

30131**HIGH DENSITY SNP ARRAY ANALYSIS OF PATIENTS CARRYING THE TP53 R337H MUTATION**Diego Davila Paskulin, NAKACHI I, VARELLA-GARCIA M. **Orientador:** PATRICIA ASHTON PROLLA**Unidade/Serviço:** Centro de Pesquisa Experimental

The p53 tumor suppressor gene is a pivotal regulator of different cellular pathways including apoptosis, DNA damage, oncogene activation, or hypoxia. Structurally, it consists of a homotetramer, and each of its monomers is composed of 393 amino acids. Well-defined domains can be identified in the protein, including an N-terminal transactivation domain, a proline-rich region, a central and highly conserved DNA-binding domain, a tetramerization domain, and unstructured basic domains at its Cterminus. p53 suppresses cellular transformation by regulating the expression of an array of different genes, encoding both proteins and microRNAs, and is involved in growth arrest, DNA repair, apoptosis, and senescence pathways. Germline mutations in TP53 are the underlying defect of Li-Fraumeni Syndrome, an autosomal dominant disorder characterized by predisposition to multiple early-onset cancers. Most mutations in the TP53 gene affect the DNA binding domain and result in missense substitutions giving rise to altered proteins that have a considerable longer half-life than the wild-type protein, resulting in accumulation of the mutant protein, at least in transfected or neoplastic cells. In Brazil, a germline mutation at codon 337 (c.G1010A, p.R337H), which is present in about 0.3% of the population of Southern Brazil, has been found associated with adrenocortical tumors in adults, choroid plexus carcinoma in children, breast cancer, and Li-Fraumeni/Li-Fraumeni-like syndromes. Structural and functional studies have demonstrated that the p.R337H protein displays a pH-dependence, rendering the protein inactive only under certain conditions of increased intracellular pH, which could explain its lower overall malignant potential. In this study, we analyzed the genomic alterations present in ten patients carrying the TP53 R337H mutation using high-density SNP genotyping arrays to discover new imbalanced regions associated with p.R337H (GPPG 08-022). Fluorescent in situ Hybridization was used to validate these regions in adrenocortical carcinoma and breast cancer patients. Single-nucleotide polymorphism array data analysis allowed us to detect chromosomal segment of copy neutral loss of heterozygosity (CN-LOH) in addition to copy number alterations. Our results show gains in 12p13.3-12p11.23, 16p13.3-16q24.3, amplifications in 1q24.2-1q25.3, deletions in 2p25.3-2q37.3 and 17p13.1 and copy neutral loss of heterozygosity in 11p15.5-p11.2 and 17p13.1 in patients with TP53 p.R337H mutation. The investigated chromosomal regions, in particular those with CN-LOH, point out to new chromosomal regions associated with LFS patients carrying the TP53 p.R337H mutation.