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Li- Fraumeni Syndrome

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Abstract

Aim

The aim is to do a literature review on Li-Fraumeni syndrome

Background

Li-Fraumeni syndrome is a rare cancer predisposition hereditary disorder characterised as autosomal dominant. It was named after two American physicians, Frederick per Li and Joseph F. Fraumeni, who recognized the syndrome after reviewing the medical records and death certificate of 648 childhood rhabdomyosarcoma patients. The syndrome is linked to germ line mutations of p53 tumour suppressor gene, which encodes a transcription factor (p53) that normally regulates the cell cycle and prevents genomic mutation by phagocytises or enabling the programmed cell death of the defective cell. In this article, a brief account on the Li-Fraumeni syndrome is attempted.

Keywords: Li-fraumeni syndromes

INTRODUCTION

Li-Fraumeni syndrome is an inherited autosomal dominant disorder that is manifested by a wide range of malignancies that appear at an unusually early age.[1] Li-Fraumeni syndrome is also known as the Sarcoma, Breast, Leukaemia, and Adrenal Gland (SBLA) cancer syndrome. This cancer predisposition syndrome is inherited as an autosomal dominant disorder and is associated with abnormalities in the tumour protein p53 gene (*P53*). Both conditions significantly increase the chances of developing multiple cancers beginning in childhood; however, the pattern of specific cancers seen in affected family members is different.[2] It is only a factor or a cause that pave way for many cancers because it destroys the controlling activity of the p53 gene in the cell. This p53 gene is located at the chromosome **17p13.1**. So any malignant or a tumour cell which has formed by genetic mutations is not destroyed. Since the cell division rate of the cell is very high it divides fast and cause many cancer syndromes. Moreover, the families have inherited mutations.[3]

Clinical definitions for Li-Fraumeni syndrome

Many clinical definitions have been proposed to define or to detect a Li-Fraumeni syndrome. Some of them are

The classic Li-Fraumeni syndrome (LFS*)*

This was explained by Li et al., in 1988 according to this definition

- → A probands with a sarcoma diagnosed before age 45 years
- → A first-degree relative with any cancer before age 45 years
- → A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age

Chompret criteria

This was explained by Bougeard et al., in 2015. According to this definition

- → <u>Familial presentation:</u>
  Probands with tumour belonging to LFS tumour spectrum (e.g., premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumour, adrenocortical carcinoma) before age 46 years, and at least one first or second-degree relative with LFS tumour (except breast cancer if probands has breast cancer) before age 56 years or with multiple tumours;
- → <u>Multiple primary tumours:</u>
  Probands with multiple tumours (except multiple breast tumours), two of which belong to LFS tumour spectrum and first of which occurred before age 46 years;
  <u>rare tumours:</u>
  Patient with adrenocortical carcinoma, choroid plexus tumour, or rhabdomyosarcoma of embryonic anaplastic subtype, irrespective of family history;
  <u>Early-onset breast cancer:</u>
  Breast cancer before age 31 yr.[4]

Birch criteria

- → a proband with any childhood cancer or sarcoma, brain tumour or adrenal cortical carcinoma diagnosed before age 45,
- → a first or second degree relative with a typical LFS malignancy (sarcoma, leukaemia, or cancers of the breast, brain or adrenal cortex) regardless of age at diagnosis
- → a first or second degree relative with any cancer diagnosed before age 60[4]

Eeles criteria

- → Two first or second-degree relatives with LFS-related malignancies at any age.[4]

Physiology of Li-Fraumeni syndrome

Li-Fraumeni syndrome links to the gene TP53. Mutations can be inherited or can arise early in embryogenesis or it is present in one of the parent's germ cells. Approximately 70% of Li-Fraumeni syndrome and 40% of Li-Fraumeni–like families have gremlin mutations in the *TP53* tumour suppressor gene. Over 767 gremlin mutations and 29, 881 somatic mutations have been identified in the *TP53* gene.[5]

The TP53 gene is located on band 17p13.1, coding for 53-kd nuclear protein transcription factor that has important regulatory control over cell division, specifically the DNA repair processes, and apoptosis that inhibits the production of tumour or an abnormal cell.

Somatic*TP53* tumour suppressor gene mutations are common in sporadic human cancers. This shows the importance of*TP53* in cancer. Alterations in this gene cause the development of cancer. A broad range of cell line and transgenic animal experiments on the action of the gene show direct involvement of *TP53* mutations in malignant transformation. Mutation of p53 function are the result of either loss of function of wild type p53, increased or aberrant protein function, or dominant negative effects of the mutated protein.[6]

P53 gene and the ubiquitin ligase HDM2 has shown to interact with one another. E3 and E4 ubiquitin ligase UBE4B to induce the polyubiquitination and degradation of p53, which resulting in apoptosis of medulloblastoma and ependymoma cells. Over expression of UBE4B was also associated with amplification of its gene in brain tumours.

These laboratory data support the hypothesis of constitutional mutations as the etiology of Li-Fraumeni syndrome. Although inactivation of *TP53* confers a predisposition to cancer, this alone is not sufficient because not all families with classic Li-Fraumeni syndrome or Li-Fraumeni–like syndrome have detectable alterations of *TP53*. The absence of detectable germ line *TP53* mutations in some families suggests that other genes might be involved in the syndrome or that the p53 protein may undergo posttranslational alterations.

Specifics of the inherited *TP53* mutation may have a significant effect on the cancer phenotype in the affected family. Most Li-Fraumeni syndrome–associated *TP53* defects involve missense point mutations occurringin a hot-spot region of exons 5-8, a portion of the gene that codes for the core DNA-binding domain of the protein. Missense mutations lead to a stable but inactive protein, which accumulates in the nucleus of tumour cells. Frame shift, nonsense, and splice-site mutations can also be present, but there is no accumulation of protein. Constitutional mutations in the hot spot region display more aggressive cancer phenotypes than patients with other *TP53* mutations and those patients that appear to lack any heritable defect. Families with mutations in the hot spot region include those with younger probands at the time of cancer diagnosis. Mutations in exons 5-8 are also associated with a higher overall incidence in family members with breast cancer and CNS tumours diagnosed when patients are younger than 45 years, suggesting a higher rate of penetration of the cancer phenotype in families with these types of inherited *TP53* defects.[6]

Single nucleotide polymorphisms in both *TP53* and *MDM2*, an integral component of p53 function, appear to influence the age of cancer onset in Li-Fraumeni syndrome. Short telomeres are also associated with younger age of onset of first cancer in Li-Fraumeni syndrome families. Genomic copy number variation, used as a marker of genetic instability, is higher in patients with germ line *TP53* mutations than in healthy controls.[7]

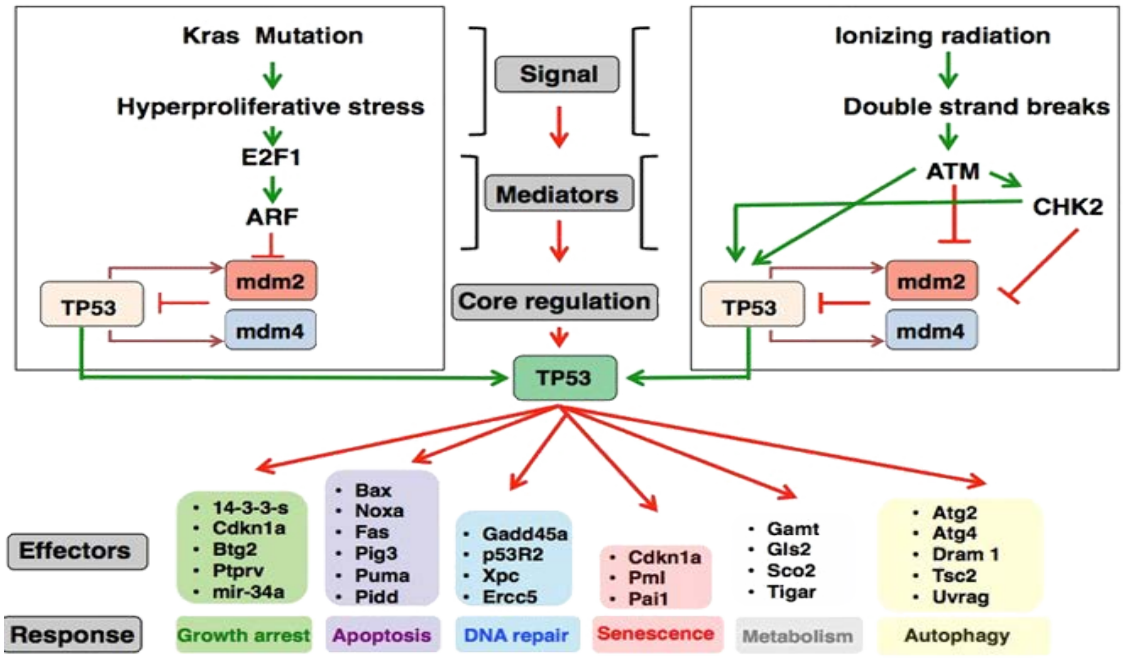


Image 1- overall activity of p53

Prevalence of Li-Fraumeni syndrome globally

The Li-Fraumeni syndrome was first observed in United States. Now it affects less than 200,000 people in the US population. One U.S. registry of Li-Fraumeni syndrome patients suggests that about 400 people from 64 families have this disorder. In European population, it affects one in 2000 people. It is common among the orphan population. It was previously thought that the incidence of the syndrome is one in 5000 and it has become one in 20000 of the world population[8]

Prevalence in sexes

The Li-Fraumeni syndrome is very common in women population than in men. Kelly D. Gonzalez and co. [5] Has done a study to demonstrate the syndrome. First, they have selected DNA from 530 patients for genotyping p53 gene, which was obtained from their peripheral blood. They then collected the personal and family history adding the type of genetic mutation occurred. They have found 91 patients of 530 having mutations. In their study breast, cancer was the common cancer seen. In the patients. Most of them came under Eeles and Chompret classification. According to them, the sex specificity was not significant, but females are more susceptible to the syndrome. The common cancer occurring in females are breast cancer (Jonathan D. Wasserman ET all). [9]

Inheritance of Li-Fraumeni syndrome

Normally, every cell has two copies of each gene; one inherited from the mother and one inherited from the father (paternal). Li-Fraumeni syndrome has an autosomal dominant inheritance pattern, which means even if a mutation happens in only one of the two copies of the *TP53* gene, the person or the daughter will have Li-Fraumeni syndrome. Most people with Li-Fraumeni syndrome have one normal copy of *TP53* and one mutated copy of *TP53*, because they have inherited both the copies from the parent *(image-3*). However, it is estimated that 25% of people with Li-Fraumeni syndrome do not have any family history of the condition (example a case by Ami P. Javari et.al); they have a *de novo* mutation in the *TP53* gene. Regardless of whether a person inherits a mutation or the mutation occurs for the first time in a person, that person has a 50% chance of passing on the normal copy of the *TP53* gene and a 50% chance of passing on the mutated copy of the gene to his/her child. A brother, sister, or parent of a person who has a mutation also has a 50% chance of having the same mutation

Options exist for couples interested in having a child when they know that one of them carries a gene mutation that increases the risk for this hereditary cancer syndrome. Pre implantation genetic diagnosis (PGD) (*image-4*) is a medical procedure done in conjunction with in-vitro fertilization (IVF). It allows people who carry a specific known genetic mutation to have children who do not carry the mutation. A woman's eggs are removed and fertilized in a laboratory. When the embryos reach a certain size, one cell was removed and is tested for the hereditary condition in question. The parents can then choose to transfer embryos that do not have the mutation. PGD has been in use for over two decades, and had been used for several hereditary cancer predisposition syndromes. However, this is a complex procedure with financial, physical, and emotional factors to consider before starting. [6]

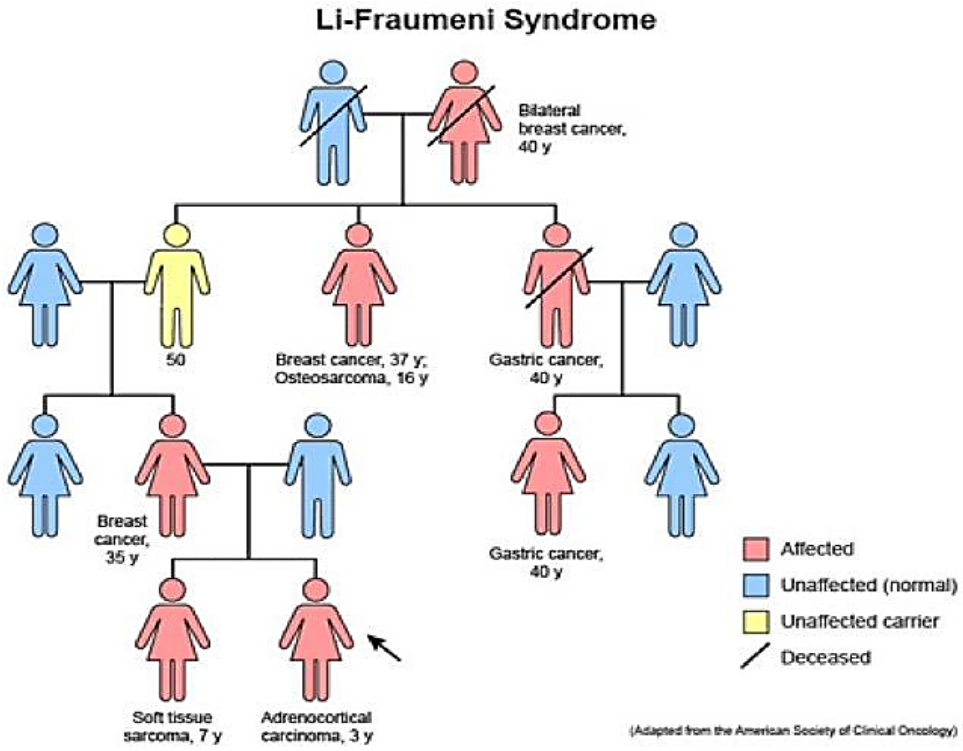


Image-3 inheritance pattern

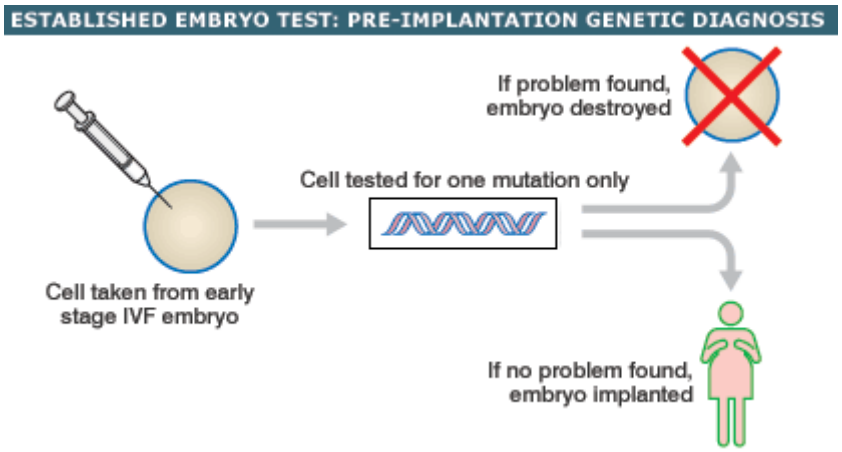
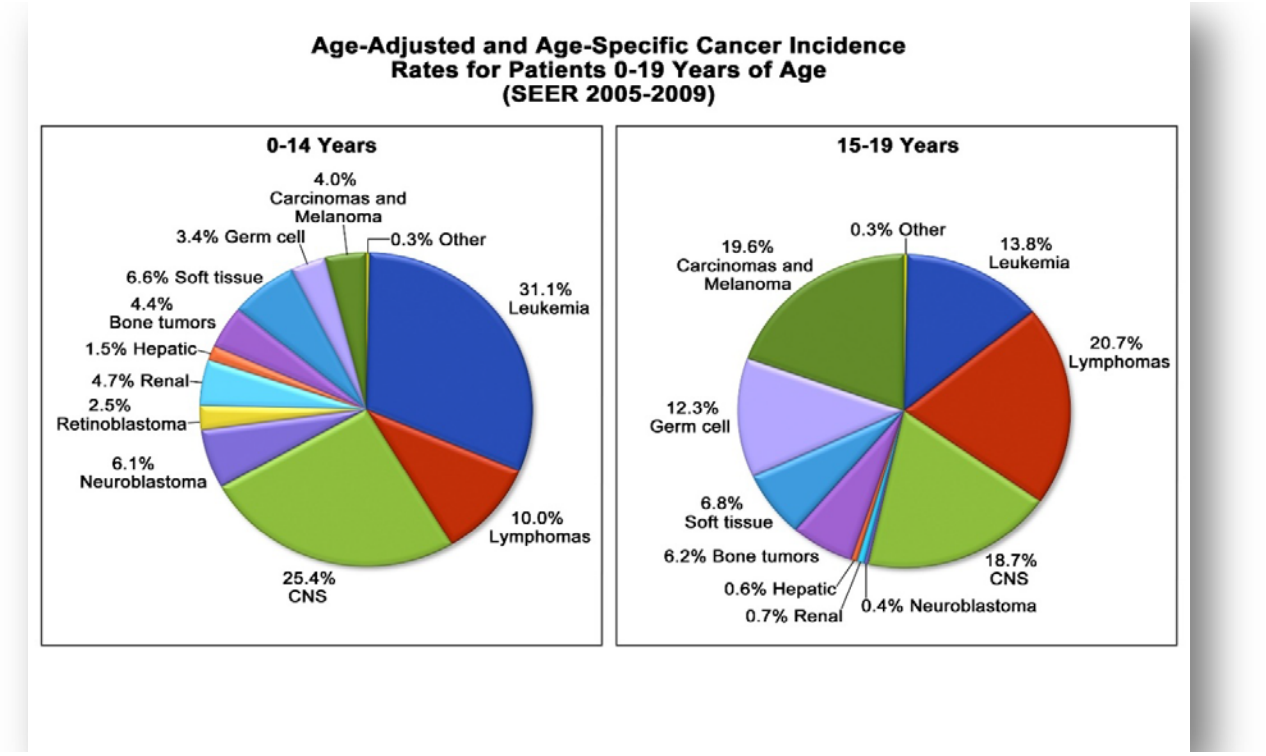


Image-4 Preimplantation genetic diagnosis



Age specificity in Li-Fraumeni syndrome

Specific type of cancer occurs in specific age group. The syndrome mostly occurs in young childhood years and age below 30.

✓ Children

They mostly develop adenocarcinoma. It also causes brain tumour, bone carcinoma etc…

✓ Adults

In adult the onset is significant with the features like pain, illnesses, particularly headaches, bone pain, or abdominal discomfort all are seen. Most common cancer is breast cancer followed by brain tumour, melanoma, leukaemia, soft tissue carcinoma. [4]

Risk of Li-Fraumeni syndrome

The lifetime risk for a person with LFS to develop any type of cancer is 90%. Approximately 50% of these cancers will be diagnosed before age 30. In a study of 200 people with a *TP53* gene mutation who had a previous diagnosis of cancer, 15% developed a second, 4% developed a third cancer, and 2% developed a fourth cancer, with the highest risk of additional cancers being in those diagnosed with their first cancer during childhood. However, some people with LFS will never develop cancer. [7]

Cases of Li-Fraumeni syndrome

✓ Ilic et. Al has diagnosed a family case in which the members of the family were diagnosed with various cancers. The father who was 24 years old was diagnosed and treated for osteosarcoma of the maxilla died in the first year. His younger brother was admitted for osteosarcoma of the mandible three years later and a year later at the age of 24 years he had no sign of the loco

regional recurrence. Then their mother was operated for glioblastoma multiform brain cancer and ductal carcinoma and died 2 years later[(2)]

- ✓ Tena Sanabria ME et. al has diagnosed a case the family history is that the grandfather had melanoma and aunt had osteoblastic osteosarcoma of left femur bone. An eight and a half years old child with a history of a CNS tumour and two years later, a melanoma. The symptoms that he observed was impaired motor function of the left half of the body and pain upon ipsilateral gait; swelling of left iliac chest. He also found a positive result for fine needle aspiration cytology and the X-Ray shows osteoblastic osteosarcoma. The case which was examined by Tena Sanabria ME et. al shows an evident association between both choroid plexus carcinoma and osteoblastic osteosarcoma and the patient's family history. So they have concluded that the professionals handling sarcoma in children should take care of multiple familial cancer syndromes.[(3)]
- ✓ Ami P. Javari has done a case presentation in which they observed a typical Li-Fraumeni syndrome. In their case, an 11-year-old girl was diagnosed for a bump in the left calf that gradually increased in size. Then a biopsy of the bump was done; it revealed that she had Rhabdomyosarcoma. She was given chemotherapy along with radiation therapy. After one year recurrence was observed and amputation of left limb was done at the age of 12 years. Later a palpable bump in the right lower ribs was found and diagnosis was chondrosarcoma. Next at the age of 18 she was found to have a cyst in one of her vulva; that was a stage one leiomyosarcoma. Her family history shows that her grandfather had bladder cancer at age 85, her great aunt had uterine cancer around age 40 and her great uncle had lung cancer at an unknown age; Neither her mother or brother had any cancer syndromes. At the age of 27 she underwent germline genetic testing for any gene mutations and her testing revealed that heterozygous splice site mutation in TP53, IVS6-2A>G, and no other mutations in cancer-related genes. At the age of 27 she underwent her routine MRI and was found to have 5mm abnormality in left breast; it was a invasive ductal carcinoma with ER positive, PR pos-itive, HER2 positive(3+ on immunohistochemistry). She underwent lumpectomy. She now does annual MRI examination, dermatological check up every year.[(4)]

Recent Research in Li-Fraumeni Syndrome

- ~ Suzanna et.al, in 2015 has done a research in germ line p53 mutations in breast cancer. In their study they initially collected past history and performed bi-directorial sagar sequencing of all protein encoding TP53 gene from peripheral blood lymphocytes DNA breast cancer ovaries and was found that many of them was carriers including five families have TP53 mutations[6]
- ~ Tatiane R. Bosso et.al in 2015 has done a research on genomic profiling in Li-Fraumeni syndrome in a woman and found that the Li-Fraumeni syndrome had occurred due to the different unusual karyotype 45,X/46,XX that showed papillary thyroid carcinoma fibro sarcoma of the left flank, and had no *TP53* germ line mutations[10]
- ~ John M. Parant et.al in 2010 had done a research in which zebra fish wasselected. They used forward genetic screening in zebra fish embryos that had been used to identify LFS candidate genes, which yielded a p53 mutant in the zebra fish produce sarcoma similar to that in human sarcoma. The tumour arises due to and display loss of heterozygosity (LOH). This is attributed to Knudson's two-hit hypothesis, which is the hallmark of most human autosomal dominant cancer syndromes. In addition, they also demonstrated the p53 regulatory pathway, including Mdm2 regulation in their study.[11]

CONCLUSION

Thus, Li-Fraumeni syndrome is a rare syndrome that acts as a predisposition factor for multiple cancer syndromes. The TP53 gene in cells acts as a barrier to prevent development of many cancer tumours. The importance of this gene is also discussed here. Thus there are many factors for development of Li-Fraumeni syndrome and there is also many other germline factors which act as a causative factor for this syndrome. Lot of current research are being done on Li-Fraumini syndrome.

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