Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2019.15.002741

Mitochondrial DNA Somatics Mutations in Breast, Ovarian and Oral Cancers among Senegalese Patients

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ARTICLE INFO

Received: February 25, 2019

Published: March 11, 2019

ABSTRACT

Citation: Mbacké Sembéne and Fatimata Mbaye. Mitochondrial DNA Somatics Mutations in Breast, Ovarian and Oral Cancers among Senegalese Patients. Biomed J Sci & Tech Res 15(4)-2019. BJSTR. MS.ID.002741.

Introduction

Breast Cancer

In Senegal, Breast cancer is a major health problem that affects 42% of women [1]. Further-more, among low-income countries including Senegal, individuals have a high risk for developing breast cancer. Given the well-established mitochondrial dysfunction in cancer and the high rate of somatic mutation in mtDNA, the mitochondrial genome is an under-explored avenue for insight into breast cancer pathogenesis, as well as an attractive candidate source for biomarkers. A total of involving 199 unique positions mutations were detected in the MT-CYB coding region, among which 183 positions were found in breast cancer. These mutations are the cause of 75 amino acid changes. Multiple mitochondrial genes have documented somatic mutations which may be implicated in tumor formation. Protein-coding genes found in the mitochondria belong to four different complexes of the mitochondrial respiratory chain. Complex III, of which MT-CYB is the only gene encoded by mtDNA, contains fewer documented somatic variants. Mutations in the MT-CYB gene can cause mitochondrial complex III deficiency. Most MT-CYB gene mutations that cause mitochondrial complex III deficiency change single protein building blocks (amino acids) in the cytochrome b protein or lead to an abnormally short protein. These cytochrome b alterations impair the formation of complex III, severely reducing the complex's activity and oxidative phosphorylation.

Ovarian Cancer

In Senegal, the lowest rate of mitochondrial genome mutations was noted in ovarian cancer. 50% (9/18) of the ovarian tumors analyzed contained MT-CYB mutations and all patients (18/18) have D-Loop mutations ranging from 1 to 11. The frequency of the MT-CYB mutations is 3.83% and that the D-Loop gene of 21.31%. Somatic mutation rate of D-Loop is 2.01-fold higher than the one of MT-CYB region in ovarian cancer [2]. sequenced the D-Loop region of mtDNA of 15 primary ovarian carcinomas and matched normal control tissues. Their study revealed that 20% of tumor samples carried single or multiple somatic mtDNA mutations. In the same study, a complete sequence analysis of the mtDNA genomes of another 10 pairs of primary ovarian carcinomas as and control tissues showed a high incidence (60%) of somatic mtDNA mutation. The four regions of mitochondrial genome primarily affected by these mutations were the D-Loop, 12S rRNA, 16S rRNA, and Cytochrome b, suggesting that these regions may be mitochondrial hotspots in ovarian cancer.

Oral Cancer

In Senegal, 88.63% of oral cancer tumor tissues contained mitochondrial mutations. The frequency of mutations was much higher in the non-coding D-Loop region (79.43%) relative to the MT-CYB (20.56%). The relative mutation frequency for the D-Loop was 2.99-fold higher than for the MT-CYB gene. Other studies report only a 7-fold increase in susceptibility [3]. In contrast, Lin's studies reported by direct sequencing, 62.5% somatic mutations in the D-Loop of mtDNA in oral squamous cell carcinoma patients [4]. A recent study on oral squamous cell carcinoma also found a high rate of somatic mutations in D-Loop region (85%, 203/240) [5]. The high somatic mutation rates in the aforementioned studies were comparable with the rate found in our study.

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DOI: 10.26717/BJSTR.2019.15.002741

M Backé Sembene. Biomed J Sci & Tech Res