Analysis of cosegregation of the *XAF1*-E134* variant in patients with pathogenic variants in the *TP53* gene: its relationship with clinical findings.

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Abstract

Li-Fraumeni Syndrome (LFS), one of the main hereditary syndromes in Brazil, is especially associated with the TP53-R337H variant. The *XAF1*-E134* variant forms an aggressive haplotype when cosegregated with TP53-R337H. Patients suspected of having LFS were evaluated for cosegregation and referred to Center for Human Genetics-UFG. TP53 sequencing was performed in patients and R337H variant genotyping was performed in family members. Individuals positive for TP53 were tested for *XAF1*-E134*. Among the 235 patients, 11 presented pathogenic variants in *TP53*, with 10/11 being the R337H variant. Among the patients, 9/11 also presented the XAF1-E134* variant. Of the family members, 50/353 had variants in the TP53 gene, and 45 of them were positive for the *XAF1*-E134* variant.

Introduction

Cancer is the second leading cause of death worldwide, accounting for 5% to 10% of cases. Hereditary origin. Pathogenic variants in tumor suppressor genes, such as *TP53*, increase significantly increases the risk of developing the disease. In Brazil, Li-Fraumeni Syndrome (LFS) is one of the major hereditary syndromes, especially associated with the R337H variant. The *XAF1* gene , a tumor suppressor, regulates apoptosis and modulates the transcriptional activity of TP53. through a positive feedback loop. The cosegregation of the *XAF1*-E134* variants and TP53-R337H forms a long-range haplotype associated with greater tumor aggressiveness. This study aimed to investigate this cosegregation in patients with suspected LFS.

Methods and Materials

They were referred to the Human Genetics Center-UFG by the SUS (Brazilian Public Health System) originating from the care primary and tertiary care: 588 patients with breast, ovarian, prostate cancer and sarcomas and their Family members. After pre-genetic counseling and signing of the informed consent form, venous blood was collected. for DNA extraction, followed by NGS of the coding region of the TP53 gene in patients and of Genotyping of the R337H variant in family members. Patients positive for *TP53* were evaluated. Regarding the presence of the *XAF1*-E134* variant by genotyping. (Figure 1)

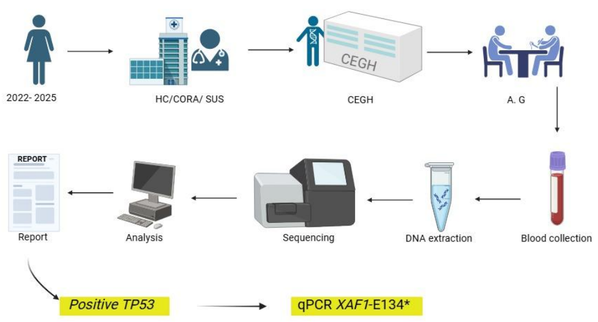


Figure 1- Methodological steps of the study

Results

Of the 588 participants analyzed, 39.97% (235) were patients and 60.03% (353) were family members. In this regard, 14 families presented pathogenic variants in the *TP53* gene, and 11/14 patients from these families were tested for *TP53*, presenting 4.68% (11/235) of pathogenic variants in this gene, with 90.91% (10) being R337H and 9.09% (1) being c.455C>T. All 11 patients were tested for the *XAF1*-E134* variant, with 81.82% (9/11) presenting a positive result and (3/11) multiple tumors (Figure 2). Among family members, 14.16% (50/353) presented variants in the TP53 gene. Of the carriers, 90% (45/50) tested positive for the *XAF1*-E134 gene*.

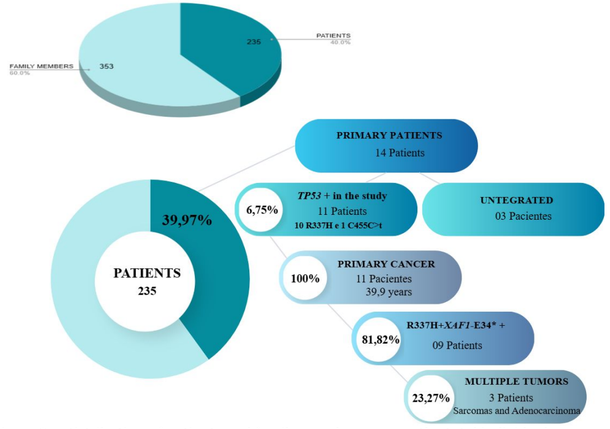


Figure 2a: Distribution of patients and family members among the total individuals analyzed in the study; Figure 2b: Distribution of patient profiles.

Discussion

The study by Pinto et al. (2020) performed genotyping of 203 cancer patients (carriers of the founder allele *TP53*-R33H) and showed a frequency of 79.31% for the XAF1-E134* variant. This study also identified the presence of cosegregation associated with the occurrence of sarcomas (OR = 6.33; Inf; p = 0.003) and multiple primary tumors (OR = 4.53; 95% CI, 1.52 in Inf; p = 0.006). The study by Gerber et al. (2022) evidenced the cosegregation of the *XAF1*-E134* variant with R337H in a female population belonging to families from the state of Paraná. Kratz et al., 2021, reviewed the International Agency for Research on Cancer (IARC) germline variant database of the *TP53* gene and found that, in 282 Brazilian carriers of the R337H allele, the extended haplotype on chromosome 17p13 also shows expression of *XAF1*-E134* in a subgroup of these individuals. Therefore, a direct implication of familial risk in relation to cancer susceptibility is suggested, although without presenting conclusive statistical data, which reinforces the importance of discussing the role of the clinical penetrance of this variant.

Conclusions

The study confirms the high incidence of the R337H variant in Brazil and its cosegregation with the *XAF1*-E134* variant. No relationship was found with other pathogenic variants of the TP53 gene. The aggressiveness associated with this extended haplotype was not statistically demonstrated in this study. The qPCR methodology for the molecular diagnosis of the *XAF1*-E134* variant is efficient in the field of medical genetics. The study reinforces the importance of *XAF1*-E134* analysis in LFS diagnostic protocols, allowing for better risk stratification, genetic counseling, and monitoring of patients and families in high-risk Brazilian populations.

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References

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