Insights into Tumor Genomics in Li-Fraumeni Syndrome: A Retrospective Study from a Large Cohort

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INTRODUCTION

Tumors in individuals with Li-Fraumeni syndrome (LFS) often display distinct clinical and biological behavior compared to sporadic cases. However, the literature on somatic profiling in LFS is limited. The largest study to date included only 22 tumors (Light et al., 2023), none from carriers of the *TP53* R337H variant. We conducted a retrospective analysis of 589 participants from the Brazilian Li-Fraumeni Syndrome Study (BLiSS) cohort to identify patients who underwent somatic tumor testing and to characterize their molecular profiles.

OBJECTIVES

To investigate the somatic molecular landscape of tumors in individuals with LFS, including tumor mutational burden (TMB), recurrent somatic alterations, clinical relevance, and to compare these profiles with those observed in the general population.

METHODOLOGY

A retrospective chart review was conducted on 589 patients with a molecular diagnosis of LFS enrolled in BLiSS. For those with somatic testing, we collected data on tumor type,TMB, microsatellite stability (MSS), copy number variation (CNV) profiles, and somatic SNVs. Binomial tests were used to compare proportions with population-based datasets. Further clustering and identification of genomic profiles based on SBS mutational signatures (SigProfiler)[2] will also be performed and the patterns will be compared among R337H and non-R377H related tumors.

RESULTS AND DISCUSSION

Thirty-five patients (5.94%) underwent somatic testing, with a total of 42 tumor analyses (including 5 tumors that were sequenced more than once during treatment). Most individuals (91.4%) carried the *TP53* R337H variant. Pulmonary adenocarcinoma was the most frequently tested tumor (57.1%), followed by leiomyosarcoma (10.4%) and glioma (9.5%). A high proportion of germline diagnoses (55.9%) were prompted by somatic testing. TMB was assessed in 20 tumors: 95% showed low TMB (mean 3.0 mutations/Mb, SD 2.53; range 0-10). All tumors were microsatellite stable. Somatic variants are detailed in **Fig 1.**

EGFR mutations were detected in 55% of pulmonary adenocarcinomas (11/20), a significantly higher rate than in the general Brazilian NSCLC population (24.2%, $p = 0.003$) and European cohorts (12.8%, $p < 0.001$). The L858R substitution was the most frequent *EGFR* oncogenic variant, identified in 30% of tumors (6/20), also significantly enriched compared to Brazilian data (6.9%, $p = 0.0018$). Most *EGFR* variants (91%) were classified as activating mutations, and 82% of tumors harbored changes potentially responsive to osimertinib.

Although differences in sequencing approaches exist (Light et al. performed WGS), all *TP53* LOH events in their cohort were associated with gain of the mutant allele, and only a single tumor (ACC) carried an additional somatic SNV in *TP53*, supporting their conclusion that point mutations are a rare mechanism of second hit. In contrast, in our R337H cohort, copy number loss with gain of the mutant allele was observed in 76.5% of tumors, but oncogenic SNVs in *TP53* were identified as second hits in 23.54%, suggesting that this mechanism may be more frequent in R337H-associated tumorigenesis. We are currently performing SigProfiler clustering for the comparison of mutational signature to further detail tumoral differences among the two groups and to test if R337H-related tumors follow unique tumorigenesis pathways.

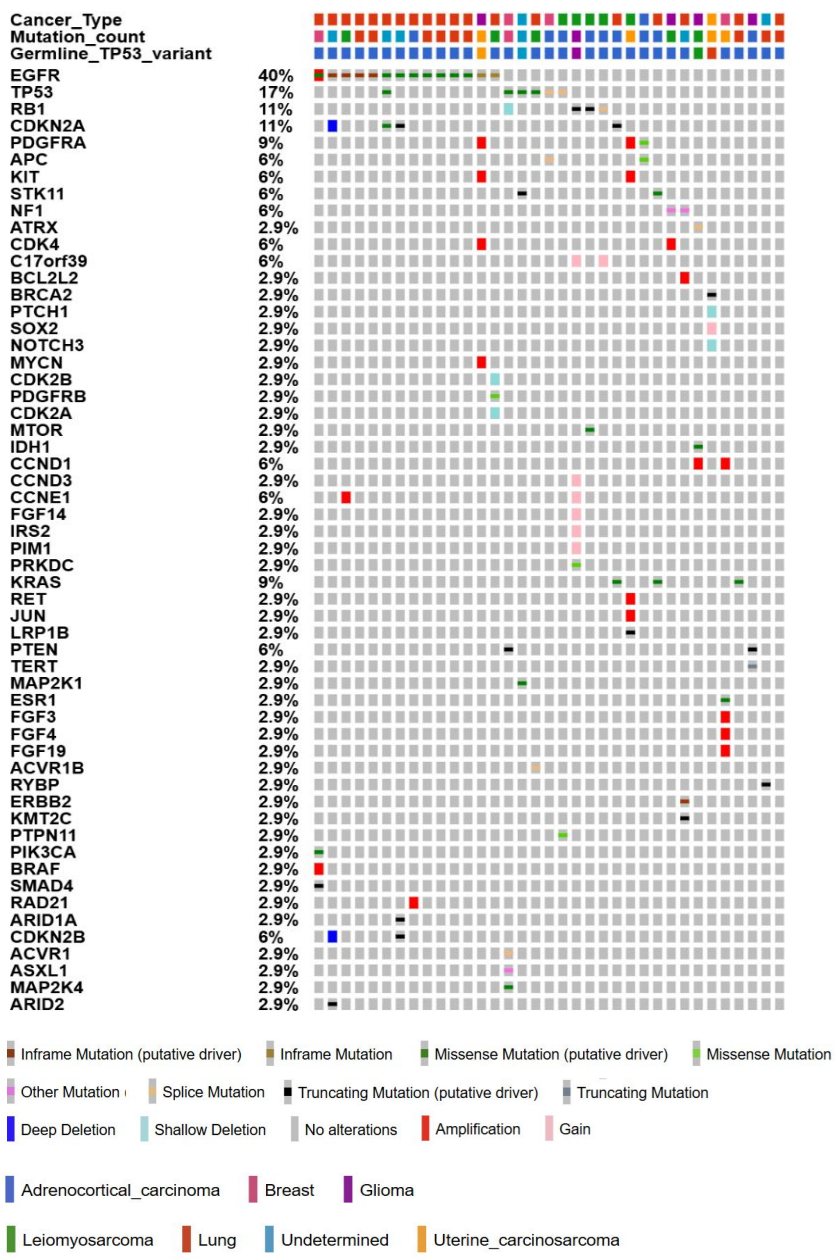

Fig 1. Oncoprint detailing the landscape of somatic variants in LFS

CONCLUSION

Somatic profiling of tumors in individuals with LFS reveals unique molecular signatures that may guide personalized management. Our study highlights the value of integrating somatic data in the care of hereditary cancer syndromes.

REFERENCES

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