LETTER TO EDITOR

Importance of diagnosis and surveillance of patients with genetic predisposition to cancer: regarding the TP53 gene

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To the editor

Li-Fraumeni Syndrome (LFS; OMIM #151623) is a hereditary cancer predisposition syndrome with an autosomal dominant inheritance pattern and a high risk of developing early-onset neoplasms at any life stage. The tumor spectrum is broad and most frequently includes tumors of the central nervous system, adrenocortical carcinoma, osteosarcomas, sarcomas, malignant hematological neoplasms, and breast cancer. Rare neoplasms such as choroid plexus tumors, acute lymphoblastic leukemia with hypodiploidy, anaplastic rhabdomyosarcoma, sonic hedgehog subtype medulloblastoma (SHH), and osteosarcoma are highly suggestive of LFS (1).

This monogenic condition was first described in 1969 by Frederick Li and Joseph Fraumeni, who observed a high frequency of different types of cancer in family groups (2). In 1990, Malkin identified a germline mutation in TP53—whose protein is considered the "guardian of the genome"—closely related to the LFS phenotype (2). Subsequent studies revealed that approximately 70% of families with LFS harbor some germline mutation in the TP53 gene (3).

The most common type of alteration found in the TP53 germline is nonsense mutations, which make up around 75% of cases. These mutations affect 97% of the residues in the DNA-binding domain. Six mutations have been identified in this domain at critical points for codons 175, 245, 248, 249, 273, and 282 (3).

Malkin et al. suggested that by 1990, around a thousand families from 172 countries suffered from LFS (4). It is evident that the number of individuals carrying mutations in the TP53 gene has increased in the last two decades due to advances in diagnostic methodologies in genomics and greater access to them. For example, Brazil has reported the highest prevalence in the world, concentrated in the South and Southeast areas of the country, estimating a prevalence of one LFS case in 300 inhabitants. This high population frequency of carriers with genetic alterations in TP53 is due to the presence of a founder pathogenic variant (p.R337H) circulating in that region (2,5). For the rest of the world, the prevalence of individuals with pathogenic and likely pathogenic mutations in TP53 is estimated to range between 1 in 3,555 to 1 in 5,476 inhabitants (6), with variable distribution and presentation.

The phenotypic characterization of LFS has evolved since the discovery of the gene. Not all patients with clinical criteria for LFS present genetic alterations in TP53, nor will all carriers of pathogenic and likely pathogenic variants in this gene develop LFS-associated neoplasms. Therefore, a new phenotypic classification for LFS, recently proposed by Kratz et al., is now considered internationally (7). Please refer to Figures 1 and 2 for a detailed explanation of the phenotypic presentation and neoplasms associated with LFS.

Currently, there are clinical practice guidelines for the management and follow-up of patients with LFS (1). To achieve this, experts worldwide have established registries of patients and families with LFS, contributing to understanding what risks exist in people with a mutation in the TP53 gene and how they should be managed. These findings have been shared with the

Cite as:
Guerrero-Juscamayta M, Franco-Bustamante K, Cruzate Cabrejos V, Manassero-Morales G, Poterico JA. Importancia del diagnóstico y la vigilancia de pacientes con predisposición genética al cáncer: a propósito del gen TP53. Investig Innov Clin Quir Pediatr. 2023;1(2):74-6. doi:10.59594/iicqp.2023.v1n2.70

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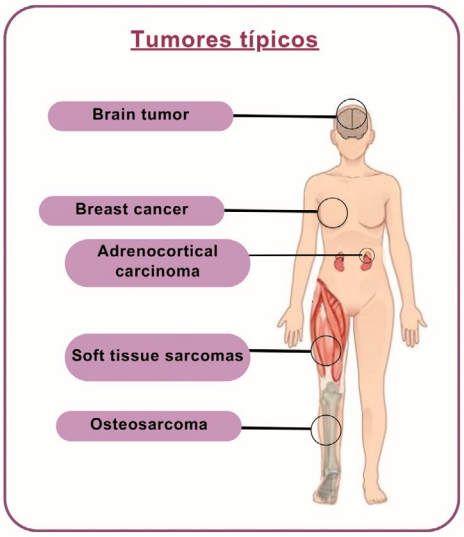
Received: 10/17/2023
Accepted: 10/23/2023
Published: 12/29/2023

A

Classic SFL Criteria	
Testing with sarcoma of diagnosis before the age of 45, and also meeting these 2 criteria	
First-degree relative with any neoplasm before age 45.	First or second-degree relative with any neoplasm diagnosed before age 45 or a sarcoma presenting at any age

SLF Genetic Testing Criteria (Chompret's Criteria)	
Category A	Category B
Person presenting with a typical tumor, before age 46 years and ≥ 1 first- or second-degree relative with a typical tumor before age 56 years (not breast cancer, if the proband had breast cancer).	• Adrenocortical carcinoma • Choroid plexus carcinoma. • Breast cancer before the age of 31 years • Osteosarcoma. • Infantile hypodiploid acute lymphoblastic leukemia • Anaplastic rhabdomyosarcoma. • Sonic hedgehog medulloblastoma.
Person with ≥ 2 tumors (do not consider multiple breast cancer), two of which are typical tumors, the first having occurred before age 46.	

B



A, Classical criteria and Chompret criteria for the diagnosis of Li-Fraumeni Syndrome. B, Typical tumors associated with Li-Fraumeni Syndrome. SFL: Li-Fraumeni syndrome. Figure based and adapted according to the publication by Kratz et al. (7).

Figure 1. Criteria for diagnosis of Li-Fraumeni Syndrome.

Li-Fraumeni spectrum					
Li-Fraumeni spectrum Phenotypic	Hereditary cancer syndromes related to *TP53* gene				
	Li-Fraumeni syndrome	Attenuated Li-Fraumeni syndrome	Incidental Li-Fraumeni syndrome	Li-Fraumeni syndrome carrier	Carrier of attenuated Li-Fraumeni synd
Person not carrying pathogenic/likely pathogenic germline variant of TP53 (or germline mosaic).	Carrier of pathogenic/likely pathogenic germline variant of TP53 (or germline mosaic).	Carrier of pathogenic/likely pathogenic germline variant of TP53 (or germline mosaic).	Carrier of pathogenic/likely pathogenic germline variant of TP53 (or germline mosaic).	Carrier of pathogenic/likely pathogenic germline variant of TP53.	Carrier of pathogenic/likely pathogenic germline variant of TP53.
y	y	y	y	y	y
No other genetic explanation.	Satisfies testing criteria for Li-Fraumeni syndrome and/or any cancer before age 18.	(History of) cancer that does not meet the testing criteria for Li-Fraumeni syndrome.	No (history of) cancer.	No (history of) cancer.	No (history of) cancer.
y		y	y	y	y
It meets the classic criteria for Li-Fraumeni syndrome or category A of the Chompret Criteria.		Cancer-free before the age of 18.	No SLF or attenuated SLF in the family.	Li-Fraumeni syndrome in the family.	Attenuated Li-Fraumeni syndrome in the family.

Definition of the clinical spectrum of Li-Fraumeni and its relation to the presence or absence of pathogenic/probably pathogenic variant, age at the time of cancer presentation, and compliance with the testing criteria for Li-Fraumeni syndrome. The figure is based on and adapted from a publication by Kratz et al. (7). The light blue color scale shows the "intensity" of the phenotype.

Figure 2. Li-Fraumeni spectrum and hereditary cancer syndromes related to TP53 gene.

medical community through scientific publications. In this way, in the United States and Canada, the implementation of clinical surveillance in individuals carrying mutations in the TP53 gene allowed for greater overall 5-year survival (88.8%) compared to those who did not receive it (59.6%) (8).

In Peru, there is no publicly available database or scientific report on families with a genetic predisposition to cancer and their geographical or ancestral distribution. It is crucial to gather information on these variables and statistics, including the types of genetic alteration and phenotype present in both adult and pediatric populations in Peru. Collecting this data

will provide a clearer picture of which population groups require higher budgetary health investment for prevention, diagnosis, and treatment.

In addition to reducing exposure to diagnostic and therapeutic radiation, avoiding carcinogens, and promoting healthy habits, as well as early detection of neoplasms, innovative perspectives are being explored in the care of patients and families with LFS. Research has been oriented towards the development of specific anticancer therapies based on genotype (9). Among these strategies, synthetic lethality and liquid biopsy have emerged as notable approaches. Synthetic lethality focuses on selectively attacking cancer cells that have mutations absent in normal cells (9). In cells with p53 mutations, the possibility of inducing synthetic lethality by inhibiting S or G2/M checkpoint regulators has been observed. However, this therapy still presents challenges that require long-term research due to the numerous variables involved (9). On the other hand, liquid biopsy also offers hope for TP53 carriers, as it can facilitate early disease detection and monitor relapses (10). Although it is still a relatively unexplored field, it shows promising possibilities for prevention, especially in countries with limited resources like Peru.

In summary, it is clear that early detection of LFS requires precise phenotypic classification. This classification can be fundamental in preventing and following up with patients at high risk of developing malignant neoplasms, developing complex treatments, and informing healthcare strategies. Furthermore, it is imperative that Peru establishes a national registry that includes patients with a genetic predisposition to cancer and that this data is adequately disseminated through scientific publications. This will not only benefit patients and their families but will also significantly advance the understanding and distribution of resources for patients with cancer and rare diseases.

Authorship contributions: MGJ, JAP conceptualized the idea. MGJ, JAP, KFB, VCC, and GMM participated in drafting and revising the manuscript.

Financing: self-financed

Conflicts of Interest: The authors declare no conflicts of interest.

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