. Li Fraumeni syndrome predisposes to gastro-esophageal junction tumours. Fam Cancer. 2024;23:29-33. PubMed PMID: 38206485.

Valdez JM, Nichols KE, Kesserwan C. Li-Fraumeni syndrome: a paradigm for the understanding of hereditary cancer predisposition. Br J Haematol. 2017;176:539–52. PubMed PMID: 27984644.

Villani A, Shore A, Wasserman JD, Stephens D, Kim RH, Druker H, Gallinger B, Naumer A, Kohlmann W, Novokmet A, Tabori U, Tijerin M, Greer ML, Finlay JL, Schiffman JD, Malkin D. 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;17:1295–305. PubMed PMID: 27501770.

Wasserman JD, Novokmet A, Eichler-Jonsson C, Ribeiro RC, Rodriguez-Galindo C, Zambetti GP, Malkin D. Prevalence and functional consequence of TP53 mutations in pediatric adrenocortical carcinoma: a children's oncology group study. J Clin Oncol. 2015;33:602-9. PubMed PMID: 25584008.

Waszak SM, Northcott PA, Buchhalter I, Robinson GW, Sutter C, Groebner S, Grund KB, Brugières L, Jones DTW, Pajtler KW, Morrissy AS, Kool M, Sturm D, Chavez L, Ernst A, Brabetz S, Hain M, Zichner T, Segura-Wang M, Weischenfeldt J, Rausch T, Mardin BR, Zhou X, Baciu C, Lawerenz C, Chan JA, Varlet P, Guerrini-Rousseau L, Fults DW, Grajkowska W, Hauser P, Jabado N, Ra YS, Zitterbart K, Shringarpure SS, De La Vega FM, Bustamante CD, Ng HK, Perry A, MacDonald TJ, Hernáiz Driever P, Bendel AE, Bowers DC, McCowage G, Chintagumpala MM, Cohn R, Hassall T, Fleischhack G, Eggen T, Wesenberg F, Feychting M, Lannering B, Schüz J, Johansen C, Andersen TV, Röösli M, Kuehni CE, Grotzer M, Kjaerheim K, Monoranu CM, Archer TC, Duke E, Pomeroy SL, Shelagh R, Frank S, Sumerauer D, Scheurlen W, Ryzhova MV, Milde T, Kratz CP, Samuel D, Zhang J, Solomon DA, Marra M, Eils R, Bartram CR, von Hoff K, Rutkowski S, Ramaswamy V, Gilbertson RJ, Korshunov A, Taylor MD, Lichter P, Malkin D, Gajjar A, Korbel JO, Pfister SM. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. Lancet Oncol. 2018;19:785-98. PubMed PMID: 29753700.

Werner-Lin A, Forbes Shepherd R, Rising CJ, Thompson AS, Huelsnitz C, Wilsnack C, Boyd P, Sleight AG, Hutson S, Khincha PP. How do young people with a hereditary cancer predisposition syndrome understand and experience cancer survivorship? "With Li-Fraumeni syndrome, it's just an intermission". Psychooncology. 2023;32:375-82. PubMed PMID: 36514197.

Winter G, Kirschner-Schwabe R, Groeneveld-Krentz S, Escherich G, Moricke A, von Stackelberg A, Stanulla M, Bailey S, Richter L, Stinemann D, Ripperger T, Escudero A, Farah R, Lohi O, Wadt K, Jongmans M, van Engelen N, Eckert C, Kratz CP: Letter to the Editor: Clinical and genetic characteristics of children with acute lymphoblastic leukemia and Li-Fraumeni syndrome. Leukemia. 2021;35:1475-9.

Wong D, Luo P, Oldfield LE, Gong H, Brunga L, Rabinowicz R, Subasri V, Chan C, Downs T, Farncombe KM, Luu B, Norman M, Sobotka JA, Uju P, Eagles J, Pedersen S, Wellum J, Danesh A, Prokopec SD, Stutheit-Zhao EY, Znassi N, Heisler LE, Jovelin R, Lam B, Lujan Toro BE, Marsh K, Sundaravadanam Y, Torti D, Man C, Goldenberg A, Xu W, Veit-Haibach P, Doria AS, Malkin D, Kim RH, Pugh TJ. Early cancer detection in Li-Fraumeni syndrome with cell-free DNA. Cancer Discov. 2024;14:104-19. PubMed PMID: 37874259.

Yurgelun MB, Masciari S, Joshi VA, Mercado RC, Lindor NM, Gallinger S, Hopper JL, Jenkins MA, Buchanan DD, Newcomb PA, Potter JD, Haile RW, Kucherlapati R, Syngal S; Colon Cancer Family Registry. Germline TP53 mutations in patients with early-onset colorectal cancer in the Colon Cancer Family Registry. JAMA Oncol. 2015;1:214-21. PubMed PMID: 26086041.

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