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

Single nucleotide alterations in the MT-*CO1* gene in breast cancer patients from Pará State, Brazil

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Introduction: Mitochondrial DNA (mtDNA) plays a critical role in cellular energy production, encoding proteins involved in the respiratory chain and oxidative phosphorylation. In this context, changes in mtDNA can influence the reprogramming of energy metabolism, one of the hallmarks of cancer. Alterations in the Cytochrome C Oxidase Subunit 1 (*CO1*) gene, for example, may compromise the integrity of Complex IV of the respiratory chain and facilitate the adaptation of cancer cells to the tumor microenvironment. **Objectives:** To identify single nucleotide variations (SNVs) in the *CO1* gene and associate them with the clinical characteristics of breast cancer patients from the state of Pará. **Methods:** Twenty-five tumor samples collected from Ophir Loyola Hospital (Belém/PA) and 25 age-matched negative control samples were analyzed. This study was approved by the Ethics Committee of the involved institutions. DNA was extracted using a commercial kit, amplified by conventional PCR, and sequenced using the Sanger method. The sequences were aligned with the GenBank reference using BioEdit, and the identified SNVs were analyzed using the MITOMAP, ClinVar, and mtDB databases. Associations between SNVs and clinical data were assessed using statistical tests in BioEstat 5.0 software, with statistical significance set at $p \leq 0.05$. Potential structural alterations in the protein were analyzed using NPS@ and ProtParam. STRING software was used to visualize the *CO1* protein interaction network. **Results:** Eight variants were identified in the tumor samples, seven of which were also found in the control group. Among these, the most frequent variant in both tumors and controls was A7146G (T415A – 25.8% and 33.3%, respectively). Although this alteration is classified as benign according to ClinVar, it causes structural changes in the final protein, particularly affecting the alpha-helix content. In contrast, T7175C (T424T – 6.4%) was exclusive to tumors, while C7235A/M (P444P – 11.1%) appeared

only in the controls. None of the variants showed a statistically significant association with molecular subtypes or clinical data from the patients. It was also noted that the *CO1* protein interacts significantly with *ND1* and *ND5* proteins, which are part of Complex I of the mitochondrial respiratory chain. **Conclusion:** It is known that alterations in Complex IV can lead to metabolic reprogramming. Although no statistically significant associations were found with molecular subtypes or clinical characteristics, possibly due to the small sample size, our data suggest structural alterations in the *CO1* protein that may affect the respiratory chain due to its interactions with other mitochondrial proteins. This study highlights the need for functional investigations of the observed SNVs, including silent mutations, to better understand their impact on metabolism, cellular energy deregulation, and breast tumorigenesis.

Keywords: Mitochondrial DNA; Complex IV; Mitochondrial Metabolism.