What 20 Years of Research Has Taught Us About the $TP53$ p.R337H Mutation

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The $p53$ tumor suppressor transcriptionally regulates a myriad of genes involved in cell cycle control, DNA repair, cell survival, and cell metabolism and represents one of the most well-studied inhibitors of tumorigenesis. Since the discovery of $TP53$ in 1979, somatic mutations have been shown to be extremely common; more than 50% of human cancers carry loss-of-function mutations in $TP53$. Inherited or germline $TP53$ mutations are rare and are involved in complex hereditary cancer predisposition disorders, and affected family members can develop diverse tumor types and multiple primary cancers at young ages. In Brazil, a fascinating history of $p53$ and cancer predisposition began in the year 2000 with identification of the $TP53$ p.R337H mutation in close association with the development of adrenocortical tumors. In these past 20 years, much has been learned about the genetics and biochemistry of this mutation, which is widespread in Brazil because of a founder effect. This review highlights the contributions of $TP53$ p.R337H research over the last 20 years, the findings of which have sparked passionate debate among researchers worldwide, to understanding cancer predisposition in Brazilian individuals and families.

**KEYWORDS:** cancer predisposition, founder mutation, haplotype, R337H, TP53.

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CANCER WHERE YOU LIVE AFFECT YOUR CANCER RISK?

Pediatric adrenocortical tumor (ACT) is an extremely rare malignancy but has a high incidence in South and Southeast Brazil. A survey analysis of children admitted to a single institution in Southeast Brazil (Santa Casa de Misericordia, São Paulo State) by Marigo et al revealed high frequencies of Hodgkin disease, renal carcinoma, and ACTs among 520 childhood malignancies over a period of 15 years. There were 12 pediatric ACTs among 418 solid tumors (2.9%); this was in clear contrast to the 16 cases among 2000 solid childhood malignancies over a 40-year period at the Great Ormond Street Hospital (formerly the Hospital for Sick Children, London, United Kingdom). Because pediatric ACTs were remarkably represented at Santa Casa de Misericordia, the authors questioned whether “it represents a genuine local phenomenon” and published their findings in the *Journal of the National Cancer Institute* in 1969.

In the same journal, side by side, Frederick Li and Joseph F. Fraumeni, Jr, published their investigation of pediatric and familial cancers to determine the origin of childhood rhabdomyosarcoma. Further studies by Li and Fraumeni showed an increased risk of breast cancer and a high frequency of soft-tissue sarcomas (STSs) as well as an excess of early onsets of multiple primary tumors in these families; this suggested an underlying familial cancer predisposition syndrome. Two independent families with children who developed multiple primary tumors, including ACTs, medulloblastoma, and rhabdomyosarcoma, were described, so the clinical syndrome reported by Li and Fraumeni was designated as a familial cancer syndrome and subsequently as Li-Fraumeni syndrome (LFS). Identifying the pattern of familial cancer segregation was important for determining the genetic association underlying LFS, and the choice to select a candidate gene inactivated in sporadic forms of cancers associated with this syndrome led to $TP53$, which to date remains the only established gene implicated in the molecular etiology of LFS.

Acquired mutations in $TP53$ are frequent and are observed in ~50% of human cancers; they are most prevalent in small cell lung, colorectal, head/neck, and epithelial ovarian cancers (according to the International Agency for Research on Cancer [IARC] database). Most of these variants are missense mutations distributed throughout the coding sequence, and the impact on the transcriptional activities of the resulting mutated protein depends on the nature of the mutation.

Mutations in exons 4 to 9, which correspond to the DNA-binding domain of the protein, particularly at codons 175,

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245, 248, 273, and 282, are the most common in both sporadic tumors and familial cases. Furthermore, families harboring mutations in this domain have a distinct family history of cancer showing early onset and a higher incidence in comparison with families harboring mutations in other p53 domains.9,10

The TP53 p.R337H variant located in the tetramerization domain of the p53 protein was first reported in a female pediatric patient with an ACT diagnosed at the age of 3 years.11 Germline or familial DNA was not available to determine whether the nature of this mutation was inherited or even germline. However, complete loss of the wild-type (WT) allele and more than 95% expression of p53 in the tumor and surrounding normal cells11 suggested the germline nature of this variant. Later, the p.R337H variant was reported as a germline mutation in a female pediatric ACT patient of Portuguese ancestry who was diagnosed at the age of 4 years and was treated at the Institut Gustave-Roussy in France.12 The patient’s family history of cancer was not remarkable but included an uncle diagnosed with a brain tumor at the age of 33 years.12

The high incidence of pediatric ACTs, an LFS core tumor type, observed in South Brazil (Paraná State) prompted investigators to verify the clinical significance of TP53 alterations in these patients. An analysis of germline DNA from 36 patients with ACTs from 34 families using a GeneChip p53 assay (Affymetrix) revealed the p.R337H variant in 35 patients.13 Although pediatric ACTs are a surrogate for identifying cancer-prone families, no apparent high incidence of cancer among relatives was observed in this series.13 Only 1 of 25 families whose history of cancer was collected for 3 generations showed a pattern of cancer distribution despite not fulfilling the classic LFS criteria.5,13 Moreover, multiple occurrences of ACTs were observed in 4 families.13 The demonstration of a founder allele was inconclusive, and this suggested that pesticides and other industrial chemicals may be involved in the origin of this mutation.13 The mutant p53-R337H protein functioned similarly to WT p53 in cell culture–based studies; however, a loss of heterozygosity with retention of the mutated allele in tumor cells and a high level of detectable nuclear p53 protein (in both tumor and normal cells)10 suggested compromised functionality of this mutant protein. Absence of a family history of cancer and impaired p53 activity suggested that this variant acts in a tissue-specific manner and contributes positively to ACT development.13

Following the initial study by Ribeiro et al,13 another independent group from Southeast Brazil (São Paulo State) detected this variant in 14 of 18 pediatric patients with ACTs, including 1 patient who was a homozygous carrier.14 They also identified the variant in 5 of 37 adult patients with ACTs.14 None of the family members who were tested and shown to be carriers developed ACTs or any other tumor type.14 To date, the most notable and well-characterized genetic risk factor for ACTs in South and Southeast Brazil is the presence of the germline TP53-R337H mutation.13,14

TP53 germline and somatic mutations found in association with human cancers have been compiled in the IARC database,6 and to date, the germline TP53 p.R337H variant is the single most commonly reported mutation (Fig. 1).

A FOUNDER TP53 MUTATION WIDESPREAD IN BRAZIL

The founder concept for the TP53 p.R337H mutation was revisited because of the observed inheritance of this variant and no documented de novo mutation.13,14 An analysis by Pinto et al15 of 2 polymorphic markers at chromosome 17 in close proximity to the TP53 locus demonstrated an identical haplotype encompassing TP53, WRAP53, and EFNB3 (chr17:7,574,017-7,617,475; GRCh37/hg19) for Brazilian patients with ACTs carrying the TP53 p.R337H mutation that was distinct from the control group, and they thereby established the founder nature of this variant. Later, a study analyzing single-nucleotide polymorphisms in the TP53 locus showed that the p.R337H allele in Brazilian carriers shared a common TP53 sequence with the patient from Portugal with an ACT11 and established the Caucasian origin of this allele.16 Identification of a conserved haplotype spanning 522 kb around TP53 in p.R337H carriers confirmed the founder effect,17 and a subsequent study supported the European/Portuguese-Iberic origin of this haplotype.18

Most recently, a detailed analysis of whole-genome sequencing data from matched blood and tumor samples of children with ACTs from Brazil19 revealed divergent haplotypes among p.R337H carriers.20 All evaluated p.R337H carriers in South and Southeast Brazil shared an identical TP53 sequence, including 1 copy (nonduplicate) of the 16-bp polymorphism in intron 3 (rs17878362), arginine at codon 72 (rs1042522), and the downstream TP53 variant that defines a Caucasian allele (rs9894946; Fig. 1).16,19,20 However, it was determined that the constitutive haplotype constructed on the same TP53 p.R337H variant, which occurs in the majority of Brazilian p.R337H carriers, is larger and has a nonsense mutation (p.E134*) in the putative tumor suppressor
XAF1 in close proximity to the TP53 locus (Fig. 1).20 The XAF1 p.E134* in concert with the TP53 p.R337H allele leads to a more aggressive cancer phenotype than either variant alone, and this has clear implications for the clinical management of carriers.20

In the largest population-based screening study, 171,649 newborns from Paraná State were genotyped, and the p.R337H variant was identified in 461 patients (0.27%).21 Another study assessed the frequency of the TP53 p.R337H variant by screening 32,130 newborns from São Paulo State, and it found that 68 (0.21%) were carriers.22 These studies21,22 have established that the germline TP53 p.R337H variant is widespread in South and Southeast Brazil and occurs at a population frequency of 0.3%. Although these original studies have not addressed the constitutive haplotype, screening haplotype-defining variants in newborns (n = 42,538) with an unknown history of cancer from South Brazil showed that 69% of p.R337H carriers also have the XAF1 p.E134* variant in the same haplotype.20

It is also important to consider that the TP53 p.R337H mutation can be observed outside the context of a founder mutation in an independent occurrence as observed in an adult patient with an ACT from Germany.23 These observations raise the question whether the TP53 p.R337H variant, constitutive haplotype, and associated polymorphisms influence the tumor phenotype.

**IS ACT THE ONLY PEDIATRIC TUMOR ASSOCIATED WITH THE TP53 P.R337H MUTATION?**

In addition to pediatric ACTs,13-15,17,19,21 the TP53 p.R337H variant is expressively associated with choroid plexus carcinoma (CPC) in the Brazilian population. In a series of 29 patients with CPC or choroid plexus papilloma admitted to Pequeno Príncipe Hospital (Paraná State) from 1992 to 2010, the p.R337H variant was observed in 14 of 22 patients (63.6%) with CPC but not in those with choroid plexus papilloma (n = 7).24
To determine the spectrum of pediatric malignancies associated with the TP53 p.R337H variant, 493 childhood cancer patients from Centro Infantil Boldrini, a referral institution in Southeast Brazil (São Paulo State), were genotyped for this variant. Results confirmed the high association of this variant with ACT (65 of 70 cases [93%]) and CPC (9 of 13 patients [69%]). This variant was also found in pediatric patients with osteosarcoma (3 of 41 [7.3%]) but was not observed in pediatric patients diagnosed with acute lymphoblastic or acute myeloid leukemia, lymphoma, Ewing sarcoma, rhabdomyosarcoma, or central nervous system (CNS) tumors (non-CPC). Moreover, the Centro Infantil Boldrini group identified the TP53 p.R337H mutation in 2 patients with concomitant ACT and neuroblastoma and investigated the frequency of this variant among patients with neuroblastoma treated at this referral institution. The TP53 p.R337H variant was identified in 7 of 83 available samples (8.4%) from a total of 178 patients with neuroblastoma.

In a different approach, 292 children diagnosed with and/or treated for LFS or Li-Fraumeni–like (LFL) core tumors (ACTs, sarcomas, CNS tumors, leukemias, germ cell tumors, and Wilms tumors) and 65 pediatric patients with non–cancer-related health issues, all regardless of their family history of cancer, were recruited by the Pediatric Oncology Service of the Hospital de Clínicas de Porto Alegre (Rio Grande do Sul State) in South Brazil.27

**FIGURE 2.** Schematic diagram of TP53 p.R337H haplotypes. Red bars represent the constitutive haplotypes observed in p.R337H carriers. All carriers of p.R337H share a common TP53 sequence (short red bar). However, the most commonly observed haplotype encompasses a region of 2 cM and harbors mutations in TP53 and XAF1 (long red bar).
Screening for the TP53 p.R337H mutation identified 11 of the 292 children with cancer (3.8%) as proband carriers (9 were diagnosed with an ACT [1 in the homozygous state], and 2 were diagnosed with a CPC) and thereby confirmed previous studies. There were no TP53 p.R337H-positive carriers among probands with osteosarcoma (n = 21), leukemia (n = 77), or Wilms tumor (n = 34).

Pediatric ACT and CPC are extremely rare tumors, and the occurrence of metachronous ACT and CPC associated with TP53 alterations has been reported. However, the co-occurrence of both tumors in the context of the TP53 p.R337H variant has never been documented, although a metachronous ACT in a pediatric patient harboring this variant has been recognized.

THE LFS CORE CANCERS AMONG CARRIERS OF THE TP53 P.R337H MUTATION

Forty-five families from South and Southeast Brazil with family histories of cancer consistent with classic LFS or LFL criteria were screened for TP53 mutations. Of the 13 index cases (28.9%) with positive TP53 results, 6 harbored the p.R337H variant. Each of these p.R337H carriers was diagnosed with STS (×3), breast cancer, renal cell carcinoma, or pediatric ACT. Three developed multiple primary malignancies, including thyroid, lung, renal, and skin cancers. A family history of cancer for p.R337H carriers included a wide spectrum of tumors, including breast and brain tumors, STSs, and ACTs. Achatz et al suggested that the tumor spectrum observed in carriers of the TP53 p.R337H mutation is similar to that observed in LFS or LFL families carrying other TP53 mutations; nevertheless, as discussed in the profiled article, all p.R337H families in this study fulfilled LFL criteria rather than strict LFS criteria. Notably, these probands and family members were tested for the constitutive haplotype, and 5 of the 6 index cases testing positive for the TP53 p.R337H variant (the patients with STS [×3], breast cancer, and renal cell carcinoma) shared the extended haplotype cosegregating both TP53 and XAF1 mutated alleles. The pediatric patient with an ACT in this study was positive only for the p.R337H variant.

The tumor spectrum for individuals and family members associated with pathogenic germline TP53 variants is wide, but the tumors most closely associated with LFS (core cancers) include premenopausal breast cancer, STS, and osteosarcoma as well as brain tumors and ACTs. Palmero et al tested for the p.R337H variant in 381 women with invasive breast cancer diagnosed between the ages of 20 and 60 years, including 87 diagnosed at or before the age of 40 years. Three cases had a past history of other cancers (2 lymphomas and 1 melanoma). The p.R337H variant was observed in 2 carriers (0.5%) and not in any of the 324 healthy women. Both carriers were diagnosed with breast cancer at a young age (under 40 years), with 1 having bilateral breast cancer. A family history of cancer for both cases revealed breast cancer in their relatives.

Breast cancer is the most common cancer in adult carriers of a germline TP53 mutation. This explains, in part, the sex difference in lifetime cancer risk (nearly 100% for women vs 73% for men). In addition, breast cancer is predictive of a germline TP53 mutation when it is diagnosed at a younger age and in family members with LFS core tumors (other than breast cancer). Recent studies have reported that breast cancers in carriers of TP53 variants are mostly ductal in histology, positive for hormone receptor and tyrosine kinase–type cell surface receptor HER2, and diagnosed at a very early age. However, a Brazilian study of 78 patients with breast cancer demonstrated that the median age at breast cancer diagnosis in a group of p.R337H carriers (n = 66) was 42 years, which was older than the median age at diagnosis (30 years) for carriers of other nonfunctional germline TP53 mutations. In addition, most patients had a positive hormone receptor status, and in contrast to other studies, HER2+ breast cancer was very similar to that observed in noncarriers of TP53 variants.

Numerous sarcoma types collectively constitute less than 1% of all cancers and often occur sporadically. However, sarcomas represent 17.4% of all cancers in TP53 germline mutation carriers and 36.8% of all cancers in patients younger than 20 years. In addition, patients with sarcomas who are older than 50 years are much less common in LFS families than the general population. In a recent study, the TP53 p.R337H mutation was screened in 502 patients diagnosed with sarcomas who were not selected by age or family history and were treated at Hospital de Cancer de Barretos (São Paulo State) between 2008 and 2016 (from a total of 701 patients with
The TP53 p.R337H variant was found in 40 samples (8%) and was confirmed to be germline in available blood DNA or normal tissue in 36 cases.\(^3\) Although the total cohort study included 58 pediatric patients, the p.R337H variant was exclusively observed in adult cases, with the youngest patient diagnosed at the age of 18 years and the oldest diagnosed at the age of 84 years (22 cases [55%] were diagnosed in patients older than 50 years);\(^3\) in contrast, in the IARC database,\(^8\) 67% of sarcomas in carriers of TP53 mutations were diagnosed before the age of 20 years.\(^3\) In addition, leiomyosarcoma accounted for 21 cases of sarcoma (52.5%) among p.R337H carriers, with 14 (67%) being diagnosed at an age older than 50 years.\(^3\) In contrast, leiomyosarcoma represented only 9.1% of the cases of sarcoma in the IARC database.\(^8,3\) Cancer was a second tumor in 7 of 8 p.R337H patients who developed multiple primary malignancies.\(^3\) Furthermore, 30 p.R337H patients reported family members with cancer, and an excess of lung and breast cancer, malignant CNS tumors, colorectal and stomach cancer, leukemia, and ACTs was documented.\(^3\) Negative family histories of cancer were annotated for approximately 15% of the p.R337H patients with sarcomas.\(^3\) Discerning sporadic cases from the germline ones can facilitate genetic counseling as well as screening and surveillance for these patients. Unfortunately, the full-length or copy number change status for TP53 was not determined in the total cohort of sarcomas,\(^3\) and information on age distributions, mutation types and frequencies, tumor types, and family histories of cancer in this Brazilian sarcoma cohort is lacking. Nevertheless, 24 of the 40 sarcoma cases harboring the p.R337H variant were included in the analysis of the constitutive haplotype, and 98% shared the haplotype harboring mutations in both tumor suppressor TP53 and tumor suppressor XAF1.\(^2\)

THE INTRICATE CANCER PHENOTYPE AMONG CARRIERS OF THE FOUNDERS P.R337H ALLELE

Because of the potential association between the p.R337H variant and breast cancer, a case-control study was conducted at the University of São Paulo Medical School of Ribeirão Preto (São Paulo State) to verify the prevalence of this variant in 28 unrelated female patients with breast cancer fulfilling the criteria for hereditary breast and ovarian cancer syndrome (HBOC) by genetic testing.\(^3\) Two (7.1%) were positive for p.R337H and negative for BRCA1 and BRCA2 pathogenic mutations. Although both patients had a family history of other tumors at the time of the investigation, they did not fulfill the classic criteria for LFS.\(^3\)

However, both patients met HBOC criteria on the basis of their personal histories and relatives diagnosed with breast cancer,\(^3\) and this demonstrated that the p.R337H variant was significantly higher among women with HBOC-related breast cancer than the general Brazilian population.\(^3\) A second study analyzed 106 unrelated high-risk patients with HBOC from Northeast Brazil (Bahia State) for mutations in BRCA1, BRCA2, CHEK2, and TP53.\(^3\) In addition to the patients’ cancer history, cancers associated with HBOC (breast, ovarian, prostate, and pancreatic) were significant among relatives. Two mutations of clinical significance were found in BRCA1 (p.R71G [c.211A>G; n = 5] and 3450del4 [c.3331_3334delCAAG; n = 4]), and 1 was found in TP53 (p.R337H [n = 1]).\(^3\) The p.R337H carrier had a family history consistent with HBOC but not LFS or LFL syndrome.\(^3\)

The p.R337H variant was also documented in phylloides breast tumors in South Brazil. In an analysis of 148 tumor samples, 8 (5.4%) were positive for this variant. A DNA analysis from nontumoral tissue was possible in 2 positive cases, and both were associated with germline p.R337H mutations.\(^3\) Positive cases were found in benign (n = 5) and malignant phylloides breast tumors (n = 3); this suggests that this variant plays a role in phylloides breast tumorigenesis.\(^3\)

Substantial clinical tumor heterogeneity and a wide range of tumor types have been observed at an increased frequency in TP53 p.R337H carriers. In an analysis of 45 unselected Brazilian patients (29 male) with non–small cell lung cancer treated at Hospital Júlia Kubitschek (Minas Gerais State), 4 (8.9%) were p.R337H carriers. None of the carriers had a family history that fulfilled the LFS criteria.\(^3\) In a study of 164 p.R337H carriers from 59 families followed at the A. C. Camargo Cancer Center (São Paulo State), 9 individuals (5.5%; 8 families) developed lung adenocarcinoma (mean age at diagnosis, 53 years). In 3 cases, lung cancer was the first and only primary tumor, and 6 patients had multiple tumors, with lung cancer being primary in 1 case, secondary in 4 cases, and concomitant with an STS in 1 case.\(^3\) Notably, 3 patients were exposed to thoracic irradiation during the treatment of a previous breast cancer.\(^3\) All 164 p.R337H patients had family histories of cancer, with 3 having more than 1 case of lung cancer. However, none of them fulfilled the classic LFS criteria as reported.\(^3\)

An analysis of the same group of families followed at the A. C. Camargo Cancer Center (São Paulo State) revealed 11 cases of thyroid carcinoma in 5 independent families.\(^3\) The overall mean age at diagnosis was 44 years (3 men and 8 women). All cases were histologically
classified as papillary carcinomas, with 2 exhibiting the follicular variant. Eight patients developed multiple primary malignancies: breast cancer (n = 5), STS (n = 2), and a case of pheochromocytoma.43 In addition, the same citation sequencing studies in lymphocytes derived from carriers of null TP53 alleles associated with LFS (Table 1).

MODULATING TP53 p.R337H FUNCTIONALITY IN CELL LINES AND MOUSE MODELS

The TP53 p.R337H allele participates in a salt bridge within the dimerization domain, and structural studies have demonstrated that the stability of this mutant protein is pH dependent.45 Most studies on the behavior of this variant on cell stress have relied on artificial constructs, where p53 is ectopically expressed in a variety of cell lines.13,46 Although these functional studies have used a construct that does not correspond to the exact sequence of the founder allele (the construct contains proline instead of arginine at codon 72), they have shown that this variant retains significant activity comparable to that of the WT.13,46 It is important to consider that the putative pH dependence of the p.R337H variant for its oligomerization and DNA interaction may not be seen in these in vitro analyses.

In a different approach, chromatin immunoprecipitation sequencing studies in lymphocytes derived from carriers of TP53 p.R337H exposed to doxorubicin revealed a moderate decrease in p53 binding sites compared to the WT sequence and closer to lymphocytes derived from carriers of null TP53 variants; this suggests an impairment of the transcriptional response to DNA damage.47 However, these studies relied on Epstein-Barr virus–immortalized lymphocytes, which could alter p53 responses.47

A recent study used human fibroblasts derived from skin biopsies of patients harboring the TP53 p.R337H and XAF1-E134* variants in homozygous and heterozygous states to evaluate p53 and cell cycle regulation pathways.20 Results supported XAF1 as a positive regulator of p53 activity.20

Studies using mouse models have yielded invaluable insights for our understanding of the p53 pathway. The generation of the p.R334H mouse model, which represents the human p.R337H homolog, is a major step in advancing our understanding of this TP53 variant. Homozygous mutant mice developed normally and exhibited longevity and cancer incidence similar to those of WT mice.48 However, mutant mice were susceptible to developing liver tumors when they were exposed to the carcinogen diethylnitrosamine in a mutant allele dose–dependent manner.48 Liver cells treated with this agent exhibited higher DNA damage and lower transactivation of p53 target genes in comparison with WT cells, and there was evidence of reduced tetramer formation consistent with impaired transcriptional activity.48 This model, however, did not recapitulate the cancer phenotype observed in Brazilian carriers of the p.R337H variant, and this suggests that additional genetic and environmental factors modulate the cancer risk phenotype in carriers.

**TABLE 1. Clinical Features of LFS-Associated Cancers in Carriers of the TP53 p.R337H Mutation**

| LFS Core Cancers | TP53 p.R337H Carriers |
|------------------|----------------------|
| ACTs             | This is the most prevalent tumor presentation in the pediatric group. Approximately 78% to 97% of pediatric ACTs in the Brazilian population harbor the TP53 p.R337H variant.13,14 ACTs also develop in adults14,20 and can occur as isolated cases, in families with multiple cases, and in families with a wide range of cancers.13,14,19,21,25,27 Metachronous ACTs have been reported,30 but second primary malignancies after an ACT diagnosis are very rare.20 There is an excessive risk of breast cancer among mothers of pediatric patients with ACTs.25 Homozygous p.R337H carriers have been described.14,21 |
| Brain tumors     | CPC is the second most prevalent tumor type in children (63% of CPCs are p.R337H).24,25,27 Multiple independent cases of CPC associated with homozygous p.R337H carriers have been documented.20 |
| Breast cancer    | This is the most common tumor in adults with frequencies of 0.5% to 8.6%.32,33 The age of onset is later in comparison with LFS-associated breast cancer.35 It tends to be negative for HER2.36 Phyllodes carcinoma has been reported.20,40 Secondary primary malignancies, including contralateral cases, have been documented in 50% of cases and are enriched in carriers of the extended haplotype.20 |
| Sarcomas         | These are rarely observed in pediatric cases.20,25,37 Leiomyosarcoma is the histologic type predominant in p.R337H carriers.37 Sarcomas are prevalent in patients older than 50 years.35 Sarcomas as primary or secondary malignancies are significantly enriched in carriers of the extended haplotype.20 |
| Others           | Thyroid (mostly papillary carcinomas), kidney, skin, and lung cancers are reported among carriers of the p.R337H variant.41-44 |

| Overlapping syndromes | TP53 p.R337H has been observed in patients tested for HBOC.38,39 |

Abbreviations: ACT, adrenocortical tumor; CPC, choroid plexus carcinoma; HBOC, hereditary breast and ovarian cancer syndrome; LFS, Li-Fraumeni syndrome.
FINAL REMARKS
An assessment of cancer risk in TP53 p.R337H carriers includes individuals and families with no history of cancer over a lifetime, others showing an apparently sporadic pattern of cancer presentation, and those with a more aggressive cancer phenotype resembling LFS.

It is important to note that an LFS diagnosis is determined by an evolving set of clinical classification criteria based on personal and family histories of cancer, with 70% of individuals who meet these criteria being positive for pathogenic TP53 variants. The TP53 p.R337H mutation represents a remarkable example of a reduced-penetrance allele, but still this disease-causing variant is present as a founder mutation in 0.3% of the population of Southeast and Southern Brazil. The haplotype cosegregating both TP53 pR337H and XAF1 E134* mutant alleles likely contributes to a more aggressive cancer phenotype comparable to carriers of pathogenic TP53 variants but clearly distinct from the classic presentation of LFS. Recognizing the constitutive haplotype in carriers of the p.R337 variant is of importance for stratifying carriers into high- and low-risk categories and thereby guiding physicians in counseling, targeted prevention, and earlier detection of tumors to improve outcomes.

This review covers 20 years of clinical and basic research concerning a single TP53 mutant widespread in Brazil. Although we have come far in understanding the biological roots, genetics, and biochemistry of the TP53 p.R337H variant, we still have to consolidate the contribution of haplotype-defining variants in cancer susceptibility in this population. Ongoing attention to not only cancer biology but also additional factors permissive to oncogenic stress is a priority in the context of the reduced-penetrance TP53 allele, as represented by the p.R337H allele.

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CONFLICT OF INTEREST DISCLOSURES
Emilia Modolo Pinto and Gerard P. Zambetti report a patent pending (“Genotyping Assays to Identify Mutations in XAF1”).

AUTHOR CONTRIBUTIONS
Emilia Modolo Pinto: Conceptualization, literature review, writing, review, and editing of the final version. Gerard P. Zambetti: Editing of the final version.

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