# BRCA1 and BRCA2 mutations in Iranian breast cancer patients: A systematic review

#### Hossein Neamatzadeh, Seyed Mostafa Shiryazdi<sup>1</sup>, Seyed Mahdi Kalantar

Department of Medical Genetics, Hematology, Oncology and Genetics Research Center, <sup>1</sup>Department of General Surgery, Breast Disease Research Center, Shahid Sadoughi Training Hospital, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

**Background:** BRCA1/2 genes mutation prevalence varies among ethnic groups and may be influenced by founder mutations. Understanding BRCA1/2 genes mutations is important for reducing breast cancer (BC) incidence, accurate risk assessment and counseling. This systematic review of the literature was conducted to addressing BRCA1/2 mutations in Iranian BC patients. **Materials and Methods:** A search for relevant articles was run on before January 2014 using MedLine, PubMed, Science Iranian Database, Google, and Web sites related to the study topic. The key words included: BC and Iran with Genes, BRCA Genes, BRCA1 and BRCA2; "Cancer Genes," and "Iran." **Results:** Thirteen articles retrieved from this search strategy were eligible for this review. The overall BRCA1 mutation rate for Iranian female BC patients was detected 31.8% (377/1183). Although this gene mutation rate for male patients is <0.01%. Eight BRCA1 mutations (c. 4837A > G, c. 3419G > A, c. 3119G > A, c. 2612C > T, c. 3113A > G, c. 2311T > C, c. 4301T > C and c. 4308T > C in BRCA1, and one BRCA2 mutation (c. 6494G > C) were found in multiple case subjects and represent candidate founder mutations. **Conclusion:** According to these studies, there is heterogeneity in BRCA mutations in Iranian BC patients.

Key words: BRCA1, BRCA2, breast cancer, familial, Iran

How to cite this article: Neamatzadeh H, Shiryazdi SM, Kalantar SM. BRCA1 and BRCA2 mutations in Iranian breast cancer patients: A systematic review. J Res Med Sci 2015;20:284-93.

# **INTRODUCTION**

Breast cancer (BC) continues to remain the commonest cause of cancer death in women worldwide. BC is increasing in regions that until recently had low rates of the disease.<sup>[1]</sup> In Asia, BC incidence peaks among women in their forties, whereas in the United States and Europe, it peaks among women in their 60's. Similarly, in Iran, BC is most common cancer among females, which comprising 24.4% of all neoplasms. The mortality rate of BC was 5.8/100,000 women in Tehran in 1998, 2.5/100,000 for a female population, and 7762 years life lost in the 18 provinces of Iran in 2001.<sup>[2]</sup> The latest data on age-specific incidence rate of BC showed that its crude incidence rate and ASR are 17.4 and 23.1/100,000, respectively. Data from the Cancer Institute show that BC highest rate is occurring in those aged between 35 and 44 years in Iran. <sup>[3]</sup> It is suggested that BC incidence among Iranian females is rising and affects at least one decade earlier than their western counterparts, with a mean age ranging from 47.1 to 48.8 years.<sup>[4]</sup> Furthermore, in Iran BC affects the majority of patients in the premenopausal age.<sup>[5]</sup>

Various risk factors for BC have identified, but a positive family history remains among the most important

ones established for BC, with first-degree relatives of patients having an approximately two-fold elevated risk. It is estimated that approximately 20-25% of this risk is explained by known BC susceptibility genes, mostly those conferring high risks, such as BRCA1 and BRCA2. Germline mutations in the BRCA1 (BC 1, early onset) and BRCA2 (BC 2, early onset) genes are the most important cause of hereditary breast and ovarian cancer. There is not a direct procedure to estimate the prevalence of BRCA1/2 mutations in the general population. In the absence of such measurement procedure, it can be assumed that nearly 50% of the mutations would be in BRCA1 and 50% in BRCA2.<sup>[6]</sup>

Since the isolation of these two genes, more than 2000 different mutations have been identified. The most common types of mutation are attributed to small insertion/deletion frameshift, non-synonymous truncation, and disruption of splice site leading to entire nonfunctional BRCA proteins.

Early works of the BC Linkage Consortium have shown that respectively 52% and 32% of families with at least four cases of BC diagnosed <60 are caused by BRCA1 and BRCA2. When selecting families with BC and one or more

Address for correspondence: Dr. Seyed Mostafa Shiryazdi, Department of General Surgery, Shahid Sadoughi Hospital, Bou Ali Avenue, Safaieh, P.O. Box 734, Yazd, Iran. E-mail: hn\_1364@yahoo.com

Received: 17-05-2014; Revised: 05-07-2014; Accepted: 15-07-2014

cases with ovarian cancer 81% of the families are explained by BRCA1 and 14% by BRCA2. However, when selecting families with four or more cases of BC diagnosed <60 and no cases of ovarian cancer or male BC only 33% could be explained by BRCA1 and BRCA2 together.<sup>[7]</sup> Moreover, based on one report of clinical referral populations that considered both BRCA1 and BRCA2 mutations together, the prevalence among those with a strong family history of cancer is estimated to be 8.7%. Additional prevalence estimates for individuals from referral populations with various levels of family history range from 3.4% (no BC diagnosed in relatives younger than age 50, no ovarian cancer) to 15.5% (BC diagnosed in a relative younger than age 50 and ovarian cancer diagnosed at any age).<sup>[8,9]</sup>

Since the overall BRCA mutation rate in Iranian BC patients has not been estimated to date, the present review was conducted to evaluate the frequency of BRCA1/2 mutations in Iranian BC patients.

## MATERIALS AND METHODS

### **Selection of publications**

The following inclusion criteria developed and applied to identify and select eligible studies: Published in English; case-control, and cross-sectional studies. Titles and abstracts were reviewed to identify studies that potentially detailed the frequency of BRCA1/2 genes mutations testing in Iranian BC patients. After the titles and abstracts had been screened, and the relevant articles identified the specific information including type of study, number of exons evaluated, number, type and classification of mutations were retrieved.

Eligible studies were excluded if: They did focus in BRCA1/2 genes mutation in another condition. Molecular biology studies, *in vivo* studies, comments, opinions, abstracts and unpublished studies were excluded.

### Literature search

The comprehensive data on BRCA1 and BRCA2 mutation in BC in Iranian patients was undertaken via a literature search. A search for relevant articles was run on or before January 2014 using Medline, PubMed, Science Iranian Database, Google, and Web sites-related to the study topic. The key words included: BC and Iran with Genes, BRCA Genes, BRCA1 and BRCA2. In order for a comprehensive search, different combinations of the terms were used. In all instances, searches were limited to studies published in English. The reference lists of articles selected for the review were also manually checked for additional literature. Studies combining and/or comparing Iranian in or outside Iran with other ethnic groups were included but only the data of the Iranian analyzed were included in this review.

## RESULTS

A flow chart showing the study selection process is presented in Figure 1. In total, 13 studies have been carried out about BRCA1/2 gene mutation in Iranian BC yet. These studies are summarized in the following:

Bar-Sade *et al.* have screened a population consist of 150 Iranian Jews, 354 of Moroccan origin, and 200 Yemenites to determine the prevalence of BRCA1 185delAG founder mutation. They found that four of Moroccan origin (1.1%) and none of the Yemenites or Iranians was a carrier of the 185delAG mutation.<sup>[10]</sup>

Ghaderi et al. carried out the first mutation detection in BRCA1 gene among Iranian BC patients. A cohort of 80 patients that 22 of those had at least one first-degree relative with any kind of cancer was screened. Their analysis was initially limited to exon 2 of BRCA1 for 185delAG in 80 Iranian BC patients by direct sequencing. None of the cohort showed the 185delAG mutation or any changes in the sequences of exon 2. They also performed a complete analysis of the entire 5.6 kb BRCA1 gene coding region in a 22 DNA sample which were selected out of 80 samples according to the patients' family history of breast or ovarian cancer, or any other cancers in their first-degree relatives. There were nine mutations (six missense and three unknown variants) in BRCA1, which three of those were placed in the intronic part of the gene. Four missense mutations were identified in exon 11. The remaining mutations were in exon 13, 16, and 18. With the exception of a point mutation in exon-16, which has not been reported previously, the remaining polymorphic sites in the BRCA1 exons have frequently been reported by others studies.[11]

Yassaee *et al.* with the collaboration of two main centers for cancer evaluated peripheral bloods of 83 women with early-onset BC under 45 years old to determine germline mutations in the BRCA1 and BRCA2 genes. BRCA1 exons 2, 3, 5, 13 and 20 and BRCA2 exons 9, 17, 18, and 23 with the single-strand conformation polymorphism assay on genomic DNA amplified by polymerase chain reaction (SSCP-PCR), and BRCA1 exons 11 and BRCA2 exons 10 and 11 by the protein truncation test (PTT) were analyzed. Ten germline mutations in the cohort were found (4 in BRCA1 and 6 in BRCA2). There were 5 frameshifts (3 in BRCA1 and 2 in BRCA2), 4 of which were novel (3 in BRCA1 and 1 in BRCA2), 3 missense changes of unknown significance (all in BRCA2) and 2 polymorphisms. One case of the cohort had 2 mutation, the first mutation in BRCA1 (12bp dup GTATTCCACTCC IVS20+48) and second mutation in BRCA2 (6261-6262insGT). The mutations were: 185-186delAG and 181-182insT in exon 2, 2335-2336delAA in exon 11, and 12bp dup GTATTCCACTCC IVS20 + 48

Neamatzadeh, et al.: BRCA1 and BRCA2 mutations in Iranian breast cancer patients



Figure 1: Study flow diagram for previous included studies

in exon 20 mutations in BRCA1, and 3979-3980insA, 6261-6262insGT and 5972C > TT1915M in exon 11, IVS16-14T > C IVS16-6T > G in exon 17, 8345A > G N2706S in exon 18 and 9266C > TT3013I in exon 23 mutations in BRCA2.<sup>[12]</sup>

Moslehi *et al.* (2002) studied a family with four cases of ovarian cancer and one case of BC in close relatives for common mutations in the BRCA1 and BRCA2 genes using SSCP of exons 2 and 20 of the BRCA1 gene and PTT on exon 11 of the BRCA1 gene and exons 10 and 11 of the BRCA2 gene. PTT demonstrated an abnormal result in exon 11 of the BRCA1 gene in the three sisters. Upon sequencing a novel c. 2031T >G mutation was found at codon 638 (BIC accession no. 6432). It was a nonsense mutation which leads to a truncated protein by replace Glutamic acid with a stop codon.<sup>[13]</sup>

For the first time, Pietschmannl *et al.* have performed a study that screened complete coding sequences and 3' and 5' UTR regions of BRCA1 and BRCA2 genes in Iranian BC patients. In addition, they used semi-quantitative fluorescent multiplex PCR to detect large rearrangements of the genes. The patient population was selection account of individuals from 10 unrelated high-risk families, which had at least three breast, breast and ovarian cancer cases as first-degree relatives, multiple cases as first, second and other relatives, bilateral BC,

and early onset of breast and/or ovarian cancer (<50 years). They found one intronic variation and a deletion/insertion insertion in the 3' untranslated region of BRCA1 in cases of 2 investigated families and 2 pathogenic mutations in the BRCA2 gene, which one of them was a novel deletion (c. 4415\_4418delAGAA).<sup>[14]</sup>

Quintana-Murci *et al.* have conducted a study to assess the prevalence of Tyr978X BRCA1 germline mutation in the general population of Iranian non-Jewish individuals and compare the BRCA1-linked haplotype of Jewish and non-Jewish mutation carriers. The population was 442 men who were unselected for personal or familial history of cancer. They were originated from different Iranian regions, including Zagros Mountains (Kordestan, Lorestan, Elam and Khuzestan), West Caspian (Gilan), East Caspian (Mazandaran), Central-North (Zanjan, Markazi, Hamadan and Semnan), Central-South (Fars, Esfahan, Hormozgan), and Eastern provinces (Khorasan, Baluchestan and Kerman). The RFLP-PCR evaluations results have shown that Tyr978X BRCA1 germline mutation not exists in any of the total 442 non-Jewish Iranian men.<sup>[15]</sup>

Mehdipour *et al.* have conducted a study of 400 case subjects with primary BC (396 women and 4 men with the mean age of 48.8±11.3 year, age range 15-95 year) to explore the contribution three Ashkenazi founder mutations (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2). There was a positive

family background of BC and other malignancies in 27.5% and 52% of patient pedigrees, respectively. The most frequent occurrence of BC across four generations revealed to be 50% in the 1<sup>st</sup> degree in the 3<sup>rd</sup> generation, 68.8% in the 2<sup>nd</sup> degree in the 2<sup>nd</sup> generation, and 59.5% in the 3<sup>rd</sup> degree in the 3<sup>rd</sup> generation. They have found only two patients with 185delAG mutation in the BRCA1 gene (2/400), which they were two sisters of the one family. However, they did not found the other two mutations, that is, 5382insC in BRCA1 gene and 6174delT in BRCA2 gene.<sup>[16]</sup>

Rassi *et al.* (2008) performed a study to determine the prevalence three Ashkenazi founder mutation (185delAG and 5382insC in BRCA1, and 6174delT in BRCA2), using 34 formalin fixed, paraffin embedded breast tissue from 16 patients with familial BC and 18 patients with non-familial BC. A total of three mutations of Ashkenazi 5382insC founder mutation were found in 16 familial BCs.<sup>[17]</sup>

Fattahi *et al.* have conducted a case–control study to detection of 5382insC and 185delAG in BRCA1 and 6174delT in BRCA2 by a multiplex PCR with allele-specific oligonucleotide primers. The study population was 250 women with sporadic BC, 55 women with a familial history of BC in their first degree-relatives and 200 healthy women. Their evaluation indicated that the mutations were detected neither in patients (250 patients with sporadic BC and 55 familial BC patients) nor in 200 healthy individuals.<sup>[18]</sup>

Saleh-gohari *et al.* (2012) have studied 27 females and three males with BC living in Kerman province, Iran. The exon 2 and partial regions covering 11 regions of the BRCA1 gene were screened for mutations by direct sequencing. Nine different mutations that were detected include: Deletion of one adenine (c. 1017delA) and insertion of one cytosine (c. 969InsC) have found as the most frequent (20%) mutation in this survey. A substitution of thymine for adenine (c. 999T>A) has detected as the second common BRCA1 gene defect (6.7%). The other mutations have identified as single nucleotide replacement including: c. 792A > C, c. 825G > C, c. 822T > A, c. 1068A > G, c. 969A > T and c. 966T > C.<sup>[19]</sup>

Keshavarzi *et al.* studied 27 patients with either early onset BC (at age  $\leq$ 35 year) or personal and/or family history of breast or ovarian cancer. All of the BRCA1 and BRCA2 genes except exons 1 and 4 in BRCA1 and exon 1 in BRCA2 were analyzed. They identified a total of 13 missense mutations, 9 in BRCA1 and 4 in BRCA2. Two of these were novel (c. 3538A > G in BRCA1 and c. 4350G > A in BRCA2). In addition, c. 3232G > A and c. 3538A > G BRCA1 mutations were found in large series of breast and ovarian cancer and matched controls.<sup>[20]</sup>

In another study, Keshavarzi et al. investigated entire coding sequences and each intron/exon boundaries of BRCA1/2 genes in 85 patients from high risk Iranian families. Thirty-six patients had a family history of BC, while 49 patients had early onset BC (<35 years) and had not previous family history of the breast or ovarian cancer. They found a higher incidence of BRCA mutations (32 BRCA1 and 6 BRCA2), which 21 mutations were novel mutations (17 BRCA1 and 2 BRCA2) and have not been previously reported. The majority of the mutations are located on exon 2 (13) and 11 (7) of BRCA1. Their results cleared that 8 BRCA1 and 1 BRCA2 mutations have found in seven of the patients with early onset BC. The co-existence of two different mutations in BRCA1 (c. 550T > A) and BRCA2 (c. 2600-70T > G) were identified in one patient with early BC and one control. In addition, a missense mutation within exon 11 of the BRCA1 (c. 3419GA) was identified in 20% of patients and 8% of controls.<sup>[21]</sup>

Kooshyar *et al.* have studied 39 patients with BC and 29 high risk healthy women, related to the patients to find to find 185delAG and 5382insC founder mutations. In addition, a 251bp fragment of BRCA1's exon 11 was analysed to determination new mutations. They found that 185delAG and 5382insC founder mutations exist in both groups studied. Two out of 39 BC patients (5.1%) and 1 out of 29 relatives (3.4%) were carriers of 185delAG mutations, and 1 patient (2.6%) was a carrier of a 5382insC mutation. In addition, 2 patients (5.1%) and 3 (10.3%) of relatives were carriers of unclassified mutations in the BRCA1 gene 251bp fragment<sup>[22]</sup> [Tables 1 and 2].

# DISCUSSION

The present review provides the identified BRCA mutations rates in Iranian BC patients to date. The 13 studies included in this study, screened a total of 1183 and 454 female and male BC patients, respectively [Tables 1 and 2].

The prevalence of BRCA mutations carriers in the general population is estimated at between 0.12% and 0.1%.<sup>[23]</sup> It is estimated that in all women, the prevalence of BRCA1 mutation is 1 in 800-1 in 1400 and the prevalence of BRCA2 mutation is slightly lower at 1 in 450-1 in 80).<sup>[24]</sup> Genetic linkage analyses have shown that the prevalence of BRCA gene mutation in familial BC and/or ovary cancer rate ranging from 45% to 90%. While, many of screening studies have shown BRCA1 mutation rate is about 6-45% and in familial BC varies from 1% to 35% worldwide.<sup>[25-27]</sup> Among early onset familial cases, 10-40% was found to be associated with BRCA1 and BRCA2 mutations. In contrast, among sporadic early-onset BC patients, the frequency of BRCA1/2 mutation ranges from 1% to 10%.<sup>[28]</sup>

Neamatzadeh, et al.: BRCA	and BRCA2 mutations in	Iranian breast cancer patients
---------------------------	------------------------	--------------------------------

Table 1: D	escrip	otive charac	teristics of	13 studies	on the	e BRCA1 mut	ations in Iranian	breast canc	er patients	
Author	Year	Study po	opulation	Technique	Exon/	Traditional	Sequence variant	Amino acid	Mutation	Frequency
		Number	Age (years)		intron	nomenclature		change	type	
Bar-Sade <i>et al.</i>	1998	354 Moroccan	37	HA/DS	2	187delAG	185delAG	-	Frameshift	0
		200 Yemenites								
		150 Iranian								
Ghadari	2001		12	DS	11.2	2420750	o 2211T\C	n l ou7711 ou	Supopumous	2
et al.	2001	22 (DC)	42	03	11.20	2430120 27210\T	0. 2612CNT	p.Leu//ILeu	Missonso	2
or un					11-3d	2/310/1		p.FI007 ILeu	Missense	5
					11-30	3232A2G	C. 3113A/G	p.Giu 1038Giy	Missense	C
					11-4	300/A/G	C. 3548A/G	p.Lys 1183Arg	Nissense	4
					13	442/1>0	C. 43081>C	p.Ser 1436Ser	Synonymous	3
						4950A/G	C. 483/A/G		Missense	3
					10310	C. 4987-92A>C	IVS 10-92A/G	: 2	-	-
					10510	C. 4987-08A2G	IVS 10-08A/G	ſ	-	3
				DTT	10518	-	IVS18+65G/A	-	-	3
Yassaee	2002	83	<45		2	-	185-186delAG^	39 (IGA)	Frameshift	
et al.				SSCP/HP	2	-	181-182ins1*	40 (IGA)	Frameshift	1
					11	-	2335-2336 delAA 12bp dupIVS20+48*	741 (TAA)	Frameshift	1
					20	_		Dup	Frameshift	1
Moslehi <i>et al.</i>	2003	1 family with 4 cases	56	SSCP-PCR		-	G2031T	-	Misssense	-
		(HOBS)								
			45-67							
Murci <i>et al.</i>	2005	442 (only males)		RFLP-PCR	2	-	-	Tyr978X	Misssense	0
Pietschmann et al.	2005	10 high risk BC families	<50	DS	1a	-	g1075C>G	-	-	7
					1b	-	g235A>G	-	-	6
					1b	-	g134T>C	-	-	6
					8	IVS7-34	g. 442-34C>T	?	-	4
					8	IVS8-58delT	g. 548-58delT	?	-	6
						2196G>A	c. 2077G>A	p.Asp693Asn	Misssense	1
						2201C>T	c. 2082C>T	p.Ser694Ser	Synonymous	6
						2430T>C	c. 2311T>C	p.Leu771Leu	Synonymous	6
					11	2731C>T	c. 2612C>T	p.Pro871Leu	Misssense	7
						3232A>G	c. 3113A>G	p.Glu1038Gly	Misssense	6
						3238G>A	c. 3119G>A	p.Ser 1040Asn	Misssense	2
						3667A>G	c. 3548A>G	p.Lys1183Arg	Misssense	6
					13	4427T>C	c. 4308T>C	p.Ser1436Ser	Synonymous	6
Pietschmann	2005				16	4956A/G	c. 4837A>G	p.Ser1613Gly	Misssense	6
et al.					16	IVS 16-68A/G	g. 4987-68A>G	?	-	6
					16	IVS 16-92A/G	g. 4987-92A>G	?	-	6
					17	-	g. 5075-53C>T	-	-	1
					18	IVS18+66G/A	g. 5152+66G>A	?	-	6
					24	-	g. 381_389 del9ins29	-	-	1
					24	-	g. 421G>T	-	-	6
					24	-	g. 1286C>T	-	-	6
Mehdipour <i>et al.</i>	2006	396 (female), 4 (male)	48.8±11.3	PCR	2	187delAG	185delAG	-	Frameshift	2
			15-95			5382insC	5385insC	-	Frameshift	0
Rassi <i>et al.</i>	2008	16 (FBC),	25-80	Multiplex-	2	187delAG	185delAG	-	Frameshift	3 (FBC)
		18 (NFBC)		PCR		5382insC	5382insC	-	Frameshift	0 (NFBC)

Contd...

Number     Age (years)     Intro     nomenclature     Change     type       et al.     56 (FEC)     32.0+7.3     PCR     5382/msC     5385/msC     -     Frameshift     0       Keshavarai     2011     27 (BC)     L135     DS     7     -     INSS-70(-CATI)     -     -     3       d: al.     50 (HF)     -     24301>C     . 2310>C     . 2164>C     . 2110>C     . 2100-B     ymonymous     3       d: al.     50 (HF)     -     . 2330>C     . 3135AG     D, Glu03BU     Misseenee     1       3332AS     C. 3110>C     . 2440-C     . 24301>C     . 24301>C     . 3105AG     . 3103AG     Misseenee     1       3332AS     C. 310SA     D, Glu03BU     Misseenee     1     . 2323C>A     . 520G>A     p, Glu1735C/U     Misseenee     1       6 di /s (male)     -     -     . 6203C>A     . 520G>A     p, Glu735C/U     . Samesnee     1       6 di /s (male)     -     -     . 6203C>A     . 520G>A     . 601732AU	Author	Year	Study p	opulation	Technique	Exon/	Traditional	Sequence variant	Amino acid	Mutation	Frequency
Fattah     200     250     56     767     200     777     778 </th <th></th> <th></th> <th>Number</th> <th>Age (years)</th> <th></th> <th>intron</th> <th>nomenclature</th> <th></th> <th>change</th> <th>type</th> <th></th>			Number	Age (years)		intron	nomenclature		change	type	
ef al.   55 (FR)   32.0:7.3   PCR   5382/ncC   5385/ncC   -   Frameshitt   0     Kenhavarzi   2011   72 (BC)   □35   DS   7   -   IVS8-79/CATT)   - <td< td=""><td>Fattahi</td><td>2009</td><td>250 (SBC)</td><td>45.1±9.2</td><td>Multiplex-</td><td>2</td><td>187delAG</td><td>185delAG</td><td>-</td><td>Frameshift</td><td>0</td></td<>	Fattahi	2009	250 (SBC)	45.1±9.2	Multiplex-	2	187delAG	185delAG	-	Frameshift	0
200 (HF)      V37 43(-T)     -	et al.		55 (FBC)	32.0±7.3	PCR		5382insC	5385insC	-	Frameshift	0
Kenhavari     2011     27     (BC)     (J3)     DS     7     -     NS7+83(TT)     -			200 (HF)	-							
ef al.   50 (HF)   9   -   IVS8 20(C4TT)   -   -   -     s a k   50 (HF)   50 (HF)   -   -   -   2430TC   0.2311TC   0.2311TL   Missense   8     2731CF   0.2311TAC   0.2311TAC   0.5211TL   Missense   15     32326CA   0.3118AC   0.5111040E   Missense   15     3337AG   0.318AC   0.511040E   Missense   13     13   4427TC   0.4308TAC   0.511040E   Missense   13     14   495AAG   0.4308TAC   0.511040E   Missense   13     10   5320CA   0.5205CA   0.5213CA   0.6117350E   Missense   1     11   186AC   0.5305CA   0.5215CA   0.6427C   p.642743K   Missense   1     11   1186AC   0.1064AG   0.143340   Missense   1   1     12   0.163547   Missense   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1   1	Keshavarzi	2011	27 (BC)	□35	DS	7	-	IVS7+83(-TT)	-	-	3
2430FC     c. 2311FC     p.16.971Les     Missensee     8       1     2323FC     c. 24162A     p.Pro871Les     Missensee     6       1     2323FC     c. 3119GA     p.Str01040An     Missensee     6       1     3238CA     c. 3119GA     p.Str1104SF     Missensee     15       3537AC     c. 4303FC     p.Str01304     Missensee     15       13     4427FC     c. 4303FC     p.Str01304     Missensee     15       20     532GCA     c. 5203GCA     p.Str03704     Missensee     16       21     22     (female)     51     DS     2     -     c. 825CC     p.Gly17364     Missensee     1       21     22     (female)     51     DS     2     -     c. 806FC     p.Gly17364     Missensee     1       21     22     (female)     51     DS     2     -     c. 806FC     p.Gly17344     Missensee     1       21     118-A2     -     0.04674     p.Lly1340     Miss	et al.		50 (HF)			9	-	IVS8-70(-CATT)	-	-	-
keshavari     273 CP     c. 2612CPT     p.PRJ 1036EJ     Missensee     8       1     3232A-G     c. 3113A-G     p.Glu1036EJ     Missensee     1       3337A-G     c. 3413A-G     p.Glu103EF     Missensee     1       13     4427P.C     c. 3438A-G     p.Glu103EF     Missensee     3       14     4956A-G     c. 43937A-G     p.Ser143GeF     Sympympuos     3       20     532CA-G     c. 5203CA     p.Glu173GU     Missense     1       16     4956A-G     c. 6325C-C     p.Glu173GU     Missense     1       20     532CA-A     c. 5205C-A     p.Glu173GU     Missense     1       11     1186-A-G     c. 1017deIA     p.Glu373U     Missense     3       11     -     c. 0690A-T     p.Glu373U     Missense     3       11     -     c. 9697A     p.Tim34A     Missense     3       11     186-A/G     c. 107deIA     p.Lu333U     Missense     3       11     186-A/G     c. 246A-A							2430T>C	c. 2311T>C	p.Leu771Leu	Synonymous	3
keshavara     2012     23 (fBC)     -							2731C>T	c. 2612C>T	p.Pro871Leu	Misssense	8
signed						11	3232A>G	c. 3113A>G	p.Glu1038Gly	Misssense	6
35372-6C     c. 3418A-6'     0.114036r     Missense     1       13     44271>C     c. 43087A-6     p.5er14369t     Missense     3       20     53220-A     c. 52030-A     0.1017361t     Synonymous     -       21     53225A     c. 52136-A     p.61073754t     Missense     1       21     2     1     -     c. 8256-C*     p.6102754g     Missense     1       21     3     (male)     51     DS     2     -     c. 8256-C*     p.6102754g     Missense     1       21     -     c. 010744H     p.192234g     Missense     1     1     -     c. 96918C*     p.619232W     Missense     3       21     11     186-PC     c. 96918C*     p.619232W     Missense     3       21     36 (FBC)     -     C     c. 9691A-7     p.619232W     Missense     3       21     36 (FBC)     -     IVS1     IVS1-206A     c. 2406A*     -     No change     2       21							3238G>A	c. 3119G>A	p.Ser1040Asn	Misssense	5
13     4427PC     c. 4303PC     9.5474356r     Synonymous     3       16     4956A5C     c. 4837A5C     p.54743561V     Missense     5       20     5322G5A     c. 5203G5A     p.610/73561U     Missense     1       21     22     (female)     51     DS     2     -     0.9617C     p.610/73561U     Missense     1       4. A.     8 (male)     51     DS     2     -     0.9617C     p.542547C     p.5027447g     Missense     1       4. A.     8 (male)     51     DS     2     -     0.10724A7     p.5472547g     Missense     3       11     186.A-GC     0.10726HA     p.193304X     Missense     3       11     186.A-GC     0.10726HA     p.19332H     Missense     3       12     36 (FBC)     -     1867     0.8907A     p.1173331F     Missense     3       47 4/     49 (NIFC)     -5     151     IS1862A     2.805A*     -     No change     2							3537A>G	c. 3418A>G*	p.Gly1140Ser	Misssense	11
Saleh-gohari     2012     222 (female)     51     DS     2     532C5A     c. 5213C5A     p.Gly 773GU     Missense     5       Saleh-gohari     2012     22 (female)     51     DS     2     -     c. 5213C5A     p.Gly 773GU     Missense     1       et al.     8 (male)     51     DS     2     -     c. 625C5C*     p.Gly 275Arg     Missense     1       -     c. 722A>C*     p.Gly 275Arg     Missense     3     1     -     c. 6969haC*     p.Gly 275Arg     Missense     3       -     -     c. 969haC*     p.Gly 275Arg     Missense     3     1     -     c. 969haC*     p.Gly 273Arg     Missense     3       -     -     c. 999h3A     p.Thr333Thr     Synorymous     2     -     -     No change     2       -     -     -     0.699h3C*     p.Gly 23Arg     Missense     1     -     -     No change     2     -     No change     2     -     -     -     No change						13	4427T>C	c. 4308T>C	p.Ser 1436Ser	Synonymous	3
Saleh-gohari     2012     22 (female)     51     DS     53     53     2     -     0.901736010     Missesnes     1       ef al.     8 (male)     51     DS     -     0.90172401     Missesnes     1       ef al.     8 (male)     51     DS     -     0.9217647     Missesnes     1       -     0.7926A70     p.587264A74     Missesnes     1     -     0.90173610     Missesnes     1       -     0.7068A76     p.587264A74     Missesnes     1     -     0.90173610     Missesnes     1       -     0.7068A76     p.90173301     Missesnes     3     1     -     0.9077A     p.11733171     Synonymous     2       -     -     0.8227A*     p.002727A*     Missesnes     1     1     1     -     0.9077A     p.11733171     Synonymous     2       ef al.     49 (NFBC)     -35     IV51     IV51     IV51-206A     0.22206A*     -     No change     3       -     <						16	4956A>G	c. 4837A>G	p.Ser1613Gly	Misssense	3
20     533CPA     0.5213CPA     0.61/0738CIU     Missennee     1       2 af d.     8 (male)     51     DS     2     -     0.60275Arg     Missennee     1       4' d.     8 (male)     51     DS     2     -     0.60275Arg     Missennee     1       4' d.     8 (male)     -     0.7028ArC*     p.601356Arg     Missennee     3       11     1186-APC     0.1063407     D.61323GV     Missennee     3       11     1186-APC     0.9691AC*     p.619333GV     Missennee     3       12     2012     36 (FBC)     -     -     0.9691A*     0.76933GV     Missennee     1       13     17     1751-206A     0.2060A*     -     No change     2       ef al.     49 (NFBC)     .35     IVS1     IVS1-206A     0.2060A*     -     No change     2       13     1362C     0.907*     p.16373CV     Missense     1       14     19<1275						20	5322G>A	c. 5203G>A	p.Glu 1735Glu	Synonymous	-
Salet-gohari   2012   22 (female)   51   DS   2   -   c. 9647C   p.Ala322Aa   Missense   1     ef al.   8 (male)   51   DS   2   -   c. 8256C*   p.Gly327Arg   Missense   1     ef al.   8 (male)   -   c. 8256C*   p.Gly323A   Missense   3     11   186.A>C   c. 107deIA   p.Lly33AV   Missense   3     -   c. 699N5C*   p.Gly323AV   Sissense   3     -   c. 969N5C*   p.Gly323AV   Sissense   1     -   c. 969N5C*   p.Gly323AV   Sissense   1     ef al.   49 (FBC)   -3   IVS1   IVS1-20C3-A   c. 246CA*   No change   2     ef al.   49 (FBC)   -3   2   127TSC   c. 87C4*   P.Leu3Stop   Missense   3     -   138C>T   c. 19C>T*   p.Ag7Cys   Missense   3     -   138C>C   c. 44A>C   p.He2Aval   Missense   3     -   193C>A   c. 74>CA   p.Ho23   Missense   3 <td></td> <td></td> <td></td> <td></td> <td></td> <td>20</td> <td>5332G&gt;A</td> <td>c. 5213G&gt;A</td> <td>p.Gly 1738Glu</td> <td>Misssense</td> <td>5</td>						20	5332G>A	c. 5213G>A	p.Gly 1738Glu	Misssense	5
ef al.   8 (male)   -   -   c. 252GC-C   p.Gly275Arg   Missense   1     -   -   c. 792A>C*   p.Scr264Arg   Missense   1     -   -   c. 106AArG   p.Gly323K   Missense   3     11   1186.A>G   c. 1017delA   p.Ly340X   Missense   3     11   -   c. 969haC*   p.Gly323K   Missense   3     11   -   c. 969haC*   p.Gly323K   Missense   3     11   -   c. 969hAT   p.Gly323K   Missense   1     12   2012   36 (FBC)   -   NS1   NS1-8C>A   c. 26GA*   -   No change   2     et al.   49 (NFBC)   □35   IVS1   NS1-8C>A   c. 24GCA*   -   No change   2     -   138C>T   c. 19C**   p.Lau3Stop   Missense   3     -   138C>T   c. 19C**   p.Re2V3H   Missense   3     -   138C>T   c. 44A>C   p.Re2V3H   Missense   3     -   193C>A   c. 74>CA	Saleh-gohari	2012	22 (female)	51	DS	2	-	c. 966T>C	p.Ala322Ala	Misssense	1
-     -     -     -     0.792k-0C*     p.6kr364kr3     Missense     1       -     -     0.1068A-G     p.Glr3364kr     Missense     3       11     1186-k>G     0.107delA     p.Lys340X     Missense     3       -     -     0.991rA     p.Glr3354K     Missense     3       -     -     0.991rA     p.Glr3331Hr     Synorymous     2       -     -     0.991rA     p.Glr3331Hr     Synorymous     2       -     -     0.820rA*     -     No change     2       ef al.     49 (NFBC)     35     VS1     VS1-20C3-K     c.240C4*     P.Le03top     Missense     1       -     138C>T     c.19C>T*     p.Arg7Cys     Missense     3     -     193C>A     c.76271rsA     -     -     2012 361     Missense     3       -     193C>A     c.76271sA     -     -     2     2     2     2     2     2     2     2     2     2     2	et al.		8 (male)			-	-	c. 825G>C*	p.Gly275Arg	Misssense	1
Keshawari     2012     36 (FBC)     -     -     0.1064PC     0.Gln35AM     Missense     3       Keshawari     2012     36 (FBC)     -     0.991PC     0.991PC     0.901PC     0.901923     Wissense     1       Keshawari     2012     36 (FBC)     -     0.991PC     0.991PC     0.9023X     Wissense     1       Keshawari     2012     36 (FBC)     -     0.991PC     0.991PC     0.9072AM     No change     2       ef al.     49 (NFBC)     0.35     IVS1     IVS1-80SA     0.246SAM     -     No change     2       61 (control)     -     1038C>T     0.19CST     p.1e23CM     Missense     3       193C>A     0.742CA     0.9CST     p.1e24SD     Missense     3       193C>A     0.742CA     0.9CST     p.1e24SD     Missense     3       193C>A     0.742CA     0.9CSC     Sponymous     5     1     103CA     1     105CA     1     1     1     1     1     1     1<						-	-	c. 792A>C*	p.Ser264Arg	Misssense	1
Keshavarzi     2012     36 (FBC)     -     0.9097A     0.0097A     0.00972A     Missense     3       Keshavarzi     2012     36 (FBC)     -     0.9097A     0.0097A     0.00972AS     Missense     1       e     -     0.9097A     0.0072AS     Missense     1     2       e     -     0.8217A     0.0072AS     Missense     1       ef al.     49 (NFBC)     0.35     IVS1     IVS1-2062A     0.2206A*     -     No change     2       ef al.     49 (NFBC)     0.35     IVS1     IVS1-2062A     0.2206A*     -     No change     3       -     1053/PC     0.810C     0.2067A     0.1907T*     0.47970S     Missense     3       -     1053/PC     0.9057C     0.1022AM     Missense     3       -     1955/PC     0.8042C     0.602C*     0.0122AM     Missense     3       -     1955/PC     0.8049C*C     0.8049C*     0.0122AM     12     12       VS2192AS     V							-	c. 1068A>G	p.Gln356Arg	Misssense	1
Keshavari     2012     36 (FBC)     -     -     0.9091X     0.Gly323X     Missense     3       Keshavari     2012     36 (FBC)     -     0.9091X     0.70331Th     Synonymous     2       et al.     49 (NFBC)     35     IVS1     IVS1-8G>A     0.2465A*     -     No change     2       et al.     49 (NFBC)     35     IVS1     IVS1-8G>A     0.2465A*     -     No change     2       61 (control)     -     1271XG     c.817C*     p.Leu3Stop     Missense     3       -     188C>T     c.069C*     p.Glu23Gin     Missense     3       -     188C>C     c.69C*C*     p.Glu23Gin     Missense     3       -     193C>A     c.74>CA     p.Pro25     Synonymous     5       -     193C>A     c.74>CA     p.He26Val     Missense     3       -     193C>A     c.74>CA     p.He27Val     Missense     3       -     195C>C     c.80+35ncctat*     -     -     -     2<						11	1186-A>G	c. 1017delA	p.Lys340X	Misssense	3
-   -   -   0.999A7   p.1R*331hr   Synonymous   2     -   -   0.997A   p.1R*331hr   Synonymous   2     -   -   0.2927A*   p.1R*331hr   Synonymous   2     ef al.   49 (NFBC)   -35   IVS1   IVS1-8G>A   c. 2-8G>A*   -   No change   2     ef al.   49 (NFBC)   -35   IVS1   IVS1-20G>A   c. 2-20G>A*   -   No change   2     -   1632C>T   c. 19C5T*   p.1eu3350p   Missense   3     -   183C>T   c. 19C5T*   p.1eu321p   Missense   3     -   193C>A   c. 19C5T*   p.1eu2431   Missense   3     -   193C>A   c. 74>CA   p.1eu241   Missense   3     -   195A>G   c.76A>G   p.1eu241   Missense   3     -   195A>G   c.76A>G   p.1eu241   Missense   3     -   195A>G   c.80-16>C   -   -   1     105   1052-16>C   c.80+96>C   -   -   -						11	-	c. 969InsC*	p.Gly323X	Misssense	3
Keshavarzi   2012   36 (FBC)   -   -   C. 9997>A   p.G. 224G>A   Missense   1     et al.   49 (MFBC)   III   III   IVS1   IVS1 eCSA   C. 2e0G>A*   -   No change   2     et al.   49 (MFBC)   III   III   IVS1   IVS1 eCSA   C. 2e0G>A*   -   No change   2     61 (control)   -   2   IIII   C. 19CF   p.Arg7Cys   Missense   3     -   138C>C   c. 69G>C*   p.Glu23GIn   Missense   3     -   193C>A   c.74A/C   p.IPe2/SU   Missense   3     -   193C>A   c.74C/TinsA   -   -   -   2     195inscatcg   c.74/TinsA   -   -   -   -   2   1   -   2   1   1   -   -   -   -   -   1   -   -   -   -   -   -   -   -   -   1   -   -   -   -   -   -   -   -   -   -   -   -						-	-	c. 969A>T	p.Gly323Gly	Synonymous	2
keshavari     2012     36 (FBC)     -     IVS     IVS1 PS1-206>A     c. 2+66>A     -     No change     2       et al.     49 (NFBC)     35     IVS1     IVS1-206>A     c. 2+60>A     -     No change     2       61 (control)     -     2     127T>G     c. 2+00>A     p. Leu3Stop     Missense     1       -     1380>T     c. 190>T*     p. Arg7Cys     Missense     3       -     193C>A     c. 44A>C     p. Ile26Val     Missense     3       -     193C>A     c. 74>CA     p. Pro25     Synonymous     5       -     195A>G     c. 76A>G     p. Ile26Val     Missense     3       -     195C>A     c. 80+9G>C     s. 0     -     -     -     1       -     IVS2+92A>G     c. 80+9G>C     s. 0     -     -     -     -     -     -     -     -     1       -     IVS2+92A>G     c. 344>G     c. 444>SdeIT     -     -     -     -     -     <						-	-	c. 999T>A	p.Thr333Thr	Synonymous	2
Keshavarzi   2012   36 (FBC)   -   IVS1   IVS1-BG>A   c. 2-8G>A*   -   No change   2     ef al.   49 (NFBC)   □35   IVS1   IVS1-20G>A   c. 2-20G>A*   -   No change   2     61 (control)   -   2   127T>G   c. 8T>G*   p.Leu3Stop   Missense   1     -   138C>T   c. 19C>T*   p. Arg7Cys   Missense   3     -   188G>C   c. 69C>C*   p.lle26Val   Missense   3     -   193C>A   c. 74>CA   p.Pro25   Synonymous   5     -   195A>G   c. 76A>G   p.lle26Val   Missense   3     -   195A>G   c. 76A>G   p.lle26Val   Missense   3     -   195A>G   c. 80+9G>C*   -   -   2   1     VS2   IVS2   IVS2+1G>C   c. 80+35insectat*   -   -   1   1     -   IVS2   VS3   C. 340C>G   e.441+83delTT*   -   -   1   1     VS2   (3.39)   c. 80+35insectat*   -						-	-	c. 822T>A*	p.Cys274Ser	Misssense	1
et al.   49 (NFBC)   35   IVS1   IVS1-20G>A   c. 2-20G>A*   -   No change   2     61 (control)   -   2   127T>G   c. 8T>G*   p.Leu3Stop   Missense   1     -   138C>T   c. 19D>T*   p. Arg7Cys   Missense   3     -   163A>C   c. 44A>C   p.Leu3Map   Missense   3     -   193C>A   c. 74>CA   p.Pro25   Synonymous   5     -   193C>A   c. 76>CA   p.He26Val   Missense   3     -   193C>A   c. 76>CA   p.He26Val   Missense   3     -   195inscatetg   c. 76>C   p.He26Val   Missense   2     IVS2   IVS2+16>C   c. 80+16>C   -   -   1     -   IVS2+16>C   c. 80+35inscata*   -   -   1   1     IVS1   IVS2   IVS2+16>C   c. 80+35inscata*   -   -   1   1     IVS2   IVS2   IVS3   c. 349C>G*   p.Hur7Arg   Missense   2   1     IVS8   IVS87-80	Keshavarzi	2012	36 (FBC)	-		IVS1	IVS1-8G>A	c. 2-8G>A*	-	No change	2
61 (control)   -   2   127T>G   c. 8T>G*   p.Leu3Stop   Missense   1     -   138C>T   c. 19C>T*   p. Arg7Cys   Missense   2     -   163A>C   c. 44A>C   p.lle26Val   Missense   3     -   193C>A   c. 74>CA   p.lle26Val   Missense   3     -   1VS2   IVS2-VSC   c. 80+GSC*   -   -   1     IVS2   1VS2 (3-39)   c. 80+35inscatat*   -   -   1   1     IVS5   TIccatafA   c. 212-BA>C*   -   2   2   1   1 </td <td>et al.</td> <td></td> <td>49 (NFBC)</td> <td>□35</td> <td></td> <td>IVS1</td> <td>IVS1-20G&gt;A</td> <td>c. 2-20G&gt;A*</td> <td>-</td> <td>No change</td> <td>2</td>	et al.		49 (NFBC)	□35		IVS1	IVS1-20G>A	c. 2-20G>A*	-	No change	2
- 138C>T c. 19C>T* p. Arg7Cys Missense 2 - 163A>C c. 44A>C p. Ile26Val Missense 3 - 188G>C c. 69G>C* p.Glu23Gln Missense 3 - 1995A>G c. 76A>G p.Ile26Val Missense 3 - 195A>G c. 76A>G p.Ile26Val Missense 3 - 195inscatctg c. 76_77insA 2 IVS2 IVS2-1G>C c. 80-1G>C 2 IVS2 IVS2+24A>G c. 80-1G>C 2 - IVS2+24A>G c. 80-9G>C* 1 - IVS2+03>C 6. 80-9G>C* 1 - IVS2+03>C 6. 80-9G>C* 1 - IVS2 (3-39) c. 80+35insctat* 1 - IVS2 (3-39) c. 80+35insctat* 1 - IVS5 TToctatGAT c. 212-8A>G* 1 - IVS5 TToctatGAT c. 212-8A>G* p.Thr77Arg Missense 2 IVS7 230C>G c. 441+83deITT* 2 11 VIS8 IVS7+83(-TT) c. 488-70deICATT* 2 8 IVS8-70(-CATT) c. 550T>A Ser177Thr Missense 1 - 1260A>T c. 1141A>T* p.Glu575D Missense 1 - 1260A>T c. 1141A>T* p.Lys581X Synonymous 1 2430T>C c. 2311T>C p.Leu771Leu Missense 1 - 2331T>C c. 2212T>C p.Leu771Leu Missense 1 - 3232A>G c. 2814C>G p.Pro938 Pro Missense 19 - 3232A>G c. 2814C>G p.Pro938 Pro Missense 19 - 3232A>G c. 3113A>G p.Glu10380J9 Missense 28 - 313 432CA>C c. 4207A>C* p.Asr1403His Missense 28 - 313 432CA>C c. 4207A>C* p.Asr1403His Missense 28 - 313 432CA>C c. 4207A>C* p.Ser1040Asn Missense 28 - 313 432CA>C c. 4207A>C* p.Ser1040Asn Missense 28 - 313 432CA>C c. 4207A>C* p.Asr1403His Missense 29 - 3238C>A c. 3119C>A p.Ser1040Asn Missense 29 - 3238C>A c. 3119C>A p.Ser1040Asn Missense 29 - 3238C>A c. 3119C>A p.Ser1040Asn Missense 28 - 313 432CA>C c. 4207A>C* p.Asr1403His			61 (control)	-		2	127T>G	c. 8T>G*	p.Leu3Stop	Missense	1
- 163A>C c. 44A>C p. II226Val Missense 3 - 188G>C c. 69G>C* p.Glu23Gln Missense 3 - 193C>A c. 74>CA p. Pro25 Synonymous 5 - 195A>G c. 76A>G p.II226Val Missense 3 - 195A>G c. 76A>G p.II226Val Missense 3 - 195A>G c. 76-7TinsA 2 IVS2 IVS2-1G>C c. 80-1G>C 1 - 1VS2+9G>C c. 80-1G>C 1 - 1VS2+9G>C c. 80-1G>C 1 - 1VS2+3G>C c. 80-1G>C 1 - 1VS2 (3-39) c. 80+35insoctat* 1 IVS5 TroctatGAT c. 212-8A>G* 1 6 IVS5-8A>G c. 349C>G* p.Thr77Arg Missense 2 IVS7 230C>G c. 441+83delTT* 1 IVS8 IVS7+83(-TT) c. 488-70delCATT* 2 8 IVS8-70(-CATT) c. 550T>A Ser177Thr Missense 1 - 11 184A>T c. 1725A>T* p.Glu575D Missense 1 - 1260A>T c. 1141A>T* p.Lys581X Synonymous 1 2430T>C c. 2311T>C p.Leu771Leu Missense 8 2933C>G c. 3419C>A p.Fr038GP Missense 1 - 3232A>G c. 3113A>G p.Glu138GP Missense 29 3238G>A c. 3119C>A p.Ser1040Asn Missense 29 3238G>A c. 3419C>A p.Ser1040Asn Missense 21 3 4372T>C c. 4207A>C* p.Asn103815 Missense 21 3 4372T>C c. 4207A>C* p.Asn103815 Missense 21 3 4372T>C c. 4207A>C* p.Asn10315 Missense 21 3 4372T>C c. 4207A>C* p.Asn10345 Missense 21 3 4372T>C c. 4207A>			( , , , , , , , , , , , , , , , , , , ,			-	138C>T	c. 19C>T*	p. Arg7Cys	Missense	2
- 188G>C c. 69G>C* p.Glu23Gln Missense 3 - 193C>A c. 74>CA p. Pro25 Synonymous 5 - 195h>C c. 76A>G p.Ile26Val Missense 3 - 195inscatctg c. 76_77insA 2 IVS2 IVS2-1G>C c. 80-1G>C 1 - IVS2+9G>C c. 80-1G>C 7 - IVS2+34>G c. 80_24A>G* 2 - IVS2 (3-39) c. 80+35inscctat* 1 - 1 IVS5 TTcctaGAT c. 212-8A>G* 1 - 1 6 IVS5+8A>G c. 34/9C>G* p.Inr77Arg Missense 2 IVS7 230C>G c. 441+83deIT* 1 - 2 8 IVS8+70(-CATT) c. 550T>A Ser 177Thr Missense 1 - 11 184A>T c. 1725A>T* p.Isy51X Synonymous 1 1260A>T c. 141A>T* p.Isy51X Synonymous 1 1260A>T c. 2117C p.Leu771Leu Missense 8 2331T>C c. 2217C p.Leu871F0 Missense 1 - 2331T>C c. 2212T>C p.Leu871F0 Missense 1 - 2331T>C c. 2212T>C p.Leu871F0 Missense 1 - 2331T>C c. 2212T>C p.Leu871F0 Missense 1 - 2332C>G c. 3113A>G p.Glu10360j Missense 19 - 3538G>A c. 3119G>A p.Ser103048 Missense 19 - 3538G>A c. 3119G>A p.Ser103048 Missense 19 						-	163A>C	c. 44A>C	p. Ile26Val	Missense	3
-   193C>A   c. 74>CA   p. Pro25   Synonymous   5     -   195A>G   c. 76A>G   p.lle26Val   Missense   3     -   195inscatctg   c. 76_77insA   -   -   2     IVS2   IVS2-1G>C   c. 80-1G>C   -   -   1     -   IVS2+1G>C   c. 80-1G>C   -   -   2     IVS2   IVS2-1G>C   c. 80-1G>C   -   -   2     -   IVS2+1G>C   c. 80-1G>C   -   -   2     -   IVS2+1G>C   c. 80-1G>C   -   -   2     -   IVS2+1GA>C   c. 80-1G>C   -   -   1     -   IVS2 (3-39)   c. 80+35inscctat*   -   -   1     IVS5   TTcctatGAT   c. 212-8A>G   p.Thr77Arg   Missense   2     IVS7   230C>G   c. 441+83delTT   -   -   2   8     IVS7   230C>G   c. 1725A>T   p.Glu575D   Missense   5     2430T>C   c. 1725A>T   p.Glu575D   Missense   1   2430T>						-	188G>C	c. 69G>C*	p.Glu23Gln	Missense	3
- 195A>G c. 76A>G p.lle26Val Missense 3 - 195inscatctg c. 76_77insA 2 IVS2 IVS2 IVS2-1G>C c. 80-1G>C 1 - IVS2+9G>C c. 80-9G>C* 2 - IVS2 (3-39) c. 80+35inscctat* 1 IVS5 TTcctatGAT c. 212-8A>G* 1 6 IVS5-8A>G c. 349C>G* p.Thr77Arg Missense 2 IVS7 230C>G c. 441+83deITT* 1 IVS8 IVS7+83(TT) c. 488-70deICATT* 2 8 IVS8-70(-CATT) c. 550T>A Ser177Thr Missense 1 649T>A 11 1844A>T c. 1725A>T* p.Glu575D Missense 5 2331T>C c. 2211T>C p.Leu71Leu Missense 1 2430T>C c. 2311T>C p.Leu71Leu Missense 1 3232A>G c. 3419G>A* p.Glu1038Gly Missense 1 3232A>G c. 3113A>G p.Glu1038Gly Missense 29 3238G>A c. 3119G>A p.Ser1040Asn Missense 19 3538G>A c. 3419G>A* p.Asn1403His Missense 28 13 4326A>C c. 4203T>C c. 4253T						-	193C>A	c. 74>CA	, p. Pro25	Synonymous	5
- 195inscatctg c. 76_77insA 2 IVS2 IVS2-1G>C c. 80-1G>C 1 - IVS2+9G>C c. 80+9G>C* 2 - IVS2+24A>G c. 80_24A>G* 2 - IVS2 (3-9) c. 80+35inscctat* 1 IVS5 TTcctatGAT c. 212-8A>G* 1 6 IVS5-8A>G c. 349C>G* p.Thr77Arg Missense 2 IVS7 230C>G c. 441+83deITT* 1 1 VS8 IVS7+83(-TT) c. 488-70deICATT* 2 8 IVS8-70(-CATT) c. 550T>A Ser 177Thr Missense 1 649T>A 11 1844A>T c. 1725A>T* p.Glu575D Missense 1 649T>A 11 1844A>T c. 1725A>T* p.Glu575D Missense 1 2430T>C c. 2311T>C p.Leu771Leu Missense 1 2430T>C c. 2311T>C p.Leu871Pro Missense 1 3232A>G c. 3113A>G p.Glu1038Gly Missense 1 3232A>G c. 3113A>G p.Glu1038Gly Missense 29 3238G>A c. 3119G>A p.Ser 1040Asn Missense 29 3238G>A c. 349C>A* p.Glu1038Gly Missense 28 13 43264>C c. 4207A>C* p.Asn 1403His Missense 28 13 43272>G c. 4253T>G p.Leu471K5 Missense 28 13 4372T>G c. 4253T>G p.Leu47185 Missense 28 13 4372T>G c. 4253T>G p.Leu4185X Missense 1 324477>C c. 4203T>C c. 4203T>C p.Leu47185 Missense 28 13 4372T>G c. 4253T>G p.Leu473K5 Missense 12 3548G>A c. 3419G>A* p.Gly1140Ser Missense 28 13 4372T>G c. 4253T>G p.Leu473K5 Missense 12 3548G>A c. 3419G>A* p.Asn 1403His Missense 28 13 4372T>C c. 4203T>C p.Leu473K5 Missense 12 3548G>A c. 3419G>A* p.Asn 1403His Missense 14 3548C>C c. 4207A>C p.Ser 143ASER Sunonymous 14						-	195A>G	c. 76A>G	p.lle26Val	Missense	3
IVS2   IVS2-1G>C   c. 80-1G>C   -   -   1     -   IVS2+9G>C   c. 80+9G>C*   -   -   2     -   IVS2+24A>G   c. 80_24A>G*   -   -   2     -   IVS2 (3-39)   c. 80+35inscctat*   -   -   1     IVS5   TTcctatGAT   c. 212-8A>G*   -   -   1     6   IVS5-8A>G   c. 349C>G*   p.Thr77Arg   Missense   2     IVS7   230C>G   c. 441+83delTT*   -   -   1     IVS8   IVS7+83(-TT)   c. 488-70delCATT*   -   -   2     8   IVS8-70(-CATT)   c. 550T>A   Ser177Thr   Missense   1     6497>A   -   -   -   1   144A>T   c. 1725A>T*   p.Glu575D   Missense   5     2331T>C   c. 2311T>C   p.Leu771Leu   Missense   1   3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   1     3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   19   3538G>A   c. 3119G>A   p.Ser1040Asn   Missense						-	195inscatctg	c. 76 77insA	-	-	2
- IVS2+9G>C c. 80+9G>C* 2 - IVS2 (3-39) c. 80+35inscotat* 2 - IVS2 (3-39) c. 80+35inscotat* 1 IVS5 TTcctatGAT c. 212-8A>G* 1 6 IVS5-8A>G c. 349C>G* p.Thr77Arg Missense 2 IVS7 230C>G c. 441+83deIT* 1 IVS8 IVS7+83(-TT) c. 488-70deICATT* 2 8 IVS8-70(-CATT) c. 550T>A Ser177Thr Missense 1 649T>A 11 1844A>T c. 1725A>T* p.Glu575D Missense - 1260A>T c. 1141A>T* p.Lys581X Synonymous 1 2430T>C c. 2311T>C p.Leu771Leu Missense 1 3232A>G c. 3113>G p.Glu1038Gly Missense 1 3232A>G c. 3113>G p.Glu1038Gly Missense 19 3538G>A c. 3119G>A p.Ser1040Asn Missense 29 3238G>A c. 3419G>A* p.Glu1038Gly Missense 28 13 4326A>C c. 4207A>C* p.Asn1403His Missense 28 13 43272>G c. 4253T>G v.Asn1403His Missense 14 13 44272>C c. 4253T>G v.Asn1403His Missense 14 13 44272>C c. 4230R>C v.Asn1436FC v.Asn1436FC v.Nonymous 14 13 44272>C c. 4253R>C v.Asn1436FC v.Nonymous 14 13 44272>C v.Asn1425C v.Asn1425C v.Asn1436FC v.Nonymous 14 13 44272>C v.Asn1425C v.Asn1436FC v.Nonymous 14 14 4472>C v.Asn1425C v.Asn1425C v.Asn1436FC v.Nonymous 14 14 4472>C v.Asn1425C v.Asn1425C v.Asn1436FC v.Nonymous 14 14 4472>C v.Asn1425C v.Asn14						IVS2	IVS2-1G>C	c. 80-1G>C	-	-	1
- IVS2+24A>G c. 80_24A>G* 2 IVS2 (3-39) c. 80+35inscctat* 1 IVS5 TTcctatGAT c. 212-8A>G* 1 6 IVS5-8A>G c. 349C>G* p.Thr77Arg Missense 2 IVS7 230C>G c. 441+83deITT* 1 IVS8 IVS7+83(-TT) c. 488-70deICATT* 2 8 IVS8-70(-CATT) c. 550T>A Ser177Thr Missense 1 649T>A 11 1844A>T c. 1725A>T* p.Glu575D Missense - 1260A>T c. 1141A>T* p.Lys581X Synonymous 1 2430T>C c. 2311T>C p.Leu771Leu Missense 5 2331T>C c. 2121T>C p.Leu771Leu Missense 1 3222A>G c. 3113A>G p.Glu1038GJ Missense 19 3238G>A c. 3119G>A p.Ser1040Asn Missense 19 3538G>A c. 3119G>A p.Ser1040Asn Missense 19 3538G>A c. 3419G>A* p.Gly140Ser Missense 28 13 4326A>C c. 4207A>C* p.Asn1403His Missense 2 13 4372T>C c. 4308T>C p.Leu1418SX Missense 1 13 4427T>C c. 4308T>C p.Leu1418SX Missense 1 13 4427T>C c. 4308T>C p.Ser1436Ser Synonymous 14						_	IVS2+9G>C	c. 80+9G>C*	_	_	2
- IVS2 (3-39) c. 80+35insctat* 1 IVS5 TTcctatGAT c. 212-8A>G* - 1 6 IVS5-8A>G c. 349C>G* p.Thr77Arg Missense 2 IVS7 230C>G c. 441+83deITT* 1 IVS8 IVS7+83(-TT) c. 488-70deICATT* 2 8 IVS8-70(-CATT) c. 550T>A Ser177Thr Missense 1 649T>A 11 1844A>T c. 1725A>T* p.Glu575D Missense - 1260A>T c. 1141A>T* p.Lys581X Synonymous 1 2430T>C c. 2311T>C p.Leu771Leu Missense 8 2933C>G c. 2814C>G p.Pro938 Pro Missense 1 3232A>G c. 3113A>G p.Glu1038Gly Missense 29 3238G>A c. 3119G>A p.Ser1040Asn Missense 19 3538G>A c. 3419G>A* p.Glu1038Gly Missense 28 13 4326A>C c. 4207A>C* p.Asn1403His Missense 28 13 4372T>C c. 4253T>G* p.Leu1418SX Missense 1 13 4427T>C c. 4308T>C p.Ser1436Ser Synonymous 1 13 4427T>C c. 4308T>C p.Ser1436Ser Synonymous 1 13 4427T>C c. 4308T>C p.Ser1436Ser Synonymous 1 14 4427T>C c. 4308T>C p.Ser1436Ser Synonymous 1 15 4427T>C c. 4308T>C p.Ser1436Ser Synonymous 1 16 4427T>C c. 4308T>C p.Ser1436Ser Synonymous 1 17 4427T>C c. 4308T>C p.Ser1436Ser Synonymous 1 18 4427T>C						_	IVS2+24A>G	c. 80 24A>G*	_	_	2
IVS5   TTectatGAT   c. 212-8A>G*   -   1     6   IVS5-8A>G   c. 349C>G*   p.Thr77Arg   Missense   2     IVS7   230C>G   c. 441+83delTT*   -   -   1     IVS8   IVS7+83(-TT)   c. 488-70delCATT*   -   -   2     8   IVS8-70(-CATT)   c. 550T>A   Ser 177Thr   Missense   1     649T>A   -   11   1844A>T   c. 1725A>T*   p.Glu575D   Missense   -     11   1844A>T   c. 1725A>T*   p.Lgv581X   Synonymous   1     2430T>C   c. 2311T>C   p.Leu771Leu   Missense   5     2331T>C   c. 2212T>C   p.Leu871Pro   Missense   1     3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   19     3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   1     13   43272T>C   c. 4308E7   p.Ser1436Ser   <						_	IVS2 (3-39)	c. 80+35inscctat*	_	_	1
6   IVS5-8A>G   c. 349C>G*   p.Thr77Arg   Missense   2     IVS7   230C>G   c. 441+83delTT*   -   -   1     IVS8   IVS7+83(-TT)   c. 488-70delCATT*   -   2     8   IVS8-70(-CATT)   c. 550T>A   Ser177Thr   Missense   1     11   1844A>T   c. 1725A>T*   p.Glu575D   Missense   -     11   1844A>T   c. 1141A>T*   p.Lys581X   Synonymous   1     1260A>T   c. 1141A>T*   p.Leu771Leu   Missense   5     2331T>C   c. 2212T>C   p.Leu871Pro   Missense   1     3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   19     3538G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   1     13   4372T>C   c. 4207A>C*   p.Asn1403His   Missense   1						IVS5	TTcctatGAT	c. 212-8A>G*		_	1
IVS7   230C>G   c. 441+83delTT*   -   -   1     IVS8   IVS7+83(-TT)   c. 488-70delCATT*   -   -   2     8   IVS8-70(-CATT)   c. 550T>A   Ser177Thr   Missense   1     649T>A   -   -   11   1844A>T   c. 1725A>T*   p.Glu575D   Missense   -     11   1844A>T   c. 1725A>T*   p.Luy581X   Synonymous   1     2430T>C   c. 2311T>C   p.Leu771Leu   Missense   5     2331T>C   c. 2212T>C   p.Leu871Pro   Missense   1     3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   29     3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   19     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1						6	IVS5-8A>G	c. 349C>G*	p.Thr77Arg	Missense	2
IVS8   IVS7+83(-TT)   c.   488-70delCATT*   -   2     8   IVS8-70(-CATT)   c.   550T>A   Ser177Thr   Missense   1     649T>A   -   11   1844A>T   c.   1725A>T*   p.Glu575D   Missense   -   1260A>T   c.   1141A>T*   p.Lys581X   Synonymous   1     2430T>C   c.   231T>C   c.   231T>C   p.Leu771Leu   Missense   5     2331T>C   c.   2814C>G   p.Pro938 Pro   Missense   1     3232A>G   c.   3113A>G   p.Glu1038Gly   Missense   19     3538G>A   c.   3419G>A*   p.Gly1140Ser   Missense   28     13   43272T>G   c.   4253T>G*   p.Leu1418SX   Missense   1						IVS7	230C>G	c. 441+83delTT*	-	-	1
8   IVS8-70(-CATT)   c. 550T>A   Ser177Thr   Missense   1     649T>A   11   1844A>T   c. 1725A>T*   p.Glu575D   Missense   -     1260A>T   c. 1141A>T*   p.Lys581X   Synonymous   1     2430T>C   c. 2311T>C   p.Leu771Leu   Missense   5     2331T>C   c. 2212T>C   p.Leu871Pro   Missense   1     3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   29     3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   19     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   14						IVS8	IVS7+83(-TT)	c. 488-70delCATT*	-	_	2
649T>A     11   1844A>T   c. 1725A>T*   p.Glu575D   Missense   -     1260A>T   c. 1141A>T*   p.Lys581X   Synonymous   1     2430T>C   c. 2311T>C   p.Leu771Leu   Missense   5     2331T>C   c. 2212T>C   p.Leu871Pro   Missense   8     2933C>G   c. 3113A>G   p.Glu1038Gly   Missense   19     3232A>G   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   1     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14						8	IVS8-70(-CATT)	c. 550T>A	Ser 177Thr	Missense	1
11   1844A>T   c. 1725A>T*   p.Glu575D   Missense   -     1260A>T   c. 1141A>T*   p.Lys581X   Synonymous   1     2430T>C   c. 2311T>C   p.Leu771Leu   Missense   5     2331T>C   c. 2212T>C   p.Leu871Pro   Missense   8     2933C>G   c. 2814C>G   p.Fro938 Pro   Missense   1     3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   29     3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   2     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14						-	649T>A				
1260A>T   c. 1141A>T*   p.Lys581X   Synonymous   1     2430T>C   c. 2311T>C   p.Leu771Leu   Missense   5     2331T>C   c. 2212T>C   p.Leu871Pro   Missense   8     2933C>G   c. 2814C>G   p.Pro938 Pro   Missense   1     3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   29     3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   2     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14						11	1844A>T	c. 1725A>T*	p.Glu575D	Missense	-
2430T>C   c. 2311T>C   p.Leu771Leu   Missense   5     2331T>C   c. 2212T>C   p.Leu871Pro   Missense   8     2933C>G   c. 2814C>G   p.Pro938 Pro   Missense   1     3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   29     3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   2     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14							1260A>T	c. 1141A>T*	p.1 vs581X	Synonymous	1
2331T>C   c. 2212T>C   p.Leu871Pro   Missense   8     2933C>G   c. 2814C>G   p.Pro938 Pro   Missense   1     3232A>G   c. 3113A>G   p.Glu1038Gly   Missense   29     3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   2     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14							2430T>C	c. 2311T>C	p.l.eu771Leu	Missense	5
2933C>G   c. 2814C>G   p.Pro938 Pro   Missense   1     3232A>G   c. 3113A>G   p.Glu 1038Gly   Missense   29     3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   2     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14							2331T>C	c. 2212T>C	p.Leu871Pro	Missense	8
3232A>G   c. 3113A>G   p.Glu 1038Gly   Missense   25     3232A>G   c. 3113A>G   p.Glu 1038Gly   Missense   25     3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly 1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   2     13   4372T>G   c. 4253T>G*   p.Leu 1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14							2933C>G	c. 2814C>G	p.Pro938 Pro	Missense	1
3238G>A   c. 3119G>A   p.Ser1040Asn   Missense   19     3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   2     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14							3232A>G	c. 3113A>G	p.Glu 1038Glv	Missense	29
3538G>A   c. 3419G>A*   p.Gly1140Ser   Missense   28     13   4326A>C   c. 4207A>C*   p.Asn1403His   Missense   2     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14							3238G>A	c. 3119G>A	p.Ser1040Δen	Missense	19
13   4326A>C   c. 4207A>C*   p.dsj 1403His Missense   2     13   4372T>G   c. 4253T>G*   p.Leu1418SX   Missense   1     13   4427T>C   c. 4308T>C   p.Ser1436Ser   Synonymous   14							3538G>A	c. 3419G>A*	p.Glv1140.Ser	Missense	28
13 4372T>C c. 4253T>C p.Leu1418SX Missense 1 13 4427T>C c. 4308T>C p.Ser1436Ser Synonymous 14						13	4326A>C	c. 4207A>C*	p.Asn 1403His	Missense	20
13 4427T>C c. 4308T>C n Ser 1436Ser Synonymous 14						13	4372T>G	c 4253T>G*	n Leu 1/1189Y	Missense	∠ 1
						12	4427T>C	c /308T>C	n Sar 1/26Sar	Synonymous	1/1
$\frac{16}{16} \frac{10565}{16} = 0.100016000 = 0.100016000000 = 0.1000160000000 = 0.1000160000000000000000000000000000000$						16	10560>0	c 18374>C	n Ser 1613Chu	Micconco	19

Contd...

#### Neamatzadeh, et al.: BRCA1 and BRCA2 mutations in Iranian breast cancer patients

Table 1: 0	Fable 1: Contd									
Author	Year	Study	population	Technique	Exon/	Traditional	Sequence variant	Amino acid	Mutation	Frequency
		Number	Age (years)		intron	nomenclature		change	type	
					20	5324A>G	c. 5205A>G*	p.Glu 1735Glu	Synonymous	1
					20	5332G>A	c. 5213G>A	p.Gly 1738Glu	Missense	4
Kooshyar	2013	39 (BC)	49.3	SSCP-PCR	2	187delAG	185delAG	-	Frameshift	2
et al.		29 (HR)	23-72		2	5382insC	5385insC	-	Frameshift	1
					11	-	251bp fragment	-	Frameshift	2

DS=Direct sequencing; PTT=Protein truncation test; SSCP=Single-strand conformation polymorphism; BC=Breast cancer; PCR=Polymerase chain reaction; RFLP=Restriction fragment length polymorphism; FBC=Familial breast cancer; NFBC=Nonfamilial breast cancer; SBC=Sporadic breast cancer; HF=High familial; HR=High risk; HA=Heteroduplex analysis; HP=Heterozygous pattern; HOBS=Hereditary breast and ovarian cancer syndrome

Author	Vaar	Partici	inante	Technique	Exon/	Traditional	Sequence variant	AA change	Mutation	Frequency
Aution	rear	Number		rechnique	intron	nomenclature	Sequence variant	AA change	type	Frequency
Vassaga	2002	02		DTT	11	nomenolatare	6261 6262 incCT		Framachift	1
et al	2002	03	×40		11		2070 2090 inc.		Frameshift	1
or un					-		5979-5960 IIISA		Missense	1
				DS	-				Missense	1
				SSCP/HA	17		CIVS 166T>G		Splice site	I
				SSCP/HA	18		8345A>G N2706S		Missense	1
				-	23		9266C>T T3013I		Missense	1
Moslehi	2003	1 family	56	PTT	11		c.G2031T*	p.Glu638X	-	-
et al.		with 4 cases (HOBS)	45-67							
Pietschmann	2005	10 high risk	50	DS	-		g. –1235G>A			1
et al.		BC families			2		g26G>A			4
					8		g. 681+56C>T			2
					10		c. 865A>C	p.Asn289His		3
							c. 1114A>C	p.Asn372His		3
							c. 1365A>G	p.Ser455Ser		2
					11		c. 2229T>C	, p.His743His		2
							c. 2971A>G	p.Asn991Asp		2
							c. 3396A>G	p.Lys1132Lys		5
							c. 3516G>A	p.Ser1172Ser		1
							c. 3807T>C	p.Val 1269Val		8
							c. 4415_4418 delAGAA*	p.Lys 1472fsX5		1
							c. 5529A>C	p.Ala1843Ala		1
							c. 6033 6034insGT	p.Ser2012fsX28		1
					14		c. 7242A>G	p.Ser2414Ser		4
					14		g 7435+53C>T	-		2
					16		g 7806-14T>C	_		8
					21		g 8755-66T>C	_		8
Fattahi	2009	250 (SBC)	45 1+9 2	Multiplex-			6174delT			0
et al.	2007	55 (FBC)	32 0+7 3	PCR						0
		200 (HE)	-							0
Koshavarzi	2011	200 (III) 27 (BC)	35	20	10		1	n Gln373Gln	Synonymous	1
et al.	2011	50 (HE)		00	11		1	Glu 1301Glv*	Missense	1
		50 (III)			11		1 A 4770C	n Lou 1521 Lou	Synonymous	1
					11		G6722C	p.Leu 1321Leu p.VAI 2171Val	Synonymous	1
Keshavarzi	2012	36 (FBC)	25	DS	1//26	IV\$6-70T>G	c 2600-70T>G*	-	Cynonymous	1
et al.	2012	10 (NEBC)		20	11	1410456	c /182/>G	n E1301G		1
		+7 (INFDU)			11	44104/0	0. 410ZA/G	p. L 15910		1
					11	4J42A/U	0. 4// UA/G	p.L 1521L		4
						4J430/1	0. 4// 10/1	h'r 1977L		1
						0 17 1111SA	0. 0700_0704IIISA	- ~ \/0171\/		1
						0/220/0	U. U474U/U	p.vZI/IV		3

PTT=Protein truncation test; DS=Direct sequencing; SSCP=Single-strand conformation polymorphism; HOBS=Hereditary breast and ovarian cancer syndrome; PCR=Polymerase chain reaction; FBC=Familial breast cancer; SBC=Sporadic breast cancer; HF=High familial; NFBC=Nonfamilial breast cancer; BC=Breast cancer

Of the total of 1183 patients who were included in the studies 377 cases at least had a mutation in the BRCA1 gene. Therefore, based on the previous studies, the overall BRCA1 mutation rate in Iranian BC patients with various levels of family history range (with or without BC diagnosed in relatives) was estimated 31.8% (377/1183). While, this gene mutation rate for male patients is less than 0.01%. This is comparable to that of Algerian and Tunisian families BRCA1 mutation frequency, which were reported 36.4% and 37.5%, respectively. The prevalence of BRCA1 mutations reported in a study conducted on French hereditary BC and/or OC families (10.3%) is approximately 3 times less than that estimated for our community.<sup>[29]</sup> This high prevalence may be due to limited particular region of the genes, and the techniques were used.

Identification of BRCA mutations in a substantial proportion of Iranian patients indicates that these genes play a role in the incidence of BC in the Iranian population. In addition, According to these studies, there is heterogeneity in BRCA mutations in Iranian BC patients like other population.

Results shown that a total of 104 BRCA1/2 distinct mutations were identified in the interim 13 articles analysis among 377 females BC patients with or without family history, which 71 (68.8%) mutations were in BRCA1, and 33 (31.2%) were in BRCA2. Thirty-two mutations were putatively novel mutations that previously not reported. Of these, 28 of 71 in BRCA1 (39.4%) and 4 of 33 in BRCA2 (12.2%) were putatively novel mutations which previously not reported. Most of the novel mutations were missense and identified in exon 11.

As shown in Tables 3 and 4, the most common recurrent mutations in Iranian BC patients, which were repeatedly reported twice or more in different articles included: c. 4837A > G, c. 3419G > A, c. 3119G > A, c. 2612C > T, c. 3113A > G, c. 2311T > C, c. 4301T > C and c. 4308T > C

in BRCA1, c. 4771C > T and c. 6494G > C in BRCA2. However, BRCA1 c. 3419G > A mutation was identified as a novel mutation, but its prevalence was higher than expected (28/377).

The frequency range of seven common mutations is shown in Table 4. The frequency range for c. 4837A > G was between 13.6 and 30.0, for c. 3119G > A was between 18.5 and 25.0, for c. 2311T > C was between 5.9 and 30.0, for c. 5213G > Awas between 4.7 and 18.5, for c. 2612C > T was between 13.6 and 31.8, for c. 3113A > G was between 22.2 and 34.1, and for c. 4308T > C was between 11.2 and 30.0.

To the best of our knowledge, it has not introduced a founder mutation in Iranian breast and ovarian patients yet. Therefore, these mutations could represent candidate founder mutations and support testing these mutations at least for those with a family history of BC.

The effect of most of the BRCA mutations on protein is unknown and making it difficult to predict the consequences on risks of breast and ovarian cancers. Thus, many individuals undergoing genetic testing for BRCA mutations receive test results reporting a variant of uncertain clinical significance, leading to issues in risk assessment, counseling, and preventive care.<sup>[30]</sup> Based on the virtual analyses of functional compatibility for amino acid changes using SIFT and GVGD programs, 4 of the 8 most frequent variants in BRCA1 (i.e. p.Ser1613Gly, p.Ser1040Asn, p.Pro871Leu, and p.Glu1038Gly) were predicted to have an impact on protein structure (Align-GVGD, http: www.//agvgd.iarc.fr/) and SIFT (http://www.sift.bii.a-star.edu.sg/).<sup>[31]</sup>

In well-defined populations based on ethnicity, founder mutations in the BRCA1 and BRCA2 genes have been found to account for a higher proportion of breast and ovarian cancer than in the general population. Three

Table 3: Ir	ncidence of	more freque	nt BRC1 mutations in the	Iranian BC patie	ents	
Variant	Exon/intron	AA changes	Times reported (n=214)* (%)	All mutant** (%)	All patient (n=377) %	All population (n=1183) %
c. 3113A>G	11	p.Glu1038Gly	46 (21.5)	154 (29.8)	12.2	3.8
c. 4837A>G	16	p.Ser 1613Gly	30 (14.01)	154 (19.5)	7.9	2.5
c. 3419G>A	11	p.Gly1140Ser	28 (13.08)	85 (32.9)	7.4	2.3
c. 3119G>A	11	p.Ser 1040Asn	26 (12.14)	132 (19.7)	6.9	2.2
c. 4308T>C	13	p.Ser1436Ser	26 (12.1)	154 (16.8)	6.9	2.2
c. 2612C>T	11	p.Pro871Leu	18 (8.4)	69 (26.00)	4.8	1.5
c. 2311T>C	11	p.Leu771Leu	17 (7.9)	154 (11.0)	4.5	1.4
c. 3418A>G	11	p.Ser1140Gly	11 (5.1)	27 (40.7)	2.9	0.92
c. 3548A>G	11	p.Lys1183Arg	10 (4.6)	42 (26.2)	2.6	0.84
c. 5213G>A	20	p.Gly 1738Glu	9 (4.2)	112 (8.0)	2.3	0.76
185delAG	2	-	7 (3.2)	924 (0.75)	1.8	0.60
5382insC	2	-	1 (0.46)	774 (0.12)	0.02	0.08
c. 2212T>C	11	p.Leu871Pro	8 (3.7)	85 (9.4)	2.1	0.67

\*Among studies that identified or targeted the mutation (it may the mutation had or not had frequency); \*\*Among studies that had the mutation incidence (only studies that had reported). BC=Breast cancer; BRC1=BReast CAncer susceptibility gene 1

Variant	Frequency	Percentage	Range
c. 4837A>G	3/22ª	13.6	13.6-30.0
	6/20 <sup>b</sup>	30.0	
	3/27°	11.2	
	18/85 <sup>d</sup>	21.2	
c. 3119G>A	5/20 <sup>b</sup>	25.0	18.5-25.0
	5/27°	22.3	
	19/85 <sup>d</sup>	18.5	
c. 2311T>C	3/22ª	13.6	5.9-30.0
	6/20 <sup>b</sup>	30.0	
	3/27°	11.2	
	5/85ď	5.9	
c. 5213G>A	5/27°	18.5	4.7-18.5
	4/85 <sup>d</sup>	4.7	
c. 2612C>T	3/22ª	13.6	13.6-31.8
	7/20 <sup>b</sup>	31.8	
c. 3113A>G	6/22ª	27.2	22.2-34.1
	6/20 <sup>b</sup>	30.0	
	6/27°	22.2	
	29/85 <sup>d</sup>	34.1	
c. 4308T>C	3/22ª	13.6	11.2-30.0
	6/20 <sup>b</sup>	30.0	
	3/27°	11.2	
	14/85 <sup>d</sup>	16.4	

Table 4: Incidence of recurrent BRC1 mutations in the

<sup>2</sup>22 with at least one first-degree relative with any kind of cancer, 1 with ovarian cancer history, 1 male case had BC history; <sup>b</sup>10 high risk BC families; <sup>c</sup>Personal and/ or family history of breast or ovarian cancer; <sup>d</sup>36 with family history of BC, 49 patients with early onset BC without a family history. BC=Breast cancer

specific mutations (185delAG, 5382insC in BRCA1, and 6174delT in BRCA2 occur in 36% of breast/ovarian cancer families. Interestingly, it is reported that 185delAG mutation occurs at a very high frequency of 18.0% in families of Ashkenazi Jews with breast/ovarian cancer. This mutation also occurs at a frequency of 1% among the Ashkenazi general population.[32] Based on the previous studies results, Ashkenazi Jewish founder mutations 185delAG and 5382insC (BRCA1) rates among Iranian BC patients were estimated approximately 0.75% (7/924) and 0.13% (1/774), respectively. However, some studies have supported that Ashkenazi Jewish founder mutations is not restricted to this particular ethnic subgroup and occurs in non-Ashkenazi Jewish ethnic groups at rates similar to the Ashkenazi population, with a similar genetic background for all Jewish mutation carriers. These mutations are not frequent mutation in Iranian BC patients.<sup>[10]</sup>

According to the Pietschmann *et al.* (2009) and Keshavarzi *et al.* (2012) studies, which have sequenced most coding regions of BRCA1 and BRCA2, Exons 2 and 11 in BRCA1 harbor 13.2% (7/53) and 28.3% (15/53) of the BRCA mutations, respectively.<sup>[14,21]</sup> For the BRCA2, the overall frequency of 4075delGT was 0.02 (95% CI: 0.00–0.03, P=0.51 for heterogeneity test).

## CONCLUSION

Until date, no other such analysis study on BC in Iran has been published. The major advantage of this review is help to determining the spectrum of BRCA mutations in Iranian BC patients and must be strengthened with further studies with a larger cohort in order to determine the rate of the BRCA mutations in the Iranian general population and to determine the existence of founder mutations. Although, these studies were limited by some reasons, they are useable to provide appropriate cancer prevention, screening, and counseling strategies based on the mutation data. Therefore, a new BC risk assessment based BRCA mutations data were created for the Iranian population.

## AUTHOR'S CONTRIBUTION

All authors equally contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. HN contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SMS contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SMK contributed in the conception of the work. SMK contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

# REFERENCES

- 1. Abdulrahman GO Jr, Rahman GA. Epidemiology of breast cancer in Europe and Africa. J Cancer Epidemiol 2012;2012:915610.
- Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. Ann Oncol 2009;20:556-63.
- 3. Heidari Z, Mahmoudzadeh-Sagheb HR, Sakhavar N. Breast cancer screening knowledge and practice among women in southwest of Iran. Acta Med Iran 2008;46:321-8.
- 4. Kolahdoozan S, Sadjadi A, Radmard AR, Khademi H. Five common cancers in Iran. Arch Iran Med 2010;13:143-6.
- 5. Harirchi I, Kolahdoozan S, Karbakhsh M, Chegini N, Mohseni SM, Montazeri A, *et al.* Twenty years of breast cancer in Iran: Downstaging without a formal screening program. Ann Oncol 2011;22:93-7.
- 6. Antoniou AC, Gayther SA, Stratton JF, Ponder BA, Easton DF. Risk models for familial ovarian and breast cancer. Genet Epidemiol 2000;18:173-90.
- Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998;62:676-89.
- 8. Karami F, Mehdipour P. A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int 2013;2013:928562.
- 9. Nelson HD, Huffman LH, Fu R, Harris EL, U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: Systematic evidence

review for the U.S. Preventive Services Task Force. Ann Intern Med 2005;143:362-79.

- 10. Bar-Sade RB, Kruglikova A, Modan B, Gak E, Hirsh-Yechezkel G, Theodor L, *et al.* The 185delAG BRCA1 mutation originated before the dispersion of Jews in the diaspora and is not limited to Ashkenazim. Hum Mol Genet 1998;7:801-5.
- 11. Ghaderi A, Talei A, Farjadian S, Mosalaei A, Doroudchi M, Kimura H. Germline BRCA1 mutations in Iranian women with breast cancer. Cancer Lett 2001;165:87-94.
- 12. Yassaee VR, Zeinali S, Harirchi I, Jarvandi S, Mohagheghi MA, Hornby DP, *et al*. Novel mutations in the BRCA1 and BRCA2 genes in Iranian women with early-onset breast cancer. Breast Cancer Res 2002;4:R6.
- Moslehi R, Kariminejad MH, Ghafari V, Narod S. Analysis of BRCA1 and BRCA2 mutations in an Iranian family with hereditary breast and ovarian cancer syndrome. Am J Med Genet A 2003;117A: 304-5.
- Pietschmann A, Mehdipour P, Mehdipour P, Atri M, Hofmann W, Hosseini-Asl SS, *et al.* Mutation analysis of BRCA1 and BRCA2 genes in Iranian high risk breast cancer families. J Cancer Res Clin Oncol 2005;131:552-8.
- Quintana-Murci L, Gal I, Bakhan T, Quach H, Sayar SH, Shiri-Sverdlov R, *et al.* The Tyr978X BRCA1 mutation: Occurrence in non-Jewish Iranians and haplotype in French-Canadian and non-Ashkenazi Jews. Fam Cancer 2005;4:85-8.
- Mehdipour P, Hosseini-Asl S, Savabi-EA, Habibi L, Ehsan Alvandi E, Atri M. Low frequency of 185delAG founder mutation of BRCA1 gene in Iranian breast cancer patients. J Cancer Mol 2006;2:123-7.
- Rassi H, Houshmand M, Hashemi M, Majidzadeh K, Akbari MH, Panahi MS. Application of multiplex PCR with histopathologic features for detection of familial breast cancer in formalin-fixed, paraffin-embedded histologic specimens. Tsitol Genet 2008;42:55-62.
- Fattahi MJ, Mojtahedi Z, Karimaghaee N, Talei AR, Banani SJ, Ghaderi A. Analysis of BRCA1 and BRCA2 mutations in southern Iranian breast cancer patients. Arch Iran Med 2009;12:584-7.
- Saleh Gohari N, Mohammadi-Anaie M, Kalantari-Khandani B. BRCA1 gene mutations in breast cancer patients from Kerman Province, Iran. Iran J Cancer Prev 2012;5:210-5.
- Keshavarzi F, Noughani AE, Ayoubian M, Zeinali S. Sequence variants of BRCA1 and BRCA2 genes in four Iranian families with breast and ovarian cancer. Iran J Public Health 2011;40:57-66.
- Keshavarzi F, Javadi GR, Zeinali S. BRCA1 and BRCA2 germline mutations in 85 Iranian breast cancer patients. Fam Cancer 2012;11:57-67.

- Kooshyar MM, Nassiri M, Mahdavi M, Doosti M, Parizadeh A. Identification of germline BRCA1 mutations among breast cancer families in Northeastern Iran. Asian Pac J Cancer Prev 2013;14:4339-45.
- 23. Balmaña J, Díez O, Rubio IT, Cardoso F, ESMO Guidelines Working Group. BRCA in breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2011;22 Suppl 6:vi31-4.
- 24. Bougie O, Weberpals JI. Clinical considerations of BRCA1- and BRCA2-mutation carriers: A review. Int J Surg Oncol 2011;2011:374012.
- Moatter T, Aban M, Khan S, Azam I, Pervez S. BRCA1 status in Pakistani breast cancer patients with moderate family history. J Coll Physicians Surg Pak 2011;21:680-4.
- 26. Song CG, Hu Z, Yuan WT, Di GH, Shen ZZ, Huang W, et al. BRCA1 and BRCA2 gene mutations of familial breast cancer from Shanghai in China. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2006;23:27-31.
- 27. De Leon Matsuda ML, Liede A, Kwan E, Mapua CA, Cutiongco EM, Tan A, *et al.* BRCA1 and BRCA2 mutations among breast cancer patients from the Philippines. Int J Cancer 2002;98:596-603.
- Carraro DM, Koike Folgueira MA, Garcia Lisboa BC, Ribeiro Olivieri EH, Vitorino Krepischi AC, de Carvalho AF, et al. Comprehensive analysis of BRCA1, BRCA2 and TP53 germline mutation and tumor characterization: A portrait of early-onset breast cancer in Brazil. PLoS One 2013;8:e57581.
- 29. Laraqui A, Uhrhammer N, Lahlou-Amine I, El Rhaffouli H, El Baghdadi J, Dehayni M, *et al*. Mutation screening of the BRCA1 gene in early onset and familial breast/ovarian cancer in Moroccan population. Int J Med Sci 2013;10:60-7.
- 30. Millot GA, Carvalho MA, Caputo SM, Vreeswijk MP, Brown MA, Webb M, *et al.* A guide for functional analysis of BRCA1 variants of uncertain significance. Hum Mutat 2012;33:1526-37.
- 31. Solano AR, Aceto GM, Delettieres D, Veschi S, Neuman MI, Alonso E, *et al.* BRCA1 And BRCA2 analysis of Argentinean breast/ovarian cancer patients selected for age and family history highlights a role for novel mutations of putative south-American origin. Springerplus 2012;1:20.
- 32. Vaidyanathan K, Lakhotia S, Ravishankar HM, Tabassum U, Mukherjee G, Somasundaram K. BRCA1 and BRCA2 germline mutation analysis among Indian women from south India: Identification of four novel mutations and high-frequency occurrence of 185delAG mutation. J Biosci 2009;34:415-22.

Source of Support: Nil, Conflict of Interest: None declared.