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ORIGINAL ARTICLE

A comprehensive reference for *BRCA1/2* genes pathogenic variants in Iran: published, unpublished and novel

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Abstract

BRCA1 and *BRCA2* are two prominent genes that account for about 20–40% of inherited breast cancer. Mutations in these genes are often associated with clustering of especially early-onset cancers in the family. The spectrum of *BRCA* variants showed a significant difference between geographic regions and ethnicities. The frequency and spectrum of *BRCA* mutations in Iran, a country in southwest Asia, have not yet been thoroughly studied. Here, for the first time, all published and not published *BRCA* pathogenic variants are presented. Among 1040 high risk families (1258 cases) which were detected, 116 families were found to carry pathogenic variants in either *BRCA1* or *BRCA2*. Altogether 89 distinct types of pathogenic variants have been detected in Iran, including 41 in *BRCA1* and 48 in *BRCA2*. 16 out of 89 mutations had not been previously reported in Iran and are presented for the first time in this article, among which 4 mutations are novel worldwide. 20% of families had one of the seven most commonly observed mutations, including c.81-1G > C, c.66_67delAG, c.4609C>T, c.1568delT, c.1961delA, in *BRCA1* and: c.3751_3752insA, c.8585dupT in *BRCA2*. Combining the data from published articles and our study which has not been published before, a comprehensive table is created as a reference for entire *BRCA* pathogenic variants and their frequencies in Iran.

Keywords Hereditary breast cancer · *BRCA* mutations · Pathogenic variants · Iran

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and the second leading cause of cancer-related death worldwide among women [1, 2]. The disease is caused by a combination of genetic, environmental, lifestyle, and reproductive risk factors. Iran; with a population of around 81 million people from more than 10 ethnic groups; is located in the southwest of Asia. The median age at diagnosis of BC in Iran is a decade lower than western countries [3–5]. The same situation is reported in some other countries of the Middle East and Mediterranean districts [6]. The differences in BC statistics such as the incidence and median age at diagnosis between Iran and western countries can be related to the lifestyle factors and genetic profile of the populations. A part of this genetic profile is related to cancer-predisposing genes responsible for hereditary BCs which compose around 5% to 10% of all BCs. Approximately half of the hereditary breast and ovary cancers are thought to be due to *BRCA1* or *BRCA2* mutations, which are inherited in an autosomal-dominant pattern [7]. Increasing evidence suggests that the frequencies and characteristics of BRCA1/2 germline mutations in human hereditary breast and ovary cancers largely depend on race and ethnicity [8]. For example, c.303T > G, c.4122_4123delTG, c.1623dupG, and c.5324T > G in *BRCA1* are frequently observed in the African familial breast cancer patients [9]; *BRCA1* ex9-12del is often seen in Mexican patients with hereditary breast and ovary cancers [10]; the *BRCA2* mutation c.7480C>T is enriched in Korean patients with familial

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breast cancer [11]; 185delAG (c.66_67delAG) and 5382insC (c.5263_5264insC) in *BRCA1* and 6174delT (c.5946delT) in *BRCA2* are most common variants in people of Ashkenazi Jewish descent [12–14]. *BRCA* mutations have been extensively studied in European and North American peoples, but much less are known about them in populations originating from Asia, Africa, and Latin America, although these constitute the majority of human populations. Using information from Western patients to interpret *BRCA* mutations in patients of non-Western origin can potentially lead to misdiagnoses. So, knowledge of the ethnic-specificity of variations of the *BRCA* genes is urgently demanding. Also, the determination of the most prevalent pathogenic variants and the possible recurring variations through the population (founder mutations) in these two genes make further population-based screenings more possible.

In this study which conducted by Motamed Cancer Institute (MCI) of Iran, the authors aimed to present all *BRCA* pathogenic variants detected; published or unpublished; by Hereditary Cancer Clinic (HCC) of MCI and all other clinics across the country to build a comprehensive reference for all pathogenic variants of *BRCA* genes across the country until date.

Materials and methods

All published papers on pathogenic *BRCA* mutations in the Iranian population were reviewed. Also, pathogenic variants, which were detected in HCC of MCI were included. In addition, some pathogenic variants were reported from the patients of other laboratories across the country, including Medical Genetics Laboratory of Genome, GENEOCELL Medical Genetics Laboratory, and Taban Laboratory. However, methods for the identification of pathogenic mutations in these labs have not been identified. This study was approved by the Ethics Committee of MCI.

Patients

Nearly 2100 cases from different ethnic groups were referred to HCC of MCI for cancer genetic counseling from the time of its establishment in 2005. Among the 2100 cases, 1049 were estimated as high risk in the genetic counseling process according to the updated versions of NCCN criteria, but just 470 cases (280 families) accepted to be tested and provided written consent to undergo genetic analysis for the detection of *BRCA1/2* mutations. All these cases were referred to HCC by the clinicians of MCI and other centers in the country. In genetic counselling process of each proband, the pedigree of the family was illustrated for at least three generations and all the probands information, including demographic data, past medical history, reproductive state and life style variables related to cancer risk factors.Other family members' important information like cancer type and age at diagnosis and death were gathered as much as possible. High-risk non-affected probands were offered firstly to invite their available youngest affected relative for genetic counseling and genetic testing. Otherwise, the proband herself was tested informing her regarding the disadvantages of such testing.

DNA extraction

Peripheral blood samples were obtained from patients and the genomic DNA was extracted from peripheral blood leukocytes using Promega DNA Purification Kit. Cat no.: A1620 (Promega Corporation, Madison, USA). The quality of DNA was determined by spectrophotometric analysis and gel electrophoresis.

BRCA1 and *BRCA2* entire gene sequencing

All coding exons of *BRCA* genes and at least 20 base pairs of flanking intronic regions were amplified by Sanger sequencing or Next-Generation Sequencing (NGS).

Polymerase chain reaction (PCR) amplification and Sanger sequencing

The entire coding regions plus 20–50 bp of intronic flanking sequences around all coding exons of *BRCA1* (NM_007294.3), *BRCA2* (NM_000059.3) were amplified using 28 and 30 pairs of primers, respectively. After cleaning the PCR product, cycle sequencing was carried out using the ABI 3130 capillary sequencer. Sequencing was performed separately in both forward and reverse directions.

Next-generation sequencing

NGS was used from 2015, especially for those cases with heterogeneous types of cancer in their family. Genetic testing with a multi-gene hereditary cancer panel was performed for some patients. The panel consisted of primer pools that target all coding exons. Following data analysis, annotation of single-nucleotide variants, splice site alterations, and short insertions/deletions were performed. All detected pathogenic variants were confirmed by Sanger sequencing.

Multiplex ligation-dependent probe amplification (MLPA)

Patients without pathogenic variants were selected for MLPA analysis to check the copy number variations (CNV) in *BRCA* genes. MLPA was carried out using the commercial

kits P002-C2 and P002-D1 for *BRCA1* and P090-A4 and P090-B1 for *BRCA2* (MRC-Holland, Amsterdam, The Netherlands) according to the manufacturer's instructions.

Classification of variants

Nomenclature for sequence variants was according to the Human Genome Variation Society recommendation (http://www.hgvs.org). Novel mutations, including nonsense and frame-shift that generated a premature stop codon were classified as pathogenic. Missense variations classified as class 3 or unknown in IARC_LOVD and BIC database were considered to be Variants of Uncertain Significance (VUSs) except those that have been previously reported as pathogenic variants in related literature.

Search strategies

To assess previous studies, we searched the phrases "*BRCA1*", "*BRCA2*", "gene mutations", "breast cancer" and "Iran" in Google Scholar and PubMed to gather all those articles with the same subject about Iran and Iranian BC patients. Only papers were selected that contain at least a confirmed pathogenic variant in either the *BRCA1* or *BRCA2* genes. A total of 2033 cases, were obtained from 19 articles [15–33]. To evaluate the frequency of *BRCA* mutations, we excluded articles that restricted to screening just three Ashkenazi founder mutations and case–control studies [26–33]. After excluding, a total of 11 articles containing 788 cases (760 families) were included in our analysis [15–25].

Results

Among 470 cases (280 families) who accepted to enter to our genetic analysis study, 53 families (135 females and 28 males) were proved to have *BRCA1/2* pathogenic variants. The mean age at diagnosis of *BRCA* positive affected cases was 41.2 ± 6.4, and the mean age of pathogenic variant carriers at the time of referral was 39.5 ± 7.7. Altogether 44 distinct pathogenic mutations were gathered from different cancer centers, 36 (81.8%) from MCI, 5 (11.363%) from other cancer labs (Medical Genetics Laboratory of Genome, GENEOCELL Medical Genetic Laboratory, and Taban Laboratory), and the remaining 3 of the variants (6.8%) were shared by both centers (supplementary files 1 and 2). Among these 44 mutations, 16 had not been previously reported in Iran and 4 out of 16 mutations were novel worldwide (*BRCA1*: Gly183ValfsX36, and *BRCA2*: Ser309HisfsX15, Thr2722AsnfsX8, Gln716ThrfsX3).

Previous studies

In this section, *BRCA* pathogenic variants were collected from reported articles on Iranian patients. A total of 2033 cases, were obtained from 19 articles with at least a confirmed pathogenic variant in either the *BRCA1* or *BRCA2* genes [15–33]. To summarize, 73 kinds of pathogenic *BRCA* variants were obtained from these articles (supplementary file 3). After excluding articles that restricted to screening three Ashkenazi founder mutations and case report studies [26–33], 788 cases (760 families) from 11 studies were included for the evaluation of frequency of *BRCA1* and *BRCA2* pathogenic variants [15–25]. 63 out of 760 families had a confirmed pathogenic variant in either *BRCA1* or *BRCA2*.

Discussion

The discovery of BC-predisposing genes at the beginning of the previous two decades has emerged new concepts and activities in cancer prevention worldwide. Before that, the preventive activities were just limited to lifestyle changes, but nowadays, "Hereditary Cancer Clinics" using "mutation-based preventive protocols" are a principal part of each cancer clinic around the world. The patients and their family members are referred to these clinics based on the criteria of current protocols and the genetic tests are done for the cases that are at significant risk for being a carrier of pathogenic variants, especially in high penetrance genes like *BRCA1/2*. The carriers themselves then will select to participate in preventive or early detection programs according to the information which is given during the genetic counseling process. For each country, it is a critical infrastructure to have a database containing all pathogenic variants of *BRCA* genes and their frequency in the population. Consanguinity rates in some particular countries like Iran are high, and so, there is a more special need to establish such databases due to the higher probability of developing specific-population mutations. Such databases can serve as a guide for risk assessment, genetic counseling of *BRCA* mutation carriers, and also developing population-based screening panels. Targeting to make such a database in Iran, we are collecting all unpublished and published *BRCA* pathogenic variants in the Iranian population. Firstly, *BRCA* mutations were studied in 470 high-risk breast cancer cases (280 families) which were referred to HCC of MCI and other cancer centers in Iran. We extended this study up to 1258 cases (1040 families) by combining our data with published studies involving 788 cases (760 families) [15–25] to assess the spectrum and frequency of *BRCA* mutations in Iranian population more accurately. Combining our data with published studies, 89

Table 1 List of most common BRCA mutations in Iranian families

Number of families	dbSNP rs	BIC:genomiclevel	HGVS:genomiclevel	HGVS protein level	Gene
4	rs80358018	IVS2-1G>C	c.81-1G>C	p.Leu30X	*BRCA1*
3	rs80357713	185delAG	c.66_67delAG	p.Glu23ValfsX17	*BRCA1*
3	rs80357522	2080delA	c.1961delA	p.Lys654SerfsX47	*BRCA1*
3	rs1555591543	1687	c.1568delT	p.Leu523TrpfsX9	*BRCA1*
3	rs80357229	4728	c.4609C>T	p.Gln1537Ter	*BRCA1*
4	rs397507683	3979insA	c.3751_3752insA	p.Thr1251AsnfsX14	*BRCA2*
3	rs80359720	8813insT	c.8585dupT	p.Glu2863ArgfsX6	*BRCA2*

distinct pathogenic *BRCA* variants were reported in this study (supplementary file 4). These mutations in companion with novel mutations introduced in other studies will help us to form a comprehensive source for all of the *BRCA1/2* mutations in all populations. Recently, three Ashkenazi founder mutations in *BRCA1* and *BRCA2* genes, including 185delAG, 5382insC (*BRCA1*) and 6174delT (*BRCA2*) have been detected in many populations [12–14], among these are Byelorussian [34], Icelanders [35], Polish [36], Spanish [37] and Russian [38] populations. The frequency of these mutations has been investigated in several studies in Iranian populations: Bar-Sade et al. carried out the study to determine the prevalence of *BRCA1* 185delAG founder mutation among 150 Iranian Jews, 354 of Moroccan origin, and 200 Yemenites. This mutation was found only in four Moroccan cases (1.1%) [28]. Mehdipour et al. investigated 400 patients with primary BC to determine the prevalence of three founder mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*). In their study, 185delAG was found in three patients from two families. However, the other two mutations, 5382insC in *BRCA1* and 6174delT in *BRCA2*, were not found in any of the 400 patients [31]. The prevalence of these mutations was also evaluated in 250, 55 and 200 BC patients, first degree relatives of patients and healthy women, respectively by Fattahi et al. These mutations were not found in any of the studied groups [33]. Also, *BRCA1* 185delAG founder mutation was not detected in a cohort of 80 patients in the study conducted by Ghaderi et al. [29]. The prevalence of three founder mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*) were determined among 16 patients with familial BC and 18 patients with non-familial BC. A total of three 5382insC mutations were found in 16 familial BC families [32]. Kooshyar et al. reported that 185delAG mutation is seen in patients with BC (2/39) and their first-degree relatives (1/29). Also, only one patient was found to carry the 5382insC founder mutation [30]. In the current study, 116 of 1040 high-risk families were found to carry pathogenic variants in either *BRCA1* or *BRCA2*. To evaluate the frequency of *BRCA* mutations in the Iranian population, we excluded articles that restricted to screening three founder mutations and case reports. Our results showed that the most commonly *BRCA1* mutation was c.81-1G>C (IVS2-1G>C), which was found in 4 of 116 families carrying a *BRCA* pathogenic variant. Also *BRCA1* mutations c.66_67delAG (one of the Ashkenazi founder mutations), c.1961delA (2080delA), c.1568delT (1687delT) and c.4609C>T (Q1537X), each one found in three families. Most commonly *BRCA2* mutations were c.3751_3752insA (3979insA) and c.8585dupT (8813insT), which were found in 4 and 3 families, respectively (Table 1). Our results showed that 20% of families had one of these seven most common mutations (Table 1). Although IVS2-1G>C which is one of the most common mutations in Iran, is infrequent in European population [39]. IVS2-1G>C activates a cryptic splice site within exon 3 that removes the first seven nucleotides of exon 3 [40]. *BRCA1* c.1961delA is one of the pathogenic variants with recurrences above 6.0% in Spain [41] and has also been reported in Asian populations [42, 43]. This study has provided a comprehensive information about the spectrum and frequency of *BRCA* mutations of these two genes in Iran and might be used for designing population-based screening in the future.

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Author contributions KM-A designed and coordinated research and wrote the manuscript. Also patient recruitment and all genetic counsellings of MCI were done by him. SZ performed the experiments, analyzed the data, and collected information from previous studies. NA performed the experiments and analyzed the data. FY wrote the manuscript and collected data from previous studies. RE, LF, AT, and MT have contributed to the interpretation of the data, and the revision of the manuscript. MS and MZ provided us with some of the unpublished data that were collected as part of this study. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare that there are no conflict of interests.

Ethical approval This study with research ethics code IR.ACECR.IBCRC.REC.1397.018 has been approved by the Ethics Committee of MCI.

Informed consent The patients/participants provided their written informed consent to participate in this study.

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