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The Cancer Control Challenge:
Better Understanding It to Better Face It

COMPREHENSIVE ANALYSIS OF THE MUTATIONAL LANDSCAPE IN GASTRIC ADENOCARCINOMA TRANSCRIPTOMES FROM THE STATE OF PARÁ

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Introduction: Gastric cancer remains a critical obstacle for oncologists worldwide, particularly in prevalent regions of high incidence such as East Asia and Latin America — mainly elevated in Brazil's northern and northeastern states. This prevalence is attributed to GC's pronounced molecular heterogeneity and the lack of validated prognostic biomarkers. Mutational studies aim to map the genomic alterations present, facilitating the identification of novel oncogenic targets. Furthermore, these alterations often manifest as distinctive mutational patterns — known as mutational signatures — linked to endogenous and exogenous processes. Characterizing these signatures can reveal strategies to mitigate GC's public-health burden. Accordingly, there is an urgent need for research dedicated to discovering molecular markers that can underpin improved clinical management of the disease. **Objective:** To investigate the most frequently mutated genes in gastric cancer and to characterize the distribution of mutational signatures, with a particular focus on the molecular peculiarities of a regional Brazilian cohort. **Methodology:** We analyzed 102 GC tumor samples collected from patients at João de Barros Barreto University Hospital (HUJBB), under ethics approval CEP/HUJBB n. 47580121.9.0000.5634 (Plataforma Brasil). Genomic data curation was performed using Broad Institute pipelines. Somatic variants were called with VarDict. For mutation refinement, we employed two filtering strategies: (i) the criteria defined by Jessen et al. (2021); and (ii) functional impact assessment via SIFT and PolyPhen-2. Filtered mutations were processed with the Maftools R package, and mutational signatures were extracted using the MutationalPatterns package. **Results:** Filtering strategy (i) yielded 90 high-confidence somatic mutations, while strategy (ii) identified over 99,000 variants subject to functional annotation. The most recurrently altered genes— *TXNIP, FTH1, JAK1, CHD4*, and *DDX5* — are all implicated in tumorigenesis. Established GC-associated genes such as *ARID1A, KRAS, CDH1,* and *APC* displayed mutation frequencies consistent with the literature. Notably, *TP53* — commonly reported as the top mutated gene in GC — was altered in only 7% of our samples, suggesting a cohort-specific molecular profile. Conversely, *CTNNB1* mutations appeared in 21% of cases, exceeding typical GC frequencies. Dominant mutational signatures were SBS5, SBS6, and SBS3. SBS3 is linked to chronic Helicobacter pylori infection, “BRCAness,” and sustained inflammation; SBS6 reflects DNA-repair defects and microsatellite instability (MSI); and SBS5 is ubiquitous across multiple cancers, though its etiology remains incompletely understood. **Conclusion:** Our analysis revealed recurrent mutations in *TXNIP, FTH1, JAK1, CHD4,* and *DDX5*, a high incidence of *CTNNB1* alterations, and an unusually low *TP53* mutation rate, underscoring the unique molecular landscape of this regional cohort. The predominance of SBS3, SBS5, and SBS6 mutational signatures reflects underlying processes such as inflammation, genomic instability, and DNA repair deficiency, emphasizing the critical importance of region-specific molecular characterization in gastric cancer.