GENÉTICA

➢ Novel Compound Heterozygous Mutation c.3955_3958dup and c.5825C>T in the ATM Gene: Clinical Evidence of Ataxia-Telangiectasia and Cancer in a Peruvian Family

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ABSTRACTO: Pathogenic and likely pathogenic variants in the ATM gene are associated both with Ataxia-telangiectasia disease or ATM syndrome and an increased cancer risk for heterozygous carriers. We identified a novel compound heterozygous mutation c.3955_3958dup (p.Asp1320delinsValTer) and c.5825C>T (p.Ala1942Val) in the ATM gene in a Peruvian patient with progressive ataxia combined with other movement disorders, mild conjunctival telangiectasia and increased alpha-fetoprotein, without history of recurrent infection or immunodeficiency. We also determined the carrier status of the family members, and we were able to detect gastric and breast cancer at an early stage during the cancer risk assessment in the mother (c.3955_3958dup). Here, we describe clinical evidence for the novel compound heterozygous mutation and c.3955_3958dup not previously reported.

➢ Influence of Sex in the Molecular Characteristics and Outcomes of Malignant Tumors

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ABSTRACTO: Background: Sex is frequently underestimated as a prognostic biomarker in cancer. In this study, we evaluated a large cohort of patients and public datasets to determine the influence of sex on clinical outcomes, mutational status, and activation of immune pathways in different types of cancer. Methods: A cohort of 13,619 Oncosalud-affiliated patients bearing sex-unrelated cancers was followed over a 20-year period. Hazard ratios (HRs) for death were estimated for female vs. male patients for each cancer type and then pooled in a meta-analysis to obtain an overall HR. In addition, the mutational status of the main actionable genes in melanoma (MEL), colorectal cancer (CRC), and lung cancer was compared between sexes. Finally, a gene set enrichment analysis (GSEA) of publicly available data was conducted, to assess differences in immune processes between sexes in MEL, gastric adenocarcinoma (GC), head and neck cancer (HNC), colon cancer (CC), liver cancer (LC), pancreatic cancer (PC), thyroid cancer (TC), and clear renal cell carcinoma (CCRCC). Results: Overall, women had a decreased risk of death (HR = 0.73, CI95: 8%-42%), with improved overall survival (OS) in HNC, leukemia, lung cancer, lymphoma, MEL, multiple myeloma (MM), and non-melanoma skin cancer. Regarding the analysis of actionable mutations, only differences in EGFR alterations were observed (27.7% for men vs. 34.4% for women, p = 0.035). The number of differentially activated immune processes was higher in women with HNC, LC, CC, GC, MEL, PC, and TC and included

cellular processes, responses to different stimuli, immune system development, immune response activation, multiorganism processes, and localization of immune cells. Only in CCRCC was a higher activation of immune pathways observed in men. Conclusions: The study shows an improved survival rate, increased activation of immune system pathways, and an enrichment of EGFR alterations in female patients of our cohort. Enhancement of the immune response in female cancer patients is a phenomenon that should be further explored to improve the efficacy of immunotherapy.

- **Sex, immunity, and cancer**

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ABSTRACTO: The composition of the tumor microenvironment is the complex result of the interaction between tumoral and host factors. Since there are several differences in the regulation of gene circuits between sexes, mainly influenced by sex hormones, the tumor-host interaction presents some differences, leading tumors to evolve under different conditions. Nowadays, it is well known the existence of sexual dimorphism in the regulation of the immune system, where women present an improved immunity to various infectious agents and, on the other hand, a higher incidence of autoimmune diseases than men. In oncology, differences in cancer susceptibility, response to treatment, and clinical outcomes between men and women patients are well known. Recently, sex-specific differences have also been reported in mutations in driver genes and the prognostic value of several biomarkers. Sex has been a widely forgotten biomarker in cancer therapy, but it has recently acquired great relevance due to the different results seen in immunotherapy treatment.