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Platinum Priority – Prostate Cancer
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Inherited TP53 Variants and Risk of Prostate Cancer

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Abstract

Background: Inherited germline *TP53* pathogenic and likely pathogenic variants (*gTP53*) cause autosomal dominant multicancer predisposition including Li-Fraumeni syndrome (LFS). However, there is no known association of prostate cancer with *gTP53*.

Objective: To determine whether *gTP53* predisposes to prostate cancer.

Design, setting, and participants: This multi-institutional retrospective study characterizes prostate cancer incidence in a cohort of LFS males and *gTP53* prevalence in a prostate cancer cohort.

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Outcome measurements and statistical analysis: We evaluated the spectrum of *gTP53* variants and clinical features associated with prostate cancer.

Results and limitations: We identified 31 prostate cancer cases among 163 adult LFS males, including 26 of 54 aged ≥ 50 yr. Among 117 LFS males without prostate cancer at the time of genetic testing, six were diagnosed with prostate cancer over a median (interquartile range [IQR]) of 3.0 (1.3–7.2) yr of follow-up, a 25-fold increased risk (95% confidence interval [CI] 9.2–55; $p < 0.0001$). We identified *gTP53* in 38 of 6850 males (0.6%) in the prostate cancer cohort, a relative risk 9.1-fold higher than that of population controls (95% CI 6.2–14; $p < 0.0001$; gnomAD). We observed hotspots at the sites of attenuated variants not associated with classic LFS. Two-thirds of available *gTP53* prostate tumors had somatic inactivation of the second *TP53* allele. Among *gTP53* prostate cancer cases in this study, the median age at diagnosis was 56 (IQR: 51–62) yr, 44% had Gleason ≥ 8 tumors, and 29% had advanced disease at diagnosis.

Conclusions: Complementary analyses of prostate cancer incidence in LFS males and *gTP53* prevalence in prostate cancer cohorts suggest that *gTP53* predisposes to aggressive prostate cancer. Prostate cancer should be considered as part of LFS screening protocols and *TP53* considered in germline prostate cancer susceptibility testing.

Patient summary: Inherited pathogenic variants in the *TP53* gene are likely to predispose men to aggressive prostate cancer.

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1. Introduction

Prostate cancer (PrCa) is a highly heritable disease [1]. Recent data have demonstrated that approximately 5–20% of cases are associated with germline (inherited) pathogenic variants in genes associated with recognized cancer predisposition syndromes, such *BRCA2* and *ATM* [2,3]. Germline *TP53* pathogenic variants (*gTP53*) are associated with an autosomal dominant hereditary multicancer predisposition known as Li-Fraumeni syndrome (LFS) [4,5]. Patients with classic LFS develop early-onset, pediatric, and multiple primary cancers with nearly universal development of at least one cancer in their lifetime [6]; presentations with more variable penetrance are increasingly observed [5,7,8]. Panel genetic testing, largely ascertained on individuals with personal and family histories of breast cancers, has demonstrated a more expansive tumor spectrum and more variable penetrance of *gTP53* variants than previously appreciated [9]. However, there has been no documented association of PrCa with *gTP53*, outside of one case report [10]. In a recent review of the *TP53* International Agency for Research on Cancer (IARC) database [8], only 1.7% of *gTP53* patients were reported to have PrCa, far lower than the 14% lifetime risk of PrCa for average men in the USA [11]. However, this analysis is misleading given that the database is heavily skewed toward men of younger ages than those relevant to typical PrCa risk.

Guidelines advise extensive cancer screening in patients with LFS, starting in childhood, for example, yearly full-body magnetic resonance imaging (MRI) and brain imaging, targeted ultrasound, assessments for gastrointestinal and skin neoplasms, and breast screening for women [12,13]. Patients with LFS may also have an elevated risk of post-treatment secondary malignancies, for example, after radiation [14,15]. Therefore, LFS status may be considered in cancer treatment planning. For example, in women with LFS,

total mastectomy is preferred to partial mastectomy to avoid the need for radiation.

Current cancer screening guidelines for LFS patients do not include PrCa. Moreover, *gTP53* status is not currently considered in treatment planning for individuals with PrCa, which often includes decisions between radiation and surgery for patients with early-stage localized disease and regarding adjuvant or salvage radiation in those with later-stage or recurrent disease. Herein, we analyze LFS cohort data alongside laboratory-based clinical genetic testing data in PrCa cohorts, and we demonstrate that *gTP53* is associated with the development of aggressive PrCa.

2. Patients and methods

2.1. LFS and PrCa cohorts

The LFS cohort ($n = 163$ males from 132 families) was created from four datasets of families with a diagnosis of LFS (Supplementary Table 1 and Supplementary material) from Dana Farber Cancer Institute, Huntsman Cancer Institute, Memorial Sloan Kettering Cancer Center, and the University of Pennsylvania. Eligibility criteria for index cases from LFS families were as follows: (1) male sex, (2) age at last follow-up ≥ 18 yr, and (3) genetic testing confirming heterozygous *gTP53* or obligate carrier status within a family. Dates of genetic testing, PrCa diagnosis, or last follow-up and/or death were collected for all LFS men (Supplementary Table 1). The PrCa cohort ($n = 6850$ individuals) was created from four large series of PrCa patients who had undergone tumor or tumor/germline sequencing (Supplementary material). Pedigrees of patients in both cohorts were collected and examined to ensure that PrCa cases were not double counted due to enrollment in LFS registries or sequencing at more than one institution (Supplementary Fig. 1). Clinical data for both cohorts were collected in accordance with the Declaration of Helsinki guidelines and following approval from the respective institutional review boards at University of Washington, Tulane University, University of Pennsylvania, University of Utah, Memorial Sloan Kettering Cancer Institute, and Dana Farber Cancer Institute.

2.2. TP53 variant review and exclusion of somatic interference

All variants in the LFS and PrCa cohorts were referenced with ClinVar [16] and classified based on TP53-specific American College of Medical Genetics (ACMG) guidelines (Supplementary material) [17]. Subclassification of likely pathogenic or pathogenic variants as full penetrance versus attenuated variants was based on published functional data. Patients in the LFS cohorts were confirmed to have germline variants not due to somatic interference by clonal hematopoiesis of indeterminate potential or other abnormal clonal expansion [18] by testing of ancillary tissues and/or by variant segregation in families. In the PrCa cohorts, somatic interference [18] was excluded by: first, restricting to pathogenic and likely pathogenic variants with >35% variant fraction in blood; second, tumor sequencing when available to confirm presence in the cancer and in the matched normal tissue; and finally, a comparison of variant allele fractions with other observed somatic and germline variants.

2.3. Tumor analyses

Tumor next-generation sequencing data (UW-OncoPlex and MSK-IMPACT) were available for a subset of gTP53 carriers [19,20]. Tumor data were analyzed by an expert molecular pathologist (C.C.P.) for evidence of somatic TP53 second allele inactivation, including assessment of loss of heterozygosity (L.O.H.).

2.4. Statistical analysis

To calculate PrCa risk and incidence rates, the full LFS cohort was restricted to patients without a prior PrCa diagnosis at genetic testing to avoid selection and immortalization biases. Risk of PrCa diagnosis relative to the general population was then estimated using a standardized incidence ratio (SIR) comparing the observed numbers with the expected numbers of PrCa diagnoses, with the latter calculated by applying PrCa incidence rates in the population to specific ages and calendar years of follow-up. Follow-up was summarized using reverse Kaplan-Meier estimation [21], which begins at the genetic test, treats death or last follow-up without PrCa diagnosis as events, and censors PrCa diagnoses. This approach gives a robust summary of follow-up for all patients, which is used to calculate the expected number of PrCa diagnoses. The PrCa incidence rates were those observed in the Surveillance, Epidemiology, and End Results (SEER) program from 1997 to 2017 by calendar year and 5-yr age group. Incidence rates over the period of 2018–2020 were assumed to be equal to the rates observed in 2017. Significance of the SIR was evaluated using a two-sided exact Poisson test. Overall and age-specific PrCa incidence rates in the restricted cohort were calculated relative to observed person-years of follow-up, and corresponding rates in SEER were calculated relative to population totals. In the PrCa cohort, the relative risk of carrying gTP53 was compared with frequencies in the gnomAD database using a Fisher's exact test after excluding individuals with cancer (gnomAD v2.1.1 noncancer, 134 187 samples; Supplementary material).

3. Results

3.1. Incidence of PrCa in LFS

Among a cohort of LFS individuals created from datasets at four academic institutions, we identified 163 males aged ≥ 18 yr with a confirmed gTP53 likely pathogenic/pathogenic variant or obligate carrier status from 132 families (Supplementary Tables 1 and 2, and Supplementary Fig. 1). We identified PrCa in 31 of 163 (19%) adult males in this cohort, including 26 of 54 males (48%) aged ≥ 50 yr

Table 1 – Age distribution of men with prostate cancer (PrCa) in Li-Fraumeni syndrome (LFS) cohorts

Age group	Combined LFS/LFL cohorts		
	n	PrCa	%
18–29	32	0	0
30–39	35	1	2.9
40–49	42	4	10
50–59	32	15	47
60–69	15	7	47
70–79	7	4	57
≥ 80	0	0	NA
Total (w/ages)	163	31	19

LFL = Li-Fraumeni-like syndrome; NA = not available.
⁽¹⁾ Age based on cancer diagnosis age or current age if unaffected.

(Table 1). The frequency of PrCa within age deciles was similar in all four datasets (Supplementary Table 3). In a restricted analysis of 117 men who did not have a PrCa diagnosis at the time of genetic testing (Supplementary Table 1), six were diagnosed with PrCa over a median (interquartile range [IQR]) of 3.0 (1.3–7.2)s of follow-up. The risk of a PrCa diagnosis in this subgroup of LFS men was 25 times that in the general population (95% confidence interval [CI] 9.2–55; $p < 0.0001$), with incidence rates significantly elevated at all ages (Fig. 1, Table 2, and Supplementary Fig. 2).

3.2. Prevalence of gTP53 in individuals with prostate cancer

To determine the prevalence of gTP53 in PrCa patients, we analyzed four large germline or tumor sequencing datasets comprising 6850 PrCa patients (Table 3 and Supplementary Table 2), excluding cases suggestive of somatic interference [18]. We identified gTP53 in 38 patients overall (0.55% prevalence), with prevalence rates ranging from 0.27% to 0.84% across the four independent cohorts (Table 3). The relative risk of having gTP53 was significantly elevated at 9.1 (95% CI 6.2–14, $p < 0.0001$) compared with the gnomAD noncancer population database (Fig. 1). Restricting both the sequencing cohorts and the gnomAD to TP53 variants classified as likely pathogenic or pathogenic in ClinVar, the relative risk remained statistically significantly elevated at 8.7 (95% CI 4.8–16, $p < 0.0001$; Table 3).

3.3. Spectrum of gTP53 variants reveals hotspots associated with attenuated mutations

To study the spectrum of gTP53 variants and clinicopathological PrCa features, we combined gTP53 PrCa cases from the LFS and PrCa cohorts as no significant differences were observed for any variable between cohorts (Table 4). Of 67 individuals with PrCa and gTP53, 20 (30%) had classic LFS variants (Table 4). Thirty-two individuals (48%) had gTP53 variants with published evidence of being attenuated (or hypomorphic) variants, and 15 (22%) had variants suggestive of being attenuated (Table 4). Five codons associated with attenuated variants (158, 181, 282, 283, and 337) accounted for 28 of the 67 cases (42%; Fig. 1 and 2, and Supplementary Table 2). Moreover, rare attenuated variants at codon 181 ($n = 10$) were found in all series (except TCGA), and codons 158, 283, and 337 were enriched in four or more series (Supplementary Table 2). Specific TP53 variants, p.

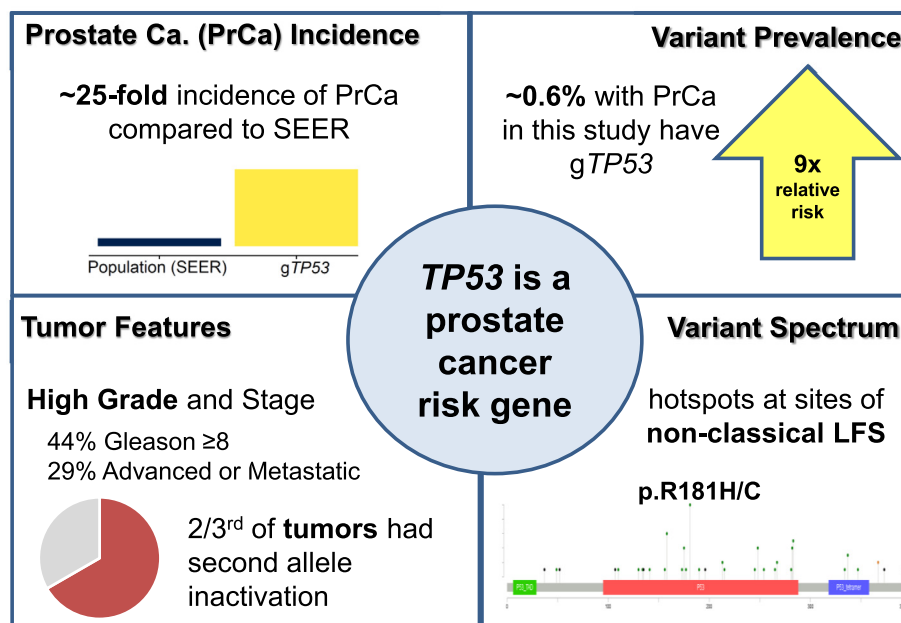


Fig. 1 – Summary of results (graphical abstract). LFS = Li-Fraumeni syndrome; PrCa = prostate cancer; SEER = Surveillance, Epidemiology, and End Results.

Table 2 – Annual prostate cancer incidence rates per 1000 in the Li-Fraumeni syndrome (LFS) and in the Surveillance, Epidemiology, and End Results (SEER) registry

Age (yr)	Restricted LFS cohort ^a		SEER	
	Rate per 1000	95% CI	Rate per 1000	95% CI
0–49	3.9	0.48–14	0.050	0.049–0.050
50–59	40	4.8–144	2.03	2.02–2.04
60–74	90	11–326	7.10	7.08–7.13
0–74	10	3.8–23	1.07	1.07–1.07

CI = confidence interval.

Results are by post hoc age at risk and all ages combined.

^a LFS cohort restricted to men with no prostate cancer diagnosis at the time of their genetic test.

R158H, p.R181H, p.R282Q, p.R283C, and p.R337H, were each significantly enriched in PrCa cohorts versus gnomAD noncancer controls, with relative risks ranging from 6.1 (for p.R283C) to 92 (for p.R158H; Supplementary Table 4).

3.4. Tumor analysis in *gTP53* carriers supports role in tumorigenesis

As a biallelic loss suggests that the *gTP53* variant contributed to cancer formation, we analyzed available prostate tumors

from *gTP53* carriers who had adequate tumor for evaluation. Ten of 15 available tumors (67%), including nine with likely or known attenuated variants, had evidence of somatic inactivation of the second *TP53* allele (Table 4 and Supplementary Table 2). The tumors without evidence of somatic inactivation had either p.R282Q or p.R283C alleles.

3.5. Clinicopathological features of *gTP53* carriers with PrCa

The median age of PrCa diagnosis in males with *gTP53* in this study was 56 (IQR: 51–60) yr (Table 4). PrCa incidence was increased compared with the SEER data in each group analyzed (Table 2 and Supplementary Fig. 2). Of individuals with *gTP53* PrCa in the combined cohorts, 26% had a personal diagnosis and 55% had a family history of an LFS core cancer. Only 26% of the families in the combined cohort did not meet any LFS diagnostic criteria. Nearly all individuals had a family history of cancer, and 30% of patients had a family history of PrCa. A family history of breast cancer was reported in 61% of the combined cohort. Of men with LFS, PrCa was the only or the most recent cancer diagnosis in 58% (18 of 31).

Table 3 – Germline *TP53* likely pathogenic/pathogenic variants in prostate cancer (PrCa) cohort compared with the general population

Cohort	Total	LP/P + VUS/LP			ClinVar LP/P		
		n (%)	RR ^a (95% CI)	p value	n (%)	RR ^a (95% CI)	p value
RL	3329	23 (0.69)	11 (7.1–18)	<0.0001	10 (0.30)	11 (5.5–23)	<0.0001
AL-1	831	7 (0.84)	14 (6.4–30)	<0.0001	5 (0.60)	22 (8.7–57)	0.002
AL-2	2191	6 (0.27)	4.5 (2.0–10)	0.0004	1 (0.05)	NA	NA
TCGA	499	2 (0.40)	6.6 (1.6–27)	0.009	0 (NA)	NA	NA
Combined	6850	38 (0.55)	9.1 (6.2–14)	<0.0001	16 (0.23)	8.7 (4.8–16)	<0.0001

AL = Academic Laboratory; CI = confidence interval; RL = reference laboratory; LP/P = likely pathogenic and pathogenic mutations; RR = relative risk; TCGA = The Cancer Genome Atlas; VUS = variants of uncertain significance.

^a gnomAD v2.1.1 noncancer, 134 187 sample data for *TP53* were downloaded and *TP53* variants classified as LP/P variants as per ClinVar or VUS/LP in ClinVar, classified as likely pathogenic in this study. The rate of LP/P and VUS/LP *TP53* variants in gnomAD was 0.059%, and the rate of ClinVar LP/P *TP53* variants in gnomAD was 0.026%.

Table 4 – Characteristics of 67 PrCa patients with confirmed gTP53

	LFS		PrCa	
	n	%	n	%
Site	n = 31		n = 36	
LFS-1	10	32	–	–
LFS-2	3	10	–	–
LFS-3	6	19	–	–
LFS-4	12	39	–	–
RL-1	–	–	7	19
RL-2	–	–	23	64
RL-3	–	–	4	11
TCGA	–	–	2	5.6
Age of PrCa diagnosis	n = 31		n = 27	
Median (IQR)	56 (50–64)		56 (51–60)	
Mutation class	n = 31		n = 36	
Classic	12	39	8	22
Reduced penetrance	16	52	16	44
Unknown	3	10	12	33
Tumor LOH	n = 6		n = 9	
LOH present	6	100	4	44
Personal cancer history	n = 31		n = 12	
None	11	35	5	42
Sarcoma	8	26	1	8.3
Adrenal cortical tumor	0	–	0	–
Brain	2	6.5	0	–
Leukemia	0	–	0	–
≥1 LFS-core cancer ^a	10	32	1	8.3
Cancer timing for MP	n = 19		n = 4	
Other cancer after PrCa	7	37	3	75
Other cancer before PrCa	7	37	1	25
Both before and after PrCa	5	26	0	–
Cancer family history	n = 31		n = 13	
None	1	3.2	1	7.7
Sarcoma	9	29	2	15
Adrenal cortical tumor	3	10	1	7.7
Brain	8	26	5	38
Leukemia	3	10	2	15
Breast age <31	4	13	0	–
Any LFS core cancer ^a	16	52	8	62
Breast (any age)	21	68	6	46
Prostate	9	29	4	31
Clinical LFS criteria	n = 28		n = 7	
Classic	4	14	1	14
Chompret	13	46	4	57
Birch and/or Eeles	19	68	4	57
No criteria met	8	29	3	43
PrCa Gleason score	n = 20		n = 14	
GS 6–7	12	60	7	50
GS 8–10	8	40	7	50
PSA at diagnosis	n = 14		n = 9	
Median (IQR)	6 (4–12)		6 (3–23)	
>20	3	21	3	33
PrCa diagnosis	n = 11		n = 7	
Screening	8	73	4	57
Incidental	1	9.1	1	14
Symptoms	2	18	2	29
Stage at diagnosis	n = 21		n = 13	
Localized (Nx or N0)	17	81	7	54
N1 or de novo M1	4	19	6	46

ACT = adrenal cortical tumor; GS = Gleason score; IQR = interquartile range; LFS = Li-Fraumeni syndrome; LOH = loss of heterozygosity; MP = multiple primary; PrCa = prostate cancer; PSA = prostate-specific antigen; RL = reference laboratory; TCGA = The Cancer Genome Atlas.

^a LFS core cancers: ACT, brain, leukemia, sarcoma, and breast age <31 yr.

Of PrCa cases, 29% were diagnosed as locally advanced (N1) or de novo metastatic disease. Similarly, 44% of gTP53 individuals had high-grade disease (Gleason ≥8; Fig. 1 and Table 4). Prostate-specific antigen (PSA) at diagnosis ranged from 1.1 to 171 ng/dl, and 68% of individuals were diagnosed by screening. Three individuals were diagnosed due to symptoms of advanced Gleason 9–10 PrCa at ages 50, 51, and 63 yr (Supplementary Table 2).

4. Discussion

We estimate the risk of PrCa diagnosis in individuals with LFS, and the frequency of rare germline pathogenic and likely pathogenic TP53 variants in a PrCa cohort. We found that LFS men have a 25-fold increased risk of PrCa compared with the general population. Further, we found that 0.55% (range 0.27–0.84%) of individuals with PrCa in a large sequencing cohort have gTP53. Tumor sequencing detected second allele inactivation in a majority of available tumor cases, supporting the biological relevance of the gTP53 variants to tumorigenesis. Collectively, these data demonstrate for the first time that gTP53 variants contribute to PrCa risk.

There is a paucity of data on PrCa risk in individuals with gTP53 [8,10]. While an analysis of LFS males in IARC [8] suggested that PrCa was enriched among cancers diagnosed in late adulthood, comparable average ages of cancer onset in LFS patients and SEER population suggested that the contribution of gTP53 variants was minimal. More recently, Shin et al [6] reported that the incidence of non-LFS-related tumors was higher in male gTP53 carriers between ages 35 and 65 yr, but PrCa was not analyzed individually. Our findings may differ from prior literature because a larger cohort of older LFS males, including families with attenuated LFS, was included.

Over half of the gTP53 variants we reported are considered attenuated or hypomorphic variants not typically associated with classic LFS. Individuals with attenuated gTP53 likely still have a multicancer predisposition syndrome of clinical significance [22,23]. We hypothesize that these individuals are more likely to live into adulthood and be at risk for developing prostate and other adult cancers, compared with those with full-penetrance gTP53 variants who typically have a severe early-onset cancer phenotype with high mortality rates at young ages.

In the PrCa sequencing cohorts, we found the relative risk of carrying gTP53 variants to be comparable with that of BRCA2 (relative risk 4.7–8.6) [24,25], a gene for which PrCa screening recommendations are modified [26,27]. This argues for consideration of PrCa screening in LFS guidelines. Moreover, since gTP53 carriers may be at an increased risk for radiation-induced sarcomas [5,14], our data may have treatment implications for gTP53 individuals with PrCa, for example, consideration of MRI versus computed tomography screening and avoidance of therapeutic radiation. The high rate of aggressive disease in our series (29% locally advanced or de novo metastatic) is consistent with prior observations that somatic TP53 variants are associated with advanced PrCa, and supports the consideration of earlier and/or more frequent screening with PSA and attention to prostate pathology on full-body MRI screening to identify disease at a stage amenable to surgical resection in male gTP53 carriers from LFS families. For example, one LFS patient in this series had a glioblastoma at age 24 yr, developed symptomatic hematospermia at age 50 yr, and was diagnosed with Gleason score 9 de novo metastatic PrCa, a situation that might have been avoided with screening. In addition, the high rate of other LFS core cancers (61%) and breast cancer at any age (61%) in the family history of the cohort highlights the potential value of cascade familial

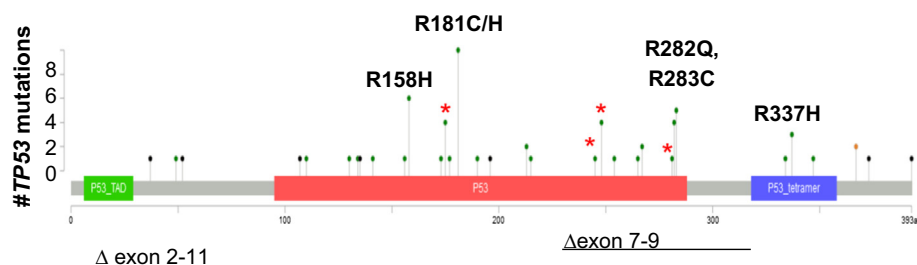


Fig. 2 – Distribution of *TP53* pathogenic and likely pathogenic variants. Lollipop plot depicts 67 germline P/LP variants in patients with prostate cancer. Green color represents missense variants, black represents truncating variants (frameshift, nonsense, and splice site), and black lines represent large deletion variants. Hotspots for prostate cancer were observed at sites of reduced penetrance variants at codons 158, 181, 282, 283, and 337. Classic LFS hotspot variants (R175H, G245S, R248Q, and R282W) are indicated with red asterisks. LFS = Li-Fraumeni syndrome; P/LP = pathogenic and likely pathogenic.

testing to reduce cancer risk in relatives of individuals with PrCa identified to have *gTP53*.

Our study has limitations—the patients represented in all series were ascertained by either clinical testing of PrCa patients or LFS status, and presumably reflect enrichment of family or personal history and younger age. Ascertainment bias is particularly important to consider for the referral laboratory series, which also had very limited clinical data. Part of the increased risk of PrCa diagnosis in the LFS cohort may be due to more frequent testing and biopsy in these men; however, it seems unlikely that this bias could explain the 25-fold increased risk relative to the general US population. In addition, the LFS cohort size is small. However, LFS is an extremely rare cancer syndrome, afflicting approximately one in 10 000–30 000 individuals [28]; therefore, centralized efforts, such as through the LiFE consortium [29], will be required to confirm the risk estimates and clinical correlations presented. It is possible that *TP53*-mutant clonal hematopoiesis of indeterminate potential could contaminate our series [18]; however, paired tumor/normal testing in sequencing cohorts was analyzed, variant allele fraction cutoffs were employed, and LFS males had ancillary tissue or familial testing, proving that the mutation was inherited. Although tumor sequencing results are supportive of mechanistic causality, additional studies would be needed to prove the role in tumorigenesis. Lastly, most individuals did not find out that they were a *gTP53* carrier until after their PrCa diagnosis and could not be utilized in SIR calculations.

Despite these limitations, our complimentary analyses showing an increased incidence of PrCa in an LFS cohort, far higher prevalence of *gTP53* variants in a PrCa cohort than in population controls, tumor data supporting a role in tumorigenesis, and biological plausibility of observing more PrCa in attenuated *gTP53* are collectively compelling. Confirmation in larger numbers of PrCa patients with paired testing of blood and tumor will be helpful, as will better understanding of modifying factors in the context of *gTP53* variants. Exact PrCa risk estimates will likely be specific to variant and population.

5. Conclusions

This study contributes to a greater understanding of *TP53*-associated cancer risk, demonstrating that adult cancers

such as PrCa in LFS are understudied and merit further attention. Attenuated or hypomorphic *gTP53* alleles provide a plausible hypothesis as to why some *gTP53* patients develop late adulthood cancers that would not have been appreciated previously in individuals with more severe *gTP53* variants that predispose to high cancer burden and earlier mortality. Screening guidelines for adults with attenuated LFS phenotypes are needed urgently. We suggest that current LFS screening guidelines be updated to consider annual PrCa screening in men with at least 10 yr of life expectancy. While *gTP53* mutation rates are low in PrCa cohorts, the clinical importance of the finding for the patient and family is significant. We suggest evaluation of *TP53* in germline genetic testing in PrCa patients, ideally by paired tumor-normal testing, to rule out somatic interference.

Author contributions: Colin C. Pritchard had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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