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Angaben zur Veröffentlichung / Publication details:

Penkert, Judith, Farina J. Strüwe, Christina M. Dutzmann, Beate B. Doergeloh, Emilie Montellier, Claire Freycon, Myriam Keymling, et al. 2022. "Genotype–phenotype associations within the Li-Fraumeni spectrum: a report from the German Registry." *Journal of Hematology and Oncology* 15 (1): 107. <https://doi.org/10.1186/s13045-022-01332-1>.

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Genotype–phenotype associations within the Li-Fraumeni spectrum: a report from the German Registry

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Abstract

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome caused by pathogenic *TP53* variants. The condition represents one of the most relevant genetic causes of cancer in children and adults due to its frequency and high cancer risk. The term Li-Fraumeni spectrum reflects the evolving phenotypic variability of the condition. Within this spectrum, patients who meet specific LFS criteria are diagnosed with LFS, while patients who do not meet these criteria are diagnosed with attenuated LFS. To explore genotype–phenotype correlations we analyzed 141 individuals from 94 families with pathogenic *TP53* variants registered in the German Cancer Predisposition Syndrome Registry. Twenty-one (22%) families had attenuated LFS and 73 (78%) families met the criteria of LFS. NULL variants occurred in 32 (44%) families with LFS and in two (9.5%) families with attenuated LFS (P value < 0.01). Kato partially functional variants were present in 10 out of 53 (19%) families without childhood cancer except adrenocortical carcinoma (ACC) versus 0 out of 41 families with childhood cancer other than ACC alone (P value < 0.01). Our study suggests genotype–phenotype correlations encouraging further analyses.

Keywords: Li-Fraumeni syndrome, *TP53*, Genotype, Phenotype, Cancer predisposition

To the editor

Li-Fraumeni syndrome (LFS; OMIM151623) is a cancer predisposition syndrome caused by pathogenic variants (PVs) in the *TP53* tumor suppressor gene and represents one of the best characterized genetic causes of cancer in children and adults [1–4]. The use of modern DNA-sequencing methods has revealed *TP53* germline PVs

in individuals who do not meet established clinical LFS criteria, leading to a Li-Fraumeni spectrum classification [5]. We analyzed factors influencing the cancer risk across this spectrum. The overall aim of such studies is to improve risk prediction to inform cancer surveillance.

Founded in 2017, the German Cancer Predisposition Syndrome Registry collects information on genotypes, personal medical details, family histories, and surveillance, as well as a range of biospecimens. The cutoff date for study inclusion for the present analysis was July 31, 2021. Patients with a germline *TP53* PV (pathogenic or likely pathogenic) or with a somatic mosaic *TP53* PV were included. All variants were curated according to

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TP53 specific guidelines [6]. Classic LFS criteria [2], Chompret criteria [4] as well as the Li-Fraumeni spectrum classification [5] were assessed. To search for genotype–phenotype correlations we used functional data from Kato [7], Giacomelli [8], Kotler [9] as well as estimated dominant negative effects based on studies by Monti [10] and Dearth [11]. We tabulated the 94 LFS families and applied the Fisher’s exact test to analyze whether the phenotypes (1) LFS versus attenuated LFS and (2) occurrence of childhood cancer other than adrenocortical carcinoma (ACC) alone versus cancer free childhood except ACC were associated with specific genotypic/functional *TP53* PV subgroups. A *P* value of <0.01 was considered statistically significant. Ethics review and informed consent were obtained.

An overview of all variants, functional data categories, and associated phenotypes including personal and family histories are provided in Additional file 1. The cohort comprises 141 individuals from 94 families; 43 (30.5%) individuals were children or adolescents <18 years,

whereas 98 (69.5%) individuals were adults. There were 98 female and 43 male patients (male-to-female ratio: 0.44). This uneven gender distribution may be due to females being tested more frequently in the context of a breast cancer diagnosis. Four cases with somatic mosaicism were reported. *TP53* PVs as well as statistically significant genotype–phenotype correlations are depicted in Fig. 1.

According to the Li-Fraumeni spectrum classification [5], the cohort included 79 individuals with *LFS*, 33 *LFS carriers* as well as 14 individuals with *attenuated LFS* and 15 *attenuated LFS carriers*. No consistent signs of anticipation were observed. In the entire cohort, 33 families (35.1%) did not meet any of the established LFS testing criteria. Thirty-four LFS patients (30.4%) had multiple (between two and five) malignancies, whereas six patients with attenuated LFS (20.7%) had a history of multiple (between two and four) malignancies. Overall, 134 neoplasms occurred in 79 LFS patients, whereas 26 malignancies occurred in 14 individuals with attenuated LFS

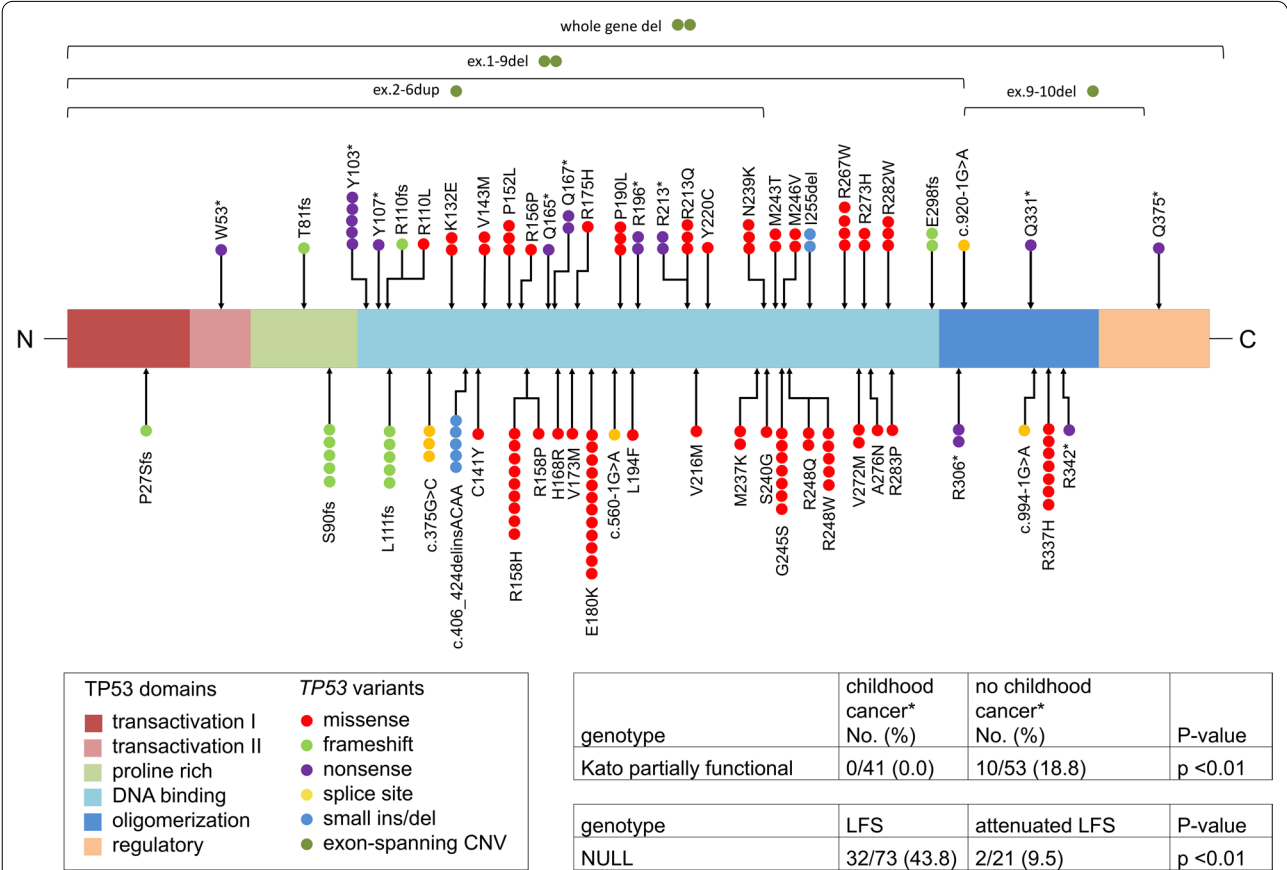
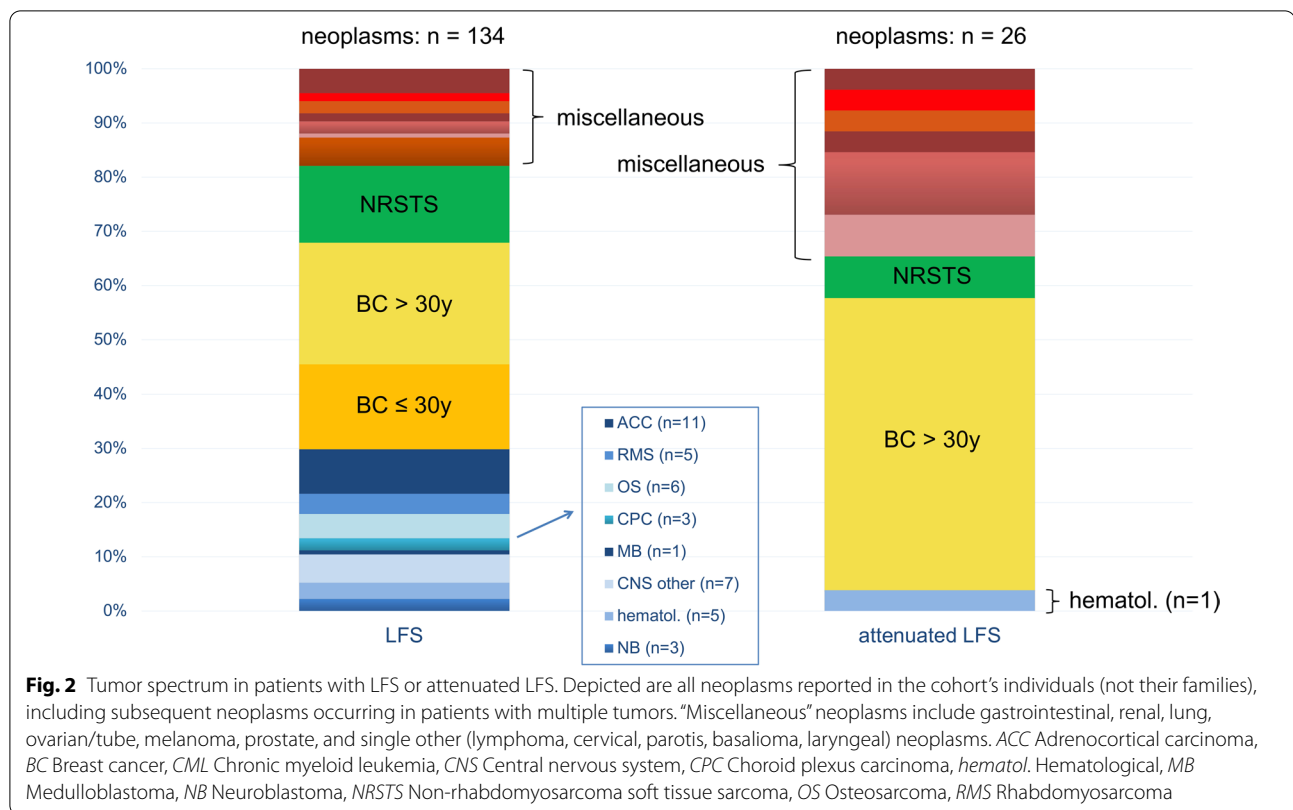


Fig. 1 Spectrum of *TP53* germline variants and statistically significant genotype-phenotype correlations. Colored spheres refer to different patients harboring the corresponding variant. Note: Y103* is based on two different nucleotide substitutions; whole gene deletions include two gross deletions with differing breakpoints. The genotype–phenotype correlation was based on data from 94 families. CNV, Copy number variation



(Fig. 2). In patients with LFS, breast cancer ≤ 30 years, osteosarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, ACC, and central nervous system tumors were diagnosed in 73 of 134 (55%) patients. In individuals with attenuated LFS, more than half of the tumors diagnosed were breast cancers > 30 years. The proportion of miscellaneous neoplasms not known to be strongly associated with *TP53* germline PVs was 34.6% in patients with attenuated LFS compared to 17.9% in patients with LFS. Altogether, 65 breast cancers occurred in the entire cohort, 26 of which were HER2+, 24 were HER2-, and for 15 tumors histological details were not available.

Kato partially functional variants were statistically significantly associated with a cancer-free childhood, apart from childhood ACC (10 out of 53 families without childhood cancer except ACC versus 0 out of 41 families with childhood cancer except ACC alone, P value < 0.01). Typical LFS childhood cancers (i.e., rhabdomyosarcoma, osteosarcoma, choroid plexus carcinoma, medulloblastoma, other brain tumors, and leukemia)—excluding ACC—occurred exclusively in individuals with NULL variants or non-functional missense variants. In general, childhood cancer occurred in more than half of the families with NULL (58.8%)

or non-functional missense (52%) variants, whereas in families with partially functional variants ACC was observed as the only childhood cancer, affecting 30% of these families. We observed a statistically significant association between NULL variants and LFS, while this variant type was rare among patients with attenuated LFS: 32 out of 73 families with LFS carried NULL variants, whereas NULL variants were present in two out of 21 families with attenuated LFS (P value < 0.01). We did not observe additional statistically significant associations when analyzing the other functional variant subgroups. Case ascertainment, differences in overall survival, family size, and/or family clustering may have introduced a potential bias and represent a limitation of our study.

Despite this limitation, these data suggest that future more detailed genotype–phenotype correlations may allow for accurate cancer risk prediction (time to first malignancy and second cancer risk) and personalized cancer surveillance. Large, international collaboration is required to reach the statistical power to make such risk predictions. Our findings are in agreement with previously published results assessing the correlation between *TP53* genotypes and various other cancer phenotypes in LFS [12, 13]. The observation that a substantial proportion of patients is missed using established

LFS testing criteria suggests that the criteria require modification.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13045-022-01332-1>.

Additional file 1. TP53 (NM_000546.5) variants, functional data categories, and associated phenotypes. Abbreviations: Acute lymphatic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma (ACC), bilateral (bilat), breast cancer (BC), carcinoma (CA), choroid plexus carcinoma (CPC), chronic lymphatic leukemia (CLL), chronic myeloid leukemia (CML), colorectal carcinoma (CRC), ductal carcinoma in situ (DCIS), estrogen receptor (ER), female (f), human epidermal growth factor receptor 2 positive (Her2+), Li-Fraumeni syndrome (LFS), lobular intraepithelial neoplasia (LIN), male (m), medulloblastoma (MB), myelodysplastic syndrome (MDS), neuroblastoma (NBL), non-small-cell lung carcinoma (NSCLC), not available (NA), osteosarcoma (OS), Primitive Neuro-Ectodermal Tumor (PNET), progesterone receptor (PR), rhabdomyosarcoma (RMS), soft tissue sarcoma (STS), triple-negative breast cancer (TNBC). Variants marked * were classified as NULL variants; to reduce complexity, smaller (less than whole exon) deletions were rated as NULL variants as well. The DNE IARC estimation, based largely on studies by Monti and Dearth, was accessed via the TP53 Database (<https://tp53.isb-cgc.org>).

Acknowledgements

We thank Christina Reimer and Editha Gnutzmann for their support.

Author contributions

CPK was involved in all aspects of the study; JP conducted the analysis and prepared the manuscript; FS, CMD, BBD, BH, BS, and TG were responsible for running the LFS registry; EM, CF, PH were involved in data interpretation, MK, HPS, CB, SF, MF, SH, UK, VR, SKB, AM, JN, AP, AR, MGS, SZ, KWP, SMP, and SS provided information on LFS patients. All authors read and approved the final manuscript.

Funding

CPK and SMP have been supported by the Deutsche Kinderkrebsstiftung (DKS2019.13). CPK has been supported by BMBF ADDress (01GM1909A). SMP, MK, and HPS have been supported by BMBF ADDress (01GM1909E). SS has been supported by BMBF ADDress (01GM1909D).

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its Additional file 1.

Declarations

Ethics approval and consent to participate

The project was approved by the Research Ethics Committee of Hannover Medical School (approval number 7233).

Consent for publication

This manuscript has not been previously published and is not under consideration for publication elsewhere.

Competing interests

The authors declare that they have no competing financial interests.

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Received: 27 June 2022 Accepted: 1 August 2022

Published online: 16 August 2022

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