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Study on Mitochondrial ATPase6 Gene Polymorphisms as a Genetic Risk Factor for Breast Cancer in Bangladeshi Women

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ABSTRACT

Background and aim: Mitochondria play a vital role in cellular energy production and apoptosis; thus, it has a critical role in cancer development. This study aimed to evaluate polymorphisms in the mitochondrial ATPase6 gene as a genetic risk factor for breast cancer in Bangladeshi women.

Materials and method: ATPase6 gene of mtDNA from sixteen breast cancer blood samples were sequenced to evaluate polymorphisms in the targeted gene. Polymorphisms are detected by comparing the sequences with the Revised Cambridge Reference Sequence (rCRS). Twelve blood samples from age-matched healthy women were also sequenced as a control to consider regional variations.

Results: The A8812C polymorphism (p= 0.0085; from Fisher Exact Test) was found in 50% of breast cancer patients. The A8812C variation (novel mutation) substitutes the Threonine (T) to Proline (P) at the 96th codon number. The PolyPhen-2 analysis predicted that, with a score of 0.999, this variant is "probably damaging." The second prediction performed by the PROVEAN program showed that, since it has a score of -5,110 (<-2,5), this substitution is "Deleterious." These data indicate that A8812C might be associated with an increased risk of breast cancer indirectly. Another interesting finding is the frequent presence (56%) of A8701G in cancer patients (p= 0.0159; from Fisher Exact Test). Based on the statistical data, this (A8701G) mutation might relate to breast cancer development.

Conclusion: It can be concluded that mutations in the ATPase6 gene, especially the A8812C polymorphism and A8701G polymorphism, can be biomarkers for breast cancer diagnosis.

1. Introduction

Breast cancer is a malignant tumor that originates from either in the lobules where the milk is produced or in the ducts that carry out the milk. Breast cancer is the most common type of cancer among women worldwide as well as in Bangladesh. Breast cancer is the most invasive and second main cause of cancer death among women. More than 24% of women in Bangladesh is affected by breast cancer, with an 11.47% mortality rate.[1] Breast cancer occurs in humans and other mammals.[2] Although breast cancer is much more frequent in women, it also occurs in males.[3] It is more than 100 times more common in women than in men, although men are likely to have poorer outcomes because of diagnosis delays. Breast cancer prognosis and survival rates vary greatly. It depends on the patient's type of cancer, stage, treatment, and geographical location. Survival rates in the Western world are high; survival rates in developing countries are much lower.[4] Several aspects of tumorigenesis cannot be explained, despite tremendous progress in identifying and characterizing nuclear oncogenes, tumor suppressor genes, and their roles in cancer development. The role of mitochondria, especially mutations in mtDNA, remains largely unclear. While evidence suggests that some mtDNA mutations play a role in certain cancer development stages, there are still many potential pitfalls in such investigations.[5] In this very important yet complicated line of research, special caution and general guidelines should be followed.[6] Based on our recent results and studies from other laboratories,[7] we propose that mtDNA mutations could function as follows in the development of cancer: cancer cells are very mutagenic either because of a carcinogenic insult or because of the compromised repair mechanism at the initial stage and at this stage, mtDNA is more likely to be

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mutated. MtDNA mutations are enriched to a certain level of heteroplasmy because of the replicative advantage of mutant mtDNA molecules, such as that previously described for mtDNA carrying the mitochondrial encephalomyopathy-related mutation, because of either the elevated ROS generation, which in turn activates the oncogenic pathways, or the increase in genome instability, or both, this would enhance tumor progression. However, after transformation, it may become more important to have a functional respiratory chain to sustain rapid cell proliferation than an inhibited one. Mutant mtDNA causing severe mitochondrial defects is selected against and diluted in some cases; residual mutant mtDNA may escape selection in other cases. In the late cancer stages, the cells are progressively adapted to a glycolytic metabolism because of the hypoxic environment. This may lead to the selection of cells in which mutations make them independent of mitochondrial function and, therefore, in such tumors, cells with homoplasmic mtDNA mutations become predominant. The involvement of mtDNA mutations may be much more prevalent in early-stage cancers than originally thought if this hypothesis is correct. Several studies have identified mutations in the mtDNA non-coding and coding regions and have investigated their possible use for early tumor detection as somatic markers.[1, 8–10] Such as ATPase6 is the subunit of complex V of ATP synthase.[11] The research object is to amplify this gene from a breast cancer patient's mitochondria and perform direct sequencing to detect potential anomalies.

ATPase6 and ATPase8 are complex V genes contributing to mtDNA maintenance by controlling ATP production and apoptosis pathway.[11] Defects in ATPase6 cause mitochondrial dysfunction underlying mtDNA-associated Leigh syndrome, a progressive brain disorder that may appear in infancy or early childhood.[12] ATPase6 mutation is also responsible for the failure of the development of immature spermatids.[13] Defects in ATPase6 are also found in-case of bilateral striatal necrosis.[14] Defective mitochondrial ATPase6 mutation causes lactic acidosis, intellectual disability, and poor growth.[15]

Considering all these findings, we are encouraged to conduct a similar study in Bangladeshi breast cancer patients to find an association between breast cancer and mtDNA code for ATP synthase. In this research, a total of 16 breast cancer blood samples were collected. Patients were affected with either stage-II or stage-III breast cancer. The specific aim of this research was to sequence the ATPase6 gene from these samples and find out whether there is any difference between the control (n=12) ATPase6 gene with the same gene of breast cancer patient's blood samples to identify whether there is any polymorphism which is positively or negatively linked with breast cancer.

2. Materials and methods

Sample Collection

A total of 16 breast cancer patients' blood samples were collected in EDTA coated tube to prevent coagulation. A total of 12 control blood samples were also collected from 12 age-matched healthy individuals for comparison. Collected blood samples were preserved at minus four degrees Celsius until DNA extraction (DNA extraction was done within three months of sample collection). All patients ' written informed consent and ethical approval were obtained from the respective hospitals' ethical committees.

Reagents and instrument

Proteinase K, Sigma p-2308(20 mg/mL, 70.2 g Na-per Chlorate/100 mL, Chloroform: iso-amyl alcohol (24:1), phenol-ethanol, iso-propano, etc. reagents are used for DNA isolation. Taq polymerase (5U), Reverse primer (10 pM/µL, forward primer (10 pM/µL), 5X PCR Buffer, Etc., reagents are used for sequencing PCR.

The concentration and purity of isolated DNA were measured by using the NanoDrop-2000 spectrophotometer. The sequences were aligned and analyzed by using both CLC genomics workbench v3.6.1 and SeqScape v2.6. The revised Cambridge Reference Sequence (rCRS), (NCBI Reference Sequence), were compared with control and cancer patient sequences: NC_012920.1) to detect polymorphisms and mutations. Detected variations (polymorphisms or mutations) were compared with the MitoMap database (http://www.mitomap.org) to find out noble variations (if any).

PCR Amplification

Two sets of primers were used to amplify the ATPase6 gene (1. forward: ACGAG TACACCGACTACGGC; reverse: TGGGTGTGGTGTGT AAATGA; and 2. forward: TTTCCCCCTCTTATTGA TCCC; reverse: GTGGCCTGTGTGTGTGTGTCTTT); and 2. forward: TTTCCCCCTCTTTGA TCCC).[16] The resultant amplicons/PCR reaction products were analyzed using 1% (w/v) agarose gel electrophoresis. 3µL of the reaction mixture was used to perform gel-electrophoresis. According to the primer's positions, the PCR product should be about 860bp for the first set of primer and 776bp for the second set of primer.

Statistical Analysis

Statistical analysis of quantified data was performed using GraphPad Prism version 7 (GraphPad Software, Inc., San Diego, CA, USA). The odds ratio was calculated, and the Fisher Exact test was performed to determine the difference between the case and control groups.

3. Results

Sequencing analysis in patients and healthy volunteers revealed several polymorphisms in ATPase6 genes. According to the Mitomap database (http://www.mitomap.org), all these polymorphisms are previously reported in healthy normal individuals. However, we detected the variation of m.8812 A>C (T96P) and m.8701A>G (T59A) in the mitochondrial ATPase6 gene (Fig. 1), which is our notable finding.

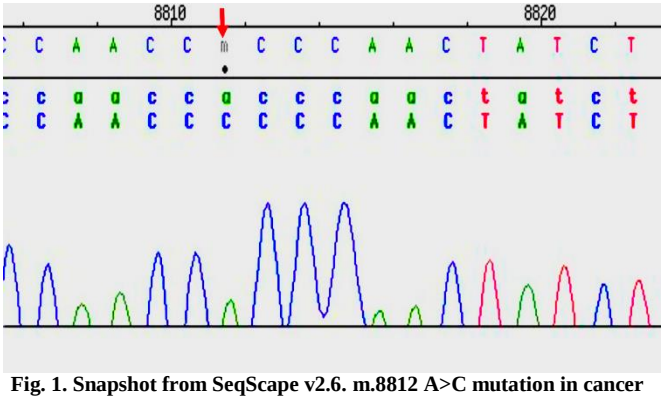

Fig. 1. Snapshot from SeqScape v2.6. m.8812 A>C mutation in cancer patient's blood sample. The red arrow shows the mutated region.

A total of 11 different polymorphisms are detected in 16 breast cancer patients' blood samples and 15 different polymorphisms in 12 control blood samples. Eleven polymorphisms found in breast cancer patients' samples are A8812C, A8701G, A8860G, C9190T, T8772C, G8886A, T8864G, G8682A, T8705C, A8853G, G9053A. However, in 50% of cases, a m.8812 A>C mutation was found in breast cancer patients (OR=22.37, 95% CI=1.15-437.91, p= 0.008) absent in healthy controls.

Table 1. Genotype frequencies of ATPase6 gene polymorphisms in cases and controls.

Polymorphism	Case (n=16)	Control (n=12)	OR	95% CI	P
A8812C	08 (50.0%)	00 (0.0%)	22.37	1.14-437.91	0.008
A8701G	09 (56.3%)	01 (8.3%)	14.14	1.46-137.30	0.016
A8860G	11 (68.8%)	10 (83.3%)	0.44	0.07-2.80	0.662
G9053A	06 (37.5%)	02 (16.7%)	3.00	0.48-18.60	0.401

A8701G, A8860G, and G9053A polymorphisms were found in both of our analyzed control and cancer patients' samples. In 56.3% cases with breast cancer, A8701G was polymorphic whereas only 8.3% was found in control (OR=14.14, 95% CI=1.45-137.30, p= 0.016). However, no significant differences were seen with A8860G and G9053A allele frequency distribution between case and control groups (p=0.662 and p=0.401, respectively).

PolyPhen-2 software (Polymorphism Phenotyping v2) was used to assess an amino acid substitution in the encoded protein. Using the straightforward physical and comparative considerations, this assessed structure, and functions of ATPase6 protein. The analysis predicted that this variant is "probably damaging" with a score of 0.9999 (Fig. 2). The second prediction performed by the PROVEAN program showed that, since it has a score of -5,110 (<-2,5), this substitution is "Deleterious."

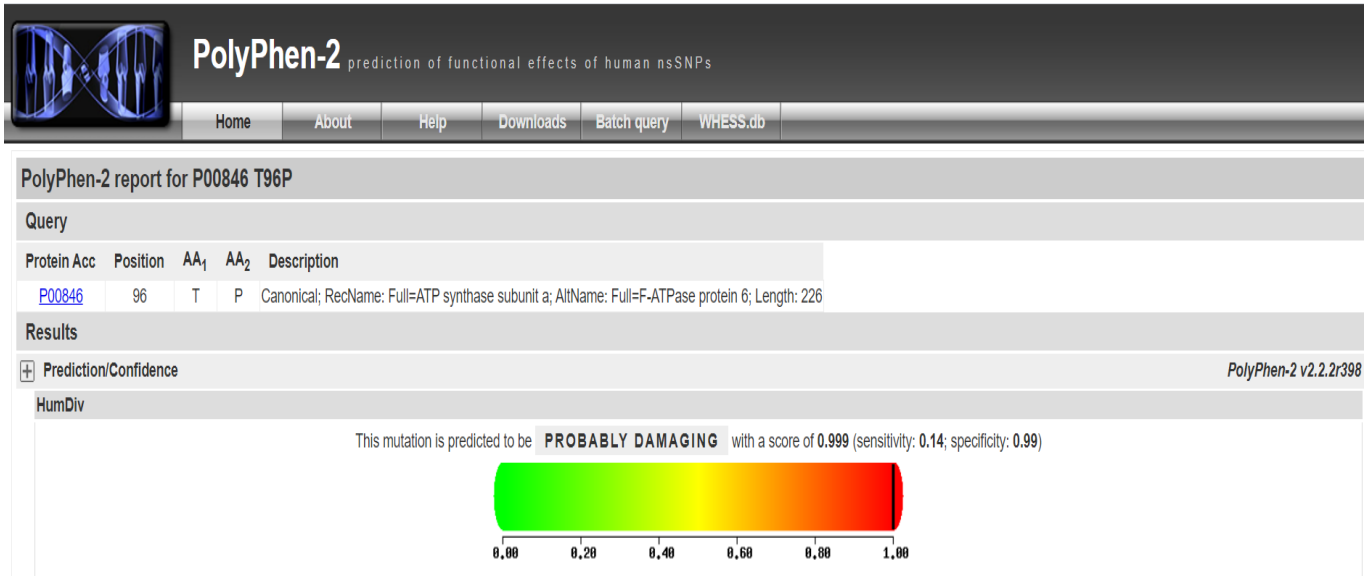

Fig. 2. Polyphe-2 analysis prediction for m.8812 A>C variation indicates a damaging effect on the translated protein.

4. Discussion

The role of mitochondrial complex V genes in ATP production and the apoptosis pathways is very important.[17] Previously, mtDNA complex V variants have a greater effect on cell transformation, elevated ROS production, and tumor progression.[18] Moreover, the molecular machinery of ATP synthase helps to programmed cell death.[19]

The ATPase6 gene's contribution, one of the complex V genes, plays a vital role in mtDNA maintenance.[17] A total of 55 variants, comprising 34 missense variants, 20 silent variants, and one nonsense variant, were found in the ATPase6 gene in a meta-analysis study carried out by Lu et al.[11] In breast cancer patients, nucleotide variations affecting the transcription of mitochondrial genes can cause mtDNA malfunction and contribute to a poorer prognosis. To date, there is no data on the correlation regarding somatic mtDNA content and breast cancer clinical and pathological characteristics. The published literature, however, suggests that mtDNA may harbor potential biomarkers for early breast cancer detection.[8, 20, 21]

Here, a case-control study was performed to evaluate the mitochondrial ATPase6 gene polymorphisms as risk factors for breast cancer in Bangladeshi women. A total of 11 polymorphisms in cancer patients and 15 polymorphisms in control samples were found in our study. Both cancerous and control samples contain A8701G, A8860G, and G9053A polymorphisms. Most of the polymorphisms detected in our study are not statistically significant, except A8812C and A8701G.

The most interesting and novel finding of our research work is A8812C polymorphism. A8812C polymorphism was not detected in any control samples, but 08 breast cancer samples out of sixteen (50%) samples contained this specific polymorphism (p=0.008). Based on the Mitomap database (https://www.mitomap.org), it can be noted that any literature did not previously report this polymorphism. This variation substitutes the Threonine (T) to Proline (P) at 96th codon number. This amino acid substitution might modulate ATPase enzyme function and promote tumorigenesis. The presence of A8812C mutation in breast cancer patients and the absence of this mutation in healthy subjects indicate that this novel mutation might be responsible for enzyme defect that regulates enzyme protein interaction during transportation and binding of cofactors. As a result, there might be a modification in cellular chemistry either by diminishing an essential component or by the accumulation of toxic substances in the pathogenesis of breast cancer.

Wallance et al. (1999) showed that A8701G mtSNP caused impairment in intracellular calcium dynamics. The mutation was also associated with the pathogenesis of some diseases.[28] The nucleotide change A to G at position 8701 in the ATP6 gene, part of the ATP synthase protein, has been demonstrated to reduce ATP synthesis and significantly impair the assembly or stability of the ATP synthase.[27] A significant variation of A8701G in breast cancer patients in our study indicated that this mutation might play an important role in ATPase6 enzyme functions. Our results indicated that in 68.8% of cancer samples, the A8860G variant was present. Although this variant is located in a poorly conserved protein region with no impact on the PolyPhen-2 software-based protein structure, the variation may still contribute to other mutations in mtDNA and nDNA.[11] Grzybowska-Szatkowska et al. (2014) reported the polymorphism of A8860G to be associated with 70% of breast cancer cases. The polymorphism A8860G causes a change in the polar threonine into a non-polar alanine at position 112, affecting protein structures.

The G9053A variant causes a mutation of the second base of the codon from AGC to AAC and then causes amino acid serine (S) to change to asparagine (N). Although the variation was not significant, a higher mutation in breast cancer patients (OR=3) in our study might be linked with breast cancer development. The G9053A polymorphism in ATPase6 was previously reported in cataract and Type II diabetes patients. They suggested that the mutation affects the ATPase protein, which leads to accelerated ATP depletion. They predicted that this ATP depletion might have something to do with cataract formation and insulin secretion. However, this mutation has never been associated with any type of cancer in any literature. Larger sample size is required before any reliable association can be made between this mutation and breast cancer.

Gene polymorphism of ATPase6 has been extensively reported in the literature.[11] The polymorphism frequency has been reported to be 79-91.66%,[17] in breast cancer, 75-100% in other forms of cancers,[23] and 92.85% -100% in neurodegenerative diseases.[11, 24–26] Various studies suggested that the ATPase enzyme's translation process is affected by mtDNA variants. This might change the amino acids in proteins that are important for enzyme functions. The mutation might also make a different translation product. Our findings led us to hypothesize that the novel variant of A8812C in mtATP6 might be an unrecognized cause of breast cancer in the Bangladeshi population. Considering the sample size of this research, further studies are needed to confirm the association of these gene polymorphisms with breast cancer by further sequencing of the whole mitochondrial genome of cancer tissues from those patients.

5. Conclusion

Diagnosis of breast cancer is of paramount importance in the management of this disease. Commonly BRCA gene marker is used as a diagnostic tool for the detection and confirmation of breast cancer. This study found one novel mutation where A is changed to C at 8812 positions of the ATPase6 gene in breast cancer patients. This has not been reported previously by any work. Moreover, the study suggests that this mutation is a significant risk of developing breast cancer in the Bangladeshi population. However, this study had a limited number of samples. Larger sample size will further strengthen the findings of this study or validate them. From this research, it can be concluded that mutations in the ATPase6 gene, especially the A8812C polymorphism and A8701G polymorphism, can be biomarkers for breast cancer diagnosis.

Conflict of Interest

The authors declared that there is no conflict of interest.

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