Phenotypic and Genotypic Spectrum Identified in a Cohort of Germline *TP53* Carriers

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Introduction

Li-Fraumeni syndrome (LFS) is an autosomal-dominantly inherited cancer predisposition syndrome caused by pathogenic variants in the tumor suppressor gene *TP53*. Individuals with LFS are at high risk to develop early onset and multiple primary tumors, the most characteristic of LFS being soft tissue sarcoma, osteosarcoma, central nervous system tumors, premenopausal breast cancer, and adrenal cortical carcinoma. Both Classic LFS and Chompret criteria are used to identify families in which to offer germline analysis of *TP53* and subsequent intensive screening protocols for carriers. However, given the wide-array of tumors associated with LFS, *TP53* is now included on most multi-gene panels for hereditary cancer. Indeed, with more than 50,000 multi-gene panel tests being performed every year, *TP53* pathogenic variants are more frequently being identified in non-classic LFS families[1]. To further investigate the *TP53* pathogenic variant spectrum and evolving LFS phenotype, we studied a cohort of LFS individuals who were referred for multi-gene panel testing for hereditary cancer risk.

Methods

All individuals were referred by physician order for the Color Hereditary Cancer Test which analyzes 30 genes in which pathogenic variants have been associated with elevated risk for hereditary breast, ovarian, uterine/endometrial, colorectal, melanoma, pancreatic, prostate, and stomach cancer. These genes are *APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A* (p14ARF and p16INK4a)*, CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11,* and *TP53.* Analysis, variant calling, and reporting focused on the complete coding sequence and adjacent intronic sequence of the primary transcript(s). Laboratory procedures were performed at the Color laboratory under CLIA and CAP compliance.

Variants were classified according to the American College of Medical Genetics and Genomics 2015 guidelines for sequence variant interpretation[2], and all variant classifications were signed out by an American Board of Medical Genetics and Genomics board certified medical geneticist. All *TP53* variants in this cohort were identified at an allelic fraction of >30%, and all individuals received reports with risk estimates and screening guidelines specific to germline *TP53* variants but that also addressed the possibility of a somatic variant, stressing the importance of follow-up. All individuals consented to have their de-identified information used in anonymized studies. All information was reported by the individual; information not reported was noted as such.

Conclusions

- Of the 31 primary probands in this cohort, all of whom were *TP53* pathogenic variant carriers, 17 (54.8%) would not have met current recommendations for genetic testing provided by the National Comprehensive Cancer Network (NCCN).
- Over half of all individuals (55.9%, (19/34)) had a personal history of cancer, with the average age at first cancer diagnosis being 39.47 years. The majority had tumors known to be associated with LFS, including breast and sarcoma. However, only 21.4% (3/14) of the breast cancer diagnoses occurred at <31 years, which is the age flagged by the NCCN as being suggestive of LFS
- Of the *TP53* pathogenic variants observed, the majority (79.4%, (27/34)) were missense variants, of which (72.7%, (24/33)) were variants located in the TP53 binding domain as has been previously observed in the majority of LFS families[3,4].
- The data presented here add support to previous studies and opinions highlighting the evolving phenotype of LFS. Further use of multi-gene panel testing will continue to expand and refine the spectrum of *TP53* pathogenic variants and risks associated with LFS, leading to improved testing guidelines and screening recommendations for pathogenic variant carriers.

References

1. Weitzel JN, Chao EC, Nehoray B, et al. *Genet Med.* 2018.
2. Richards S, Aziz N, Bale S, et al. *Genet Med.* 2015.
3. Leroy B, Anderson M, Soussi T. *Hum Mutat.* 2014.
4. Kamihara J, Rana HQ, Garber JE. *Hum Mutat.* 2014.

Results

Table 1. Demographic details

The majority of individuals in the cohort were females, over age 40 years, and of Caucasian ethnic background.

		Individuals (n)	Individuals (%)
Total		34	100%
Gender	Female	21	61.8%
	Male	13	38.2%
Age (Years)	18-30	6	17.6%
	31-40	9	26.5%
	41-50	4	11.8%
	51-65	10	29.4%
	65+	5	14.7%
Ethnicity	Caucasian	24	70.6%
	Ashkenazi Jewish	1	2.9%
	Hispanic	4	11.8%
	Asian	2	5.9%
	Unknown*	3	8.8%

*Unknown includes information not provided.

Figure 1. Pedigree of an individual with a *TP53* c.795_796delGGinsCT (p.Gly266*) pathogenic variant

The proband is a 39-year-old Hispanic female who was diagnosed with bilateral breast cancer (Br) at age 37 years. She has a family history of colon cancer (Col), breast cancer, and sarcoma (Sarc). She was found to carry the pathogenic variant *TP53* c.968_986del (p.Leu323Profs*16), which is located outside of the TP53 DNA binding domain and has not yet been reported as a germline variant in the literature.

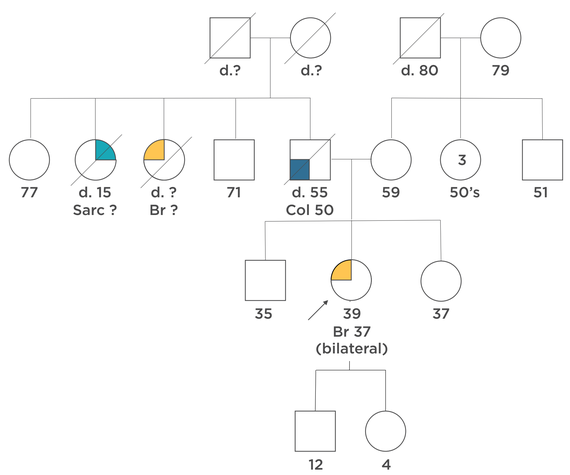


Figure 2. Pedigree of an individual with a *TP53* deletion of exons 2-10 pathogenic variant

The proband is a 47-year-old Ashkenazi Jewish male who was diagnosed with a sarcoma (Sarc) at age 40 years and prostate cancer (Pr) at age 45 years. He has no known family history of cancer. He was found to carry the pathogenic variant *TP53* deletion of exons 2-10, which has not yet been reported as a germline variant in the literature.

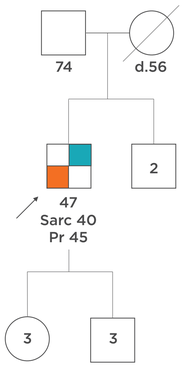


Figure 3. Pedigree of an individual with a *TP53* c.795_796delGGinsCT (p.Gly266*) pathogenic variant

The proband is a 26-year-old Caucasian female with no personal history of cancer. She has a family history of non-Hodgkin's lymphoma (NHL), salivary gland cancer (Sal), throat cancer (throat) and melanoma (Mel). She was found to carry the pathogenic variant *TP53* c.795_796delGGinsCT (p.Gly266*), which is located within the TP53 DNA binding domain and has not yet been reported as a germline variant in the literature.

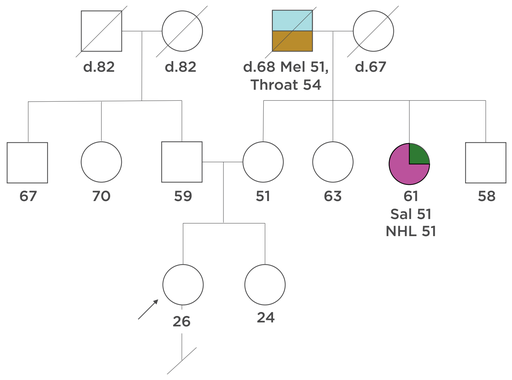


Figure 4. Tumor spectrum by type and age at diagnosis

(A) The majority of individuals had breast cancer (73.7% (14/19)), (B) with the average age of first breast cancer diagnosis occurring at 36.6 years. The other core LFS tumor reported was sarcoma. Of the four sarcomas reported, one was liposarcoma, one osteosarcoma, and two were not specified.

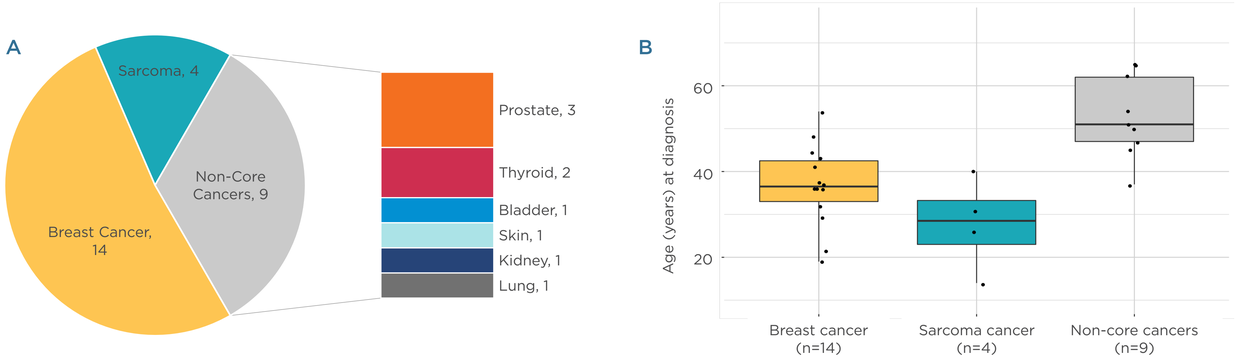
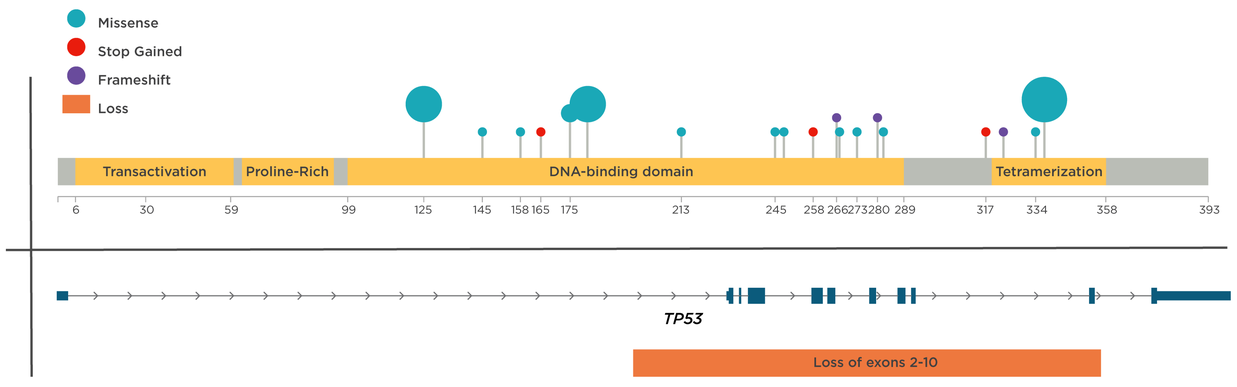


Figure 5. Pathogenic *TP53* variants identified at an allelic fraction of >30%

Single nucleotide variants and small insertions and deletions are displayed on a diagram of the TP53 protein, colored by effect of the pathogenic variant, with frequency indicated by size. Copy number variants (CNVs) are shown below the structure of the *TP53* gene. The only CNV detected in this cohort was a deletion of exons 2-10. Size of the bubble is proportional to the number of observations.