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# Genotype Versus Phenotype: The Yin and Yang of Germline *TP53* Mutations in Li Fraumeni Syndrome

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Li Fraumeni syndrome (LFS) is one of the most well-recognized cancer predisposition syndromes and serves as a paradigm for the study of heritable susceptibility to cancer. LFS was first reported in 1969 by Li and Fraumeni on the basis of the identification of four families characterized by the autosomal dominant transmission of early-onset tumors.[1,2] Individuals with LFS are predisposed to develop six core component tumors, including soft tissue and bone sarcomas, breast cancer, CNS tumors, adrenocortical carcinomas (ACCs), and acute leukemias,[3] as well as a spectrum of other neoplasms that occur less commonly but at higher frequencies and at younger ages compared with the general population.[4-7] Individuals with LFS are also prone to develop second malignant neoplasms (SMNs); the risk is greatest in those who survive cancer during childhood.[8] In 1990, it was determined that LFS is caused by heterozygous germline mutations in *TP53*, which encodes the p53 tumor suppressor.[9] Also known as the so-called guardian of the genome, p53 is a critical transcription factor that promotes cell-cycle arrest, apoptosis, and DNA repair in response to cellular stresses such as exposure to ionizing radiation.[10] Mutations that interfere with the transcriptional activity of p53 reduce its growth suppressive functions. Accordingly, individuals with LFS, who harbor one mutated copy of *TP53* in the germline, are at increased risk for tumor formation.

The discovery of *TP53* as the gene that is defective in LFS has paved the way for its analysis in cancer-prone individuals and families; more than 500 patients with LFS have been described in the literature,[11] and many more have been identified but not yet reported. It is currently estimated that the *TP53* mutation carrier rate is at least one in 5,000.[12] LFS is more common in Southern Brazil because of the presence of an R337H founder mutation that has a high population prevalence of nearly 0.3%.[13-15] The spectrum of LFS-associated *TP53* mutations can be separated into two general categories on the basis of the mutations' effects on p53 function. The first category includes missense alterations within the DNA binding domain, which confer a dominant-negative effect on wild-type p53 function, as well as enable mutated p53 to acquire additional activities that promote cancer development (these are collectively referred to as gain of function mutations). The second category includes nonsense and frame shift mutations, as well as partial or whole gene deletions, which confer a loss of function.[11]

Although initial genetic studies allowed for a better understanding of the incidence and spectrum of LFS-associated *TP53* mutations, many questions have remained unanswered regarding the relationship between *TP53* genotype and LFS phenotype. For example, what are the age-specific cancer risks for children and adults with LFS? How do these risks differ depending on the underlying *TP53* mutation? How do tumor stage, pathology, and outcome differ in individuals with LFS versus those without the condition? Finally, what are the host and/or environmental factors that influence these parameters, and how can this information be used to guide management and optimize outcome?

It has been almost 25 years since the discovery of *TP53* as the defective gene in LFS. Nonetheless, the answers to these questions have been slow to emerge. This is in part a result of the rarity of LFS; most centers amass only a limited number of affected individuals. In the article that accompanies this editorial, Bougeard et al[16] describe clinical and genetic findings from a large cohort of 214 families with LFS, including 415 *TP53* mutation carriers who were followed over a 20-year period spanning the years 1993 to 2013. For each *TP53* mutation carrier, data were collected on the number, type, and location of tumors and on the date of death. Consistent with the known increase in tumor risk in LFS,[11,17,18] 322 mutation carriers (78%) developed one or more cancers. The tumor spectrum was similar to that previously described, and in women primarily included early-onset breast cancers; 127 (79%) were diagnosed at an average age of 35 years. Soft tissue sarcomas were the second most common tumor type in adults and were observed in 27%. There was also a high incidence of childhood tumors; 22% of mutation carriers developed a cancer by age 5 years, and 41% by age 18 years. Remarkably, 18 mutation carriers (4%) developed a cancer during the first year of life. In children, the tumor spectrum mainly included osteosarcomas (30%), ACC (27%), CNS tumors (26%), and soft tissue sarcomas (23%).

In this investigation, individuals underwent comprehensive *TP53* genetic analysis, which enabled a systematic evaluation of the relationship between *TP53* genotype and clinical phenotype. Among the 214 families analyzed, 133 distinct *TP53* mutations were identified, and the spectrum matched those previously reported.[11,19,20] Comparison of the age at cancer onset between those with missense mutations (including dominant-negative mutations affecting the DNA binding domain) versus loss-of-function mutations revealed a statistically significant younger age of onset for patients with missense mutations (23.8 *v* 28.5 years). This difference was even greater when the analysis included only patients with

  

dominant-negative *TP53* DNA binding domain mutations versus those with loss-of-function mutations. As might be expected, there was enrichment for dominant-negative mutations in younger individuals; these mutations were seen in 40%, 62%, and 36% of children presenting with osteosarcoma, CNS tumors, or rhabdomyosarcoma, respectively. In contrast, and consistent with the literature,[21] the majority of patients with childhood ACC (76%) harbored mutation types other than dominant-negative mutations.

The authors are commended for completing this study, which is one of the largest and longest running of its kind. This work confirms once again the extremely high lifetime cancer risk in *TP53* mutation carriers and the strong association with breast cancer development in women and sarcoma, CNS tumors, ACC, and leukemia development in children. Despite this important observation, this study leaves many questions unanswered. For example, the study does little to increase knowledge regarding the clinical and pathologic features of the cancers that occur in LFS. Other than corroborating previously reported pathologic characteristics of LFS-associated breast cancers[22] and RMS,[23] this report provides no data on stage, histology, or response to therapy for any of the other cancers observed in the LFS cohort. One of the more problematic issues in LFS relates to SMNs, which cause significant morbidity and mortality. Unfortunately, limited information is presented regarding the latency, spectrum, and genotype-phenotype correlations that are associated with the onset of SMNs. Although it is proposed that SMNs might result from the genotoxic effects of the therapies that are administered for a primary cancer, again, minimal data on radiation exposure and no information about chemotherapy are provided. Therefore, it is not possible to establish whether or how previous therapy influences the risk and timing of development of SMNs. If these data are available, they will provide great opportunities to address and even answer the important questions posed by clinicians regarding the actual impact of therapy on the likelihood of induction of secondary tumors, or even the likelihood (or lack thereof) of treatment response.

On the basis of associations between *TP53* genotype and tumor phenotype, the authors propose to stratify clinical management depending on *TP53* mutation status. For families harboring dominant-negative *TP53* mutations in whom cancers occur early, the authors suggest that it is appropriate to test children and to institute cancer screening in those who test positive for a germline mutation. In contrast, in families with loss-of-function mutations who demonstrate later occurrence of cancers, it might be more effective to test and screen adults, particularly women, who can then be monitored for the development of breast cancer and offered preventive measures such as bilateral mastectomy. Finally, for families harboring mutations linked to ACC, perhaps *TP53* testing should be offered to children and screening should be tailored specifically to the detection of ACC.

In theory, stratifying management according to *TP53* genotype could reduce the psychological stress and financial burdens that are associated with genetic testing and cancer surveillance. However, it must be recognized that there is a wide range in the age of onset of cancers in individuals with LFS, regardless of the underlying *TP53* mutation. Indeed, as shown by the authors of this report, there is a great degree of overlap between the ages of cancer onset in individuals carrying dominant-negative versus other types of *TP53* mutations. This property makes it challenging to determine when and in whom to begin or stop surveillance. Furthermore, there is no cancer type that is exclusively associated with any class of *TP53* mutation or any specific *TP53* variant. A good example is the R337H mutation, which previously had been thought to predispose primarily to ACC. Recent reports reveal that this mutation now also predisposes to choroid plexus carcinoma[24] and to breast cancer, where its prevalence is as high as 12.1% in Brazilian women who present before the age of 45 years.[25] To understand how penetrance and expressivity are influenced in LFS, investigators are searching for the factors that cooperate with or modify the effects of mutant p53. Toward this end, several factors have been identified, including the burden of copy number variations in the genome[26]; the presence of shortened telomeres[27]; and single-nucleotide polymorphisms within *TP53*,[14,28] the p53 inhibitor *MDM2*,[28] and the miR-605 microRNA (which is induced by p53 and targets MDM2).[29] Many more such modifying factors are surely to be identified with the application of next-generation sequencing approaches during the analysis of tumor or germline tissues from individuals with LFS.

Decisions regarding *TP53* testing and tumor monitoring are crucial, given that most cancers in LFS are solid tumors for which the outcome is usually stage dependent. In children, this is true for ACC, for which advanced-stage disease predicts a poorer prognosis; 5-year overall survival is only approximately 20% for those with metastases.[30] With advanced-stage disease, complete surgical resection is more difficult and treatment usually incorporates a greater number or higher doses of chemotherapy, as well as radiation. These factors negatively influence short- and long-term outcomes, with radiation also increasing the risk for SMNs. In light of these issues, and on the basis of reports that have described positive outcomes for patients with LFS undergoing surveillance,[31,32] it seems premature to make decisions about tumor monitoring strictly on the *TP53* genotype.

Overall, the current study represents a comprehensive evaluation of an important patient cohort. Continued efforts to understand the factors that influence LFS phenotype, the interaction between these factors and *TP53* genotype, and the risks and benefits of *TP53* testing and tumor surveillance have the potential to inform the management of future patients with this or other cancer-predisposing conditions. Ultimately, it is hoped that this information will enhance the treatment of existing cancers, improve the efficacy of surveillance, and minimize or eliminate SMNs.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

## AUTHOR CONTRIBUTIONS

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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