

# Analysis of *PTEN* in two *BRCA1* and *BRCA2* wild-type familial breast cancer patients

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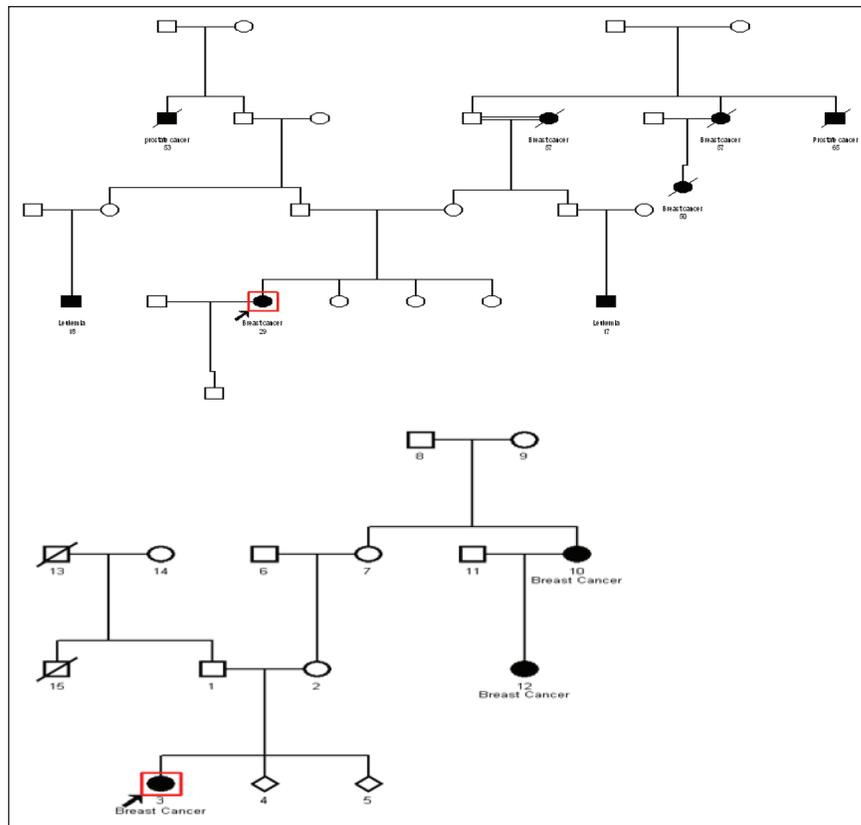
Our study was designed to sequence the entire exonic regions and intronic junctions of the *BRCA1*, *BRCA2*, and *PTEN* genes with regard to identifying the influence of *PTEN* mutations in two Iranian families with familial breast cancer and *BRCA1/2* wild-type genes [Figure 1].

Mutations in particular sets of genes are associated with an increased risk of hereditary breast and ovarian cancer (HBOC). These genes are categorized into three groups according to their impact on cancer susceptibility. The first group leading to elevated breast cancer risk (40% up to 85%)<sup>[1]</sup> with mutations of high penetrance include *BCRA1*, *BCRA2*, *TP53*, *PTEN*, and *STK11*.<sup>[2]</sup> *PTEN*

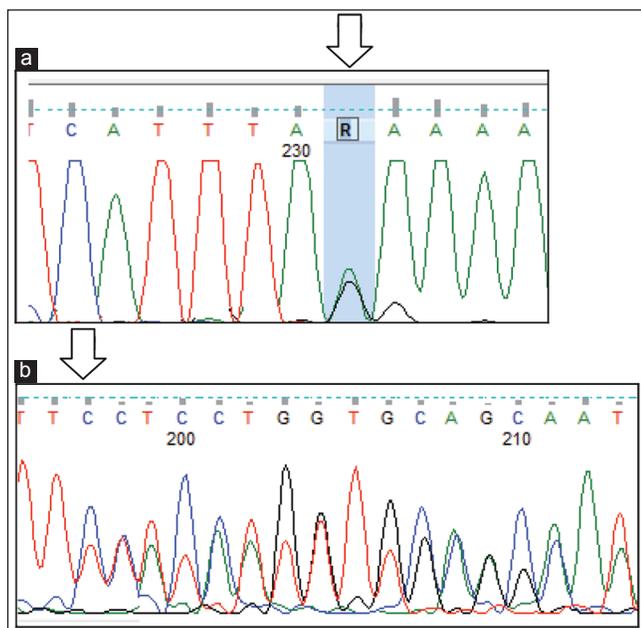
mutations, as a rare but high penetrance mutation, are considered following the two major known breast cancer susceptibility genes, *BRCA1* and *BRCA2*, in HBOC development.<sup>[3]</sup> Human genomic *PTEN* gene locus on chromosome 10q23.3 contains 9 exons encoding a 5.5 kb messenger RNA that has a 403 amino acid open reading frame.<sup>[4]</sup>

Whole gene sequencing was done for three genes in these families. The *BRCA1* and *BRCA2* in the proband of the families were normal, and no germline abnormality was found in these two genes that are mainly responsible for familial breast cancer. However, two new germline sequence variants were detected in the *PTEN* gene: One deletion (del T IVS4-29) and one single-nucleotide substitution (IVS2+65 G>A) [Figure 2a and b]. Both new changes found in the *PTEN* gene were analyzed by the two servers NetGene 2 and alternative splice site predictor. Del T IVS4-29 change was imposed in NetGene 2 site, the 3' splice site acceptor changed in the consensus sequences, but did not delete the consensus sequences. The IVS2+65 G>A variation did not cause a new change in splicing site.

Despite new achievements in this area, many factors leading to breast cancer predisposition are still



**Figure 1:** Pedigrees of the two families with familial breast cancer carrying new germline sequence variants in the *PTEN* gene: One deletion (del T IVS4-29) and one single-nucleotide substitution (IVS2+65 G>A)



**Figure 2:** (a) Heterozygous IVS2+65 G>A of the *PTEN* gene. (b) Heterozygous del IVS4-29 of the *PTEN* gene

unknown, and thus need to be identified with further investigations.

All the investigations to promote strategies of early cancer diagnosis, which is critical for the survival of affected individuals, might be advantageous.

As the main mechanism for activating the *PTEN* protein is proteasomal degradation,<sup>[5]</sup> any changes in protein structure influence the integral role of it. The specific variations that we detected may make some mute changes in the protein interactions which may prevent it from performing its task. It can be cleared by the study of protein structure in future investigations.

To the best of our knowledge, the study we present here is the first analysis of the *PTEN* gene in *BRCA1* and *BRCA2* wild-type breast and/or ovarian cancer in Iranian families.

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#### Conflicts of interest

There are no conflicts of interest.

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