Li-Fraumeni Syndrome

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Synonyms of Li-Fraumeni Syndrome

LFS

General Discussion

Summary

Li-Fraumeni syndrome (LFS) is an inherited familial predisposition to a wide range of certain, often rare, cancers. This is due to a change (mutation) in a tumor suppressor gene known as *TP53*. The resulting p53 protein produced by the gene is damaged (or otherwise rendered malfunctioning) and is unable to help prevent malignant tumors from developing. Children and young adults are susceptible to developing several multiple cancers, most notably soft-tissue and bone sarcomas, breast cancer, brain tumors, adrenocortical carcinoma and acute leukemia. Other cancers seen in LFS patients include gastrointestinal cancers and cancers of the lung, kidney, thyroid, and skin, as well as in gonadal organs (ovarian, testicular, and prostate.)

It is important to note that not everyone with a *TP53* gene mutation will necessarily develop cancer, but the risks are substantially higher than in the general population. A diagnosis of LFS is critically important so that affected families can seek appropriate genetic counseling as well as surveillance for early detection of cancer.

Introduction

LFS was first recognized in the 1969 by Drs. Frederick Li and Joseph Fraumeni, Jr., while studying pediatric and familial cancers at the National Cancer Institute. They described four families with multiple early-onset cancers in children and young adults. The syndrome was first reported in a publication as “Li-Fraumeni syndrome” in 1982 by researchers in the United Kingdom who described two families with multiple forms of cancer in young people.

In 1990, inherited variants of the *TP53* gene were discovered as the primary cause of LFS. This finding provided a special opportunity for genetic testing and clinical interventions that enable cancer prevention, early cancer detection, and cancer treatment of people with LFS. The finding also fueled further molecular research into *TP53* which is commonly found in the tumor tissue of cancer patients.

Signs & Symptoms

LFS may be suspected if someone has a personal or family history of cancers featured in LFS. In addition, there are certain rare cancers that are characteristic of the syndrome that should alert clinicians to the potential of a diagnosis of LFS. Patients and families with multiple childhood cancers, or specific rare cancers such as adrenocortical, choroid plexus carcinoma, anaplastic rhabdomyosarcoma, sonic hedgehog medulloblastoma, or hypodipoid acute lymphoblastic leukemia should alert practitioners to the potential of a hereditary cancer syndrome such as LFS. Although increasingly identified as a hereditary cancer syndrome, not all physicians are aware of the diagnosis of LFS.

Cancers most closely associated (core cancers) with LFS include:

• Soft tissue sarcoma
• Osteosarcoma
• Breast cancer
• Brain and CNS tumors (glioma, choroid plexus carcinoma, SHH subtype medulloblastoma, neuroblastoma)
• Adrenocortical carcinoma
• Acute leukemia

Other cancers may also appear, but risks are lower than for the core cancers:

• Lung adenocarcinoma
• Melanoma
• Gastrointestinal tumors (such as colon, pancreas)
• Kidney
• Thyroid
• Gonadal germ cells (such as ovarian, testicular, and prostate)

Individuals with LFS have an approximately 50% of developing cancer by age 40, and up to a 90% percent chance by age 60, while females have nearly a 100% risk of developing cancer in their lifetime due to their markedly increased risk of breast cancer. Many individuals with LFS develop two or more primary cancers over their lifetimes.

Causes

Li-Fraumeni syndrome is caused by an inherited (germline) pathogenic variant of the *TP53* tumor suppressor gene on chromosome 17. LFS was first recognized in 1969, and in 1979, *TP53* was identified in the tumor tissue of more than 50% of all cancer patients. However, it wasn't until 1990 that a *TP53* germline variant was discovered to be the cause of LFS.

LFS follows autosomal dominant inheritance. Most genetic diseases are determined by the status of the two copies of a gene, one received from the father and one from the mother. Dominant genetic disorders occur when only a single copy of an altered gene is necessary to cause a particular disease. The abnormal gene can be inherited from either parent and can result from a new mutation (gene change) in the affected individual. The risk of passing the altered gene from an affected parent to an offspring is 50% for each pregnancy. The risk is the same for males and females.

Most people with LFS have a germline *TP53* gene mutation, but in some individuals, LFS is due to a spontaneous (de novo) genetic variant that occurs in the egg or sperm cell. In such situations, the disorder is not inherited from the parents.

There are many known variations of malfunctioning *TP53*, and each can affect every person in a family differently. Most families with LFS have very high cancer incidence rates, while some others do not, and even within families, the aggressiveness of the syndrome varies. The degree to which a *TP53* variant causes cancer in a family or individual is called “penetrance.”

Individuals with LFS may also be prone to the carcinogenic risks associated with certain lifestyle or environmental exposures, such as tobacco smoking or radiation exposure. LFS patients should take preventive measures to reduce their exposures to behavioral risk factors and carcinogens.

Affected Populations

Though it is challenging to estimate to frequency in the population, there are likely over 1,000 multigenerational families worldwide with LFS. To date, inquiries on the LFS Association website have arrived from 172 countries.

There is no evidence of ethnic or geographic disparity in the occurrence of LFS, but a uniquely high prevalence of LFS has been reported in southern and southeastern Brazil. The population with LFS in this area has been associated with a highly specific variant of the *TP53* referred to as R337H. Having this particular alteration in the region led researchers to suspect one point of origin, and family lineages were traced to a common ancestor who migrated long ago from Portugal. Interestingly, though, as opposed to the 90% lifetime risk of developing cancer in most people with LFS, the population in Brazil with this “founder mutation” has roughly a 60% lifetime risk of cancers, which have relatively favorable survival rates.

Related Disorders

There are several other conditions with an increased cancer risk not related to variants of *TP53*.

Diagnosis

Li-Fraumeni syndrome is diagnosed based on the presence of a so called pathogenic or likely pathogenic variant in the *TP53* gene.

Genetic *TP53* testing is typically considered with the below delineated criteria.

Clinical Testing (Clinical Screening & Genetic Testing)

The potential of genetic testing (and the implications of the results) should always involve discussions with a genetic counselor, medical providers and family.

As delineated by the American Society of Clinical Oncology, the below criteria can be used in determining if genetic testing should be considered:

Classic LFS is diagnosed when a person has all of the following criteria:

• A sarcoma diagnosed before age 45

• A first-degree relative, meaning a parent, sibling or child, with any cancer before age 45

• A first-degree relative or second-degree relative, meaning a grandparent, aunt/uncle, niece/nephew, or grandchild, with any cancer before age 45 or a sarcoma at any age

Chompret Criteria for Clinical Diagnosis of Li-Fraumeni Syndrome is a recent set of criteria that has been proposed to identify affected families beyond the Classic criteria listed above. A diagnosis of LFS and performing *TP53* gene mutation testing is considered for anyone with a personal and family history that meets 1 of the following 3 criteria:

Criterion 1

• A tumor belonging to the LFS tumor spectrum, before the age of 46. This means any of the following diseases: soft-tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumor, adrenal cortical carcinoma, leukemia, or lung cancer, **and**

• At least 1 first-degree or second-degree family member with an LFS-related tumor, except breast cancer if the individual has breast cancer before the age of 56 or with multiple tumors

Criterion 2

• A person with multiple tumors, except multiple breast tumors, 2 of which belonging to the LFS tumor spectrum and the first of which occurred before age 46

Criterion 3

• A person who is diagnosed with adrenocortical carcinoma or a tumor in the choroid plexus, meaning a membrane around the brain, regardless of family history.

In addition, patients with anaplastic rhabdomyosarcoma, women with breast cancer prior to age 31 years, patients with hypodiploid acute lymphoblastic leukemia and SHH medulloblastoma should be tested, regardless of family history.

Li-Fraumeni-Like Syndrome (LFL) is another, similar set of criteria for affected families who do not meet Classic criteria (see above). There are 2 suggested definitions for LFL:

LFL Definition 1, called the Birch definition:

• A person diagnosed with any childhood cancer, sarcoma, brain tumor, or adrenal cortical tumor before age 45 **and**

• A first-degree or second-degree relative diagnosed with a typical LFS cancer, such as sarcoma, breast cancer, brain cancer, adrenal cortical tumor, or leukemia, at any age **and**

• A first-degree or second-degree relative diagnosed with any cancer before age 60

LFL Definition 2, called the Eeles definition:

• 2 first-degree or second-degree relatives diagnosed with a typical LFS cancer, such as sarcoma, breast cancer, brain cancer, adrenal cortical tumor, or leukemia, at any age

Other risk factors to consider, specific to breast cancer:

A woman who has a personal history of breast cancer at a younger age and does not have an identifiable mutation in breast cancer genes 1 or 2, called *BRCA1* or *BRCA2*, may have a *TP53* mutation.

A woman who is diagnosed with breast cancer before age 30 and is not found to have a BRCA mutation has an estimated 4% to 8% likelihood of having a *TP53* mutation.

Women with breast cancer diagnosed between ages 30 and 39 may also have a small increased risk of having a *TP53* mutation.

In younger woman with breast cancer, a *TP53* mutation may also occur with any of the following features: a family history of cancer, especially LFS-related cancers, a personal history of a breast tumor that is positive for estrogen (ER), progesterone (PR), and HER2/neu markers, also known as “triple-positive” breast cancer, and a personal history of an additional LFS-related cancer.

Standard Therapies

Treatment

At this time, there is no standard treatment or cure for LFS or a germline *TP53* gene variant. With some exceptions, cancers in people with LFS are treated the same as for cancers in other patients, but research continues on how to best manage those cancers involved in LFS.

Research has indicated that those individuals with LFS appear to be an elevated risk for radiation-induced cancers, so the use of radiotherapy should be approached with caution. For this reason, computed tomography (CT) scans and other diagnostic

techniques involving ionizing radiation should be limited. However, radiation therapy should not be avoided if the benefits outweigh the risks.

Since those living with LFS are susceptible to the development of a number of different cancers, individuals should ensure that they incorporate simple measures into a healthy lifestyle, such as sun protection and the avoidance of tobacco products.

It has been widely accepted that early cancer detection can greatly increase overall survival, and those diagnosed with LFS should seek to adhere to preventive screening. An expert panel of LFS researchers, oncologists, and genetic counselors has published surveillance recommendations that utilize whole body MRI screening for patients with LFS. This should be offered as soon as the diagnosis of LFS is established. In brief, the screening recommendations involve:

Children (birth to age 18 years)
• General assessment
o Complete physical exam every 3-4 months
o Prompt assessment with primary care physician for any medical concerns

• Adrenocortical carcinoma
o Ultrasound of abdomen and pelvis every 3-4 months
o In case of unsatisfactory ultrasound, blood tests every 3-4 months

• Brain tumor
o Annual brain MRI (first MRI with contrast – thereafter without contrast if previous MRI normal with and no new abnormality

• Soft tissue and bone sarcoma
o Annual whole body MRI

Adults
• General assessment
o Complete physical exam every 6 months
o Prompt assessment with primary care physician for any medical concerns

• Breast cancer
o Breast awareness (age 18 years and forward)
o Clinical breast exam twice a year (age 20 years and forward)
o Annual breast MRI screening (ages 20-75) – ideally, alternating with annual whole body MRI (one scan every 6 months)
o Consider risk-reducing bilateral mastectomy (Note that the use of ultrasound and mammography has been omitted)

• Brain tumor (age 18 years and forward)
o Annual brain MRI (first MRI with contrast – thereafter without contrast if previous MRI normal)

• Soft tissue and bone sarcoma (age 18 years and forward)
o Annual whole body MRI
o Ultrasound of abdomen and pelvis every 12 months

• Gastrointestinal cancer (age 25 years and forward)
o Upper endoscopy and colonoscopy every 2-5 years)

• Melanoma (age 18 years and forward)
o Annual dermatologic examination

Also noted, for families in which breast cancer has already made an appearance at or around age 20 – awareness and screening can be considered 5 to 10 years before the earliest age of onset known. The same is recommended for gastrointestinal cancers – consider screening 5 years before the earliest known onset of a gastrointestinal cancer in the family.

See Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome (June 2017) for more information. (https://www.lfsassociation.org/wp-content/uploads/2017/06/e38.full_.pdf)

Investigational Therapies

Numerous strategies using small molecule drugs to reactivate or modify dysfunctional *TP53* protein are being actively studied, but not yet in clinical trials with LFS patients.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government website.

For information about clinical trials being conducted at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222
TTY: (866) 411-1010
Email:

Some current clinical trials also are posted on the following page on the NORD website: https://rarediseases.org/for-patients-and-families/information-resources/news-patient-recruitment/

For information about clinical trials sponsored by private sources, contact: www.centerwatch.com

For information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/

Li-Fraumeni syndrome was “born” at the National Cancer Institute’s Division of Cancer Epidemiology and Genetics (DCEG), Bethesda, Maryland. DCEG’s Clinical Genetics Branch continues to research LFS:

https://lfs.cancer.gov/about.html#lfs

Many larger medical institutions, as well as cancer institutes, now support cancer genetics programs. In the United States, the below actively conduct LFS research and care for LFS patients:

Children's Hospital of Philadelphia (Philadelphia, PA) http://www.chop.edu/centers-programs/hereditary-cancer-predisposition-program

Dana-Farber Cancer Institute (Boston, MA) http://www.dana-farber.org/Adult-Care/Treatment-and-Support/Treatment-Centers-and-Clinical-Services/Cancer-Genetics-and-Prevention-Program.aspx

Huntsman Cancer Institute (Salt Lake City, Utah) http://healthcare.utah.edu/huntsmancancerinstitute/research/labs/schiffman/

City of Hope National Medical Center (Duarte, CA) https://www.cityofhope.org/research/beckman-research-institute/research-departments-and-divisions/population-sciences/clinical-cancer-genetics

MD Anderson Cancer Center (Houston, TX) https://www.mdanderson.org/research/departments-labs-institutes/programs-centers/li-fraumeni-study-group.html

Memorial Sloan Kettering Cancer Center (New York, NY) https://www.mskcc.org/cancer-care/risk-assessment-screening/hereditary-genetics

International centers for LFS research include:

Peter MacCallum Cancer Center (Victoria, Australia) https://www.petermac.org/research/clinical-research-trials/clinical-research/familial-cancer-research-centre

A. C. Camargo Cancer Center (Sao Paulo, Brazil) http://www.accamargo.org.br/

Hospital for Sick Children (Toronto, Canada) http://www.sickkids.ca/cancergeneticsprogram/

Manchester Centre for Genomic Medicine (Manchester, England) http://www.mangen.co.uk/index.php

Medizinische Hochschule Hannover (Hannover, Germany) https://www.mh-hannover.de/kinderonkologie.html

Please reference the LFS Association website for additional medical resources: https://www.lfsassociation.org/medical-resources/resources/

NORD Member Organizations

- Li-Fraumeni Syndrome Association
  P.O. Box 6458
  Holliston, MA 01746 United States
  Phone: (855) 239-5372
  Email:
  Website: http://www.lfsassociation.org/
- NORD's™ Rare Cancer Coalition™ (RCC)
  1779 Massachusetts Avenue NW
  Ste 500
  Washington, DC 20036 USA
  Phone: (202) 545-3971
  Email:
  Website: https://rarediseases.org/get-involved/rare-cancer-coalition/

Other Organizations

- American Cancer Society, Inc.
  250 Williams NW St
  Ste 6000
  Atlanta, GA 30303 USA
  Phone: (404) 320-3333
  Toll-free: (800) 227-2345
  Website: http://www.cancer.org
- Cancer Care, Inc.
  275 Seventh Avenue
  New York, NY 10001
  Phone: (212) 712-8400
  Toll-free: (800) 813-4673
  Email:
  Website: http://www.cancercare.org
- Genetic and Rare Diseases (GARD) Information Center
  PO Box 8126
  Gaithersburg, MD 20898-8126
  Phone: (301) 251-4925
  Toll-free: (888) 205-2311
  Website: http://rarediseases.info.nih.gov/GARD/

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