Molecular detection of BRCA1 and BRCA 2 mutations in Iran

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Introduction

Germ line mutations in breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2) are reported in breast cancer patients in a varying degree based on ethnicity and being familial versus sporadic. BRCA1 mutations are reported in up to 45% of familial and 2–30% of sporadic breast cancer patients. BRCA2 mutations are reported to account for a comparable proportion of the familial cases. Carrier individuals transmit the gene to 50% of their offspring's. Carriers have higher life long risk of developing breast cancer.

Material and Methods

Familial cases of breast cancer were recruited and entire coding region of BRCA1 and 2 genes were sequenced. Results were checked against Breast Cancer

Information Core database to find pathologic sequence variation.

(http://research.nhgri.nih.gov/projects/bic/Member/index.shtml).

Results

Sequencing analysis of BRCA1 and 2 genes four families revealed 48 variations within coding region and intron-exon boundaries, with 17 to 23 variations in each case (Table 1). Eleven of these variations have been reported to be non-pathogenic in the BIC database. Each case carried 2 to 8 variations of this kind. Thirteen unknown variation (4-9 per case) and 24 unreported variations were also found (3-10 per case).

These cases are under further bioinformatics studies to determine their possible deleterious effect.

Table 1: List of polymorphism and their appearance in each case in an affected individual in a family

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Codon, (CD) 694AGC>AGT, CD1183AAA>AGA, CD1436TCT>TCC and IVS18+73 G>A were found in all cases in homo or heterozygous state. BRCA1 exons 11, 13 and 9 have been shown to 52.09% of variations. BRCA2 exons 10, 11 and 17 have been shown to have 21.88% of variations (Table 2-3).

Conclusion

Further molecular study and bioinformatics investigation is needed to elucidate the molecular picture of BRCA1 and BRCA2 genes in Iranian patients with familial breast cancer.

In cases where several missense mutations are seen it is needed to further analyze them to determine the disease causing mutation. Sometimes this can be found by the pattern of inheritance in the affected cases or bioinformatics analysis. In other cases a missense mutation can not be found as homozygote since the mutation should be seen as heterozygote. Other methods can also be used to determine the deleterious mutation among several missense mutation. One of the main method could be population study.

Acknowledgements

The authors extend their gratitude to the patients and their willingness to participate in this study.

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Table 2: Most common variations and their frequencies in our patients

	Exon	Variation	Allele	%
1	BRCA1.Exon-13	CD1436 TCT>TCC Ser>Ser	7	7.291667
2	BRCA1.Exon-11	CD694 AGC>AGT Ser>Ser	6	6.25
3	BRCA1.Exon-18	IVS18+73	6	6.25
4	BRCA1.Exon-11	CD1183 AAA>AGA Lys>Arg	6	6.25
5	BRCA1.Exon-11	CD771 TTG>CTG Leu>Leu	5	5.208333
6	BRCA1.Exon-11	CD1038 GAA>GGA Glu>Gly	5	5.208333
7	BRCA2.Exon-10	CD599 TTT>TCT Phe>Ser	4	4.166667
8	BRCA1.Exon-2	IVS1-235 G>A	4	4.166667
9	BRCA1.Exon-16	CD1613 AGT>GGT Ser>Gly	4	4.166667
10	BRCA1.Exon-2	IVS1-134 T>C	4	4.166667
11	BRCA1.Exon-11	CD1140 GGT>AGT Gly>Ser	4	4.166667
12	BRCA2.Exon-17	IVS16-14 T>C	3	3.125

Table 3- Frequencies of variations seen in each exon in our patients

	Exon	Allele	%
1	BRCA1.Exon-11	30	31.25
2	BRCA1.Exon-13	11	11.46
3	BRCA2.Exon-10	9	9.38
4	BRCA1.Exon-2	9	9.38
5	BRCA2.Exon-11	8	8.33
6	BRCA1.Exon-18	8	8.33
7	BRCA2.Exon-17	4	4.17
8	BRCA1.Exon-16	4	4.17
9	BRCA2.Exon-12	3	3.13