ASSOCIATION OF THE MOLECULAR PROFILE OF THE TTN GENE WITH PREDISPOSITION TO GASTRIC CANCER IN A POPULATION FROM NORTHERN BRAZIL.

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Introduction: Gastric cancer ranks as the fifth most common malignancy worldwide and the fourth leading cause of cancer-related mortality, with high incidence rates in East Asia and Latin America, including Brazil. In Northern Brazil, it represents a significant public health concern, with mortality rates surpassing the national average. According to data from the National Cancer Institute (2023), gastric cancer is the second most common malignancy among men and the fifth among women in this region. Recent studies have suggested that certain genetic variants may influence susceptibility and prognosis in gastric cancer. Among these, the TTN gene—encoding titin, a giant protein involved in muscle elasticity and cellular structural integrity—has gained attention due to its high mutation frequency across several cancer types, being altered in approximately 56% of tumors. Although commonly associated with cardiovascular and muscular disorders, TTN has also been identified as one of the top ten most frequently mutated genes in gastric adenocarcinoma. Moreover, mutations in TTN have been linked to increased tumor mutational burden and poorer clinical outcomes in Asian cohorts. However, its role remains understudied in admixed populations such as those in Northern Brazil. Investigating TTN in this genetic context could reveal novel insights into cancer mechanisms and therapeutic opportunities. **Objectives:** To identify driver mutations in gastric cancer patients from Northern Brazil, enabling novel therapeutic strategies by analyzing allele frequencies and comparing them with global genomic data. **Methods:** The study included 107 admixed individuals with gastric cancer, treated at João de Barros Barreto University Hospital. Genomic DNA was extracted from peripheral blood using the Biopur Mini Spin Plus Kit and quantified with a Nanodrop 8000 spectrophotometer. DNA quality was assessed via 2% agarose gel electrophoresis. Exome libraries were prepared using Nextera Rapid Capture Exome and SureSelect Human All Exon V6 kits, following manufacturer

protocols. Sequencing was performed on the NextSeq 500 platform with the High-output v2 Kit. Variant annotation and impact prediction were conducted with SNPeff, classifying variants as modifier, low, or moderate impact based on potential effects on protein function. The study was approved by the Ethics Committee of the Federal University of Pará (CAAE: 43199815.9.0000.0018). **Results:** In this study, 102 variants were identified in the TTN gene, of which 6 are classified as modifiers, 54 as moderate (including 2 new variants), and 40 as low relevance in the mixed-population group. The new variants, located at chr2:178717224 and chr2:178664089, were evaluated by SNPeff and deemed to have moderate impact. **Conclusion:** In conclusion, our findings highlight the importance of investigating the genomic landscape of admixed populations to better understand gastric cancer susceptibility and progression. The identification of two novel moderate-impact variants in the TTN gene expands current knowledge on genetic alterations in Northern Brazilian patients. These results underscore the potential of TTN as a molecular marker for further clinical investigation. Future case-control and functional studies are warranted to assess its role in patient prognosis, tumor behavior, and its possible use in targeted screening or precision medicine strategies tailored to genetically diverse populations.

Keywords: Predisposition genetic; Gastric cancer; *TTN* gene; Northern Brazil.