Li-Fraumeni syndrome

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Identity

Note
Families with Li-Fraumeni syndrome (LFS) are defined by: a proband with a sarcoma aged under 45 years, with a first degree relative with cancer under 45 years and another first or second degree relative with any cancer under 45 years or a sarcoma at any age.

Inheritance
Autosomal dominant, high penetrance (100% lifetime risk in females, 75% in males).

Clinics

Phenotype and clinics
No associated dysmorphologies or abnormalities.

Neoplastic risk
Very high.
The main neoplastic risks are bone, cartilage and soft tissue sarcomas, early-onset female breast cancer, brain and spinal cord tumours, childhood adrenocortical tumours, Wilms’ tumour and malignant phyllodes tumours.

There is no increased incidence of a number of cancers which occur frequently within the population, such as colorectal, lung, bladder and gynaecological malignancies.

Some other tumour types occur rarely, but more frequently than expected; these include pancreas, peripheral nervous system, leukaemia and stomach.

Genes involved and proteins

TP53

Location: 17p13

DNA/RNA
Description: 11 exons, the first of which is non-coding.

Protein
Description: p53, a 393 amino acid protein.

Function: p53 is the most commonly mutated gene in human cancers possessing multiple properties; p53 has two major roles. Firstly in cell cycle arrest, predominantly in the G1 phase of the cell cycle, but also with a role in G2 and mitotic checkpoints. Secondly the induction of apoptosis (programmed cell death).

Both these are induced upon DNA damage, and the response depends on many things including the type of damage and the cell type.
p53 is a transcription factor with a central sequence-specific DNA binding domain and a N-terminal transactivation domain; upon DNA damage, the level of p53 increases markedly, and the DNA-binding properties are activated; the levels of p53 are regulated primarily post-transcriptionally (including phosphorylation and acetylation).

Mutations
Germline: there are over 200 published reports of germline mutations.

Over 75% of families with classic LFS have a germline TP53 mutation.

Lower proportions of families with some features of LFS have such mutations.

Children with adrenocortical carcinoma have an extremely high incidence of germline mutations (over 80%).

The spectrum of mutations in the germline is superficially the same as somatic mutations, but there are some significant differences.
hCHK2

Location: 22q12.1

DNA/RNA Description: 14 exons.

Protein

Description: a 543 amino acid protein with homology. To Saccharomyces cerevisiae RAD53 and Schizosaccharomyces pombe cds1.

Function: a protein kinase which is required for DNA damage and replication checkpoints; CHK2 is phosphorylated by ATM, and in turn can phosphorylate p53 at serine-20; it appears that germline hCHK2 mutations are uncommon in LFS.

References


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