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GENETICS OF BREAST CANCER AMONG MOROCCAN WOMEN: A LITERATURE REVIEW

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ABSTRACT

Introduction: Breast cancer (BC) is a heterogeneous disease defined by the accumulation of various molecular alterations that accord each tumor a specific phenotype. Our study aimed to summarize all studies conducted on genetic alterations associated with BC in Moroccan women. **Methods**: We systematically searched literature databases from the time of inception until 31 August 2021 to collect information concerning the mutation spectrum for BC in Morocco. **Results**: We identified twenty-three studies including 1858 cases. According to our literature search, twenty-nine mutations were detected in 92/468 (19.66%) patients for BRCA1/BRCA2 genes. We captured eighteen mutations dispersed in the exons 2, 3, 5, 11, 16, 17, 18, and 20 of the BRCA1 gene (c.68_69delAG, c.116G>A, c.181T>G, c.798_799delTT, c.3279delC, c.2805delA, c.1016dupA, c.2126insA, c.3453delT, c.2884C>T, c.2596C>T, c.2612C>T, c.1186A>G, c. 1100A>G, c.4942A>T, c.5062-5064delGTT, c.5095C>T and c.5309G>T). Moreover, eleven mutations dispersed in the exons 3, 10, 11, and 14 and intron 6 of the BRCA2 gene were detected (c.289G>T, c.1310_1313delAAGA, c.3381delT, c.5073dupA, c.5116_5119delAATA, c.6322C>T, c.3847_3848delGT, c.5576-5579delTTAA, c.7110delA, c.7235inG and c.517-1G>A). A few case-control studies have focused on the association of polymorphisms (SNPs) with the genetic susceptibility of developing BC in Moroccan cases in other genes. A significant association between MTHFR 677T allele (OR: 2.49, 95% CI: 1.17–5.29, p = 0.017), TP53 72Pro variant (OR 2.2, 95% CI 1.07-4.54, p = 0.03), CYP2D6*3variant (OR=2.08, CI 1.28-3.39, p=0.003) and the risk of developing BC was observed. Additionally, the rs1799793 ERCC2 polymorphism, four SNPs in APOBEC3B, and one SNP in APOBEC3A were significantly associated with BC risk ($p \leq 0.05$). **Conclusion**: This review will allow updating the Moroccan Human Mutation Database. However, large studies including more mutations and polymorphisms are required to determine the prevalence of these mutations in the Moroccan population. This could be very beneficial to guide specific and more effective therapeutic strategies in our country.

Keywords: Breast cancer, BRCA1, BRCA2, Genetic alterations, Morocco; Review; Women.

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INTRODUCTION

Breast Cancer (BC) is the most frequently diagnosed cancer (12%) in women around the world [1]. In 2018, Over 2 million cases of BC were reported, representing 24.2% of all cancers in women worldwide [2]. In less developed countries, BC is the most common cause of death (14.3%), and in developed countries, it is the cause of cancer-related mortality (15.4%) [1]. In Morocco, BC is the main tumor among women, accounting for 34.3% of all female cancers recorded between 2005 and 2007 [3]. The incidence of BC in Morocco is relatively higher than the other Maghreb countries but remains inferior compared to the Western countries where incidence rates are higher than 80 per 100,000 people

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[4].BC is a complex disease characterized by the accumulation of several molecular alterations that give each tumor a specific phenotype [5-7]. Over the past decade, molecular genetics has known a great evolution conceptually and methodologically and have made an outstanding contribution to our understanding of the etiology of genetic diseases [8]. BC results from a series of complex genetic and epigenetic events leading to a malignant transformation of a normal epithelial cell, it can occur in sporadic or hereditary forms. Most cases are sporadic, but 5 to 10 % are due to an inherited predisposition to develop BC, which transmits in an autosomal dominant form with incomplete penetrance [9,10].

Two major genes involved in the pathogenesis of breast and ovarian cancers were identified, the BRCA (breast cancer) genes: BRCA1/BRCA2. They are high penetrance tumor suppressor genes involved in the maintaining of genome integrity. Germline mutations in BRCA1 and BRCA2 account for 10% and 3-5% of ovarian and BCs respectively [11,12]. The BRCA1 and BRCA2 mutations are relatively more common among young women [13]. Therefore, investigations of these genes are of particular interest to Moroccan BC patients who are characterized by their young age to reduce BC mortality [14]. Mutations in these genes explain just a part of the familial aggregation of BC. Furthermore, other susceptibility genes have been implicated in hereditary BC not associated with the BRCA1 and BRCA2 mutations [15], among these genes, TP53 (tumor protein 53) and PTEN (Phosphatase and TENsin homolog) genes. All these mutations are located in high penetrance genes, which means that if the mutation is inherited, BC is probable [16]. The mechanisms underlying the malignant progression of BC have yet to be elucidated. Although many genetic changes are detected in these tumors, the frequency of different genetic alterations is quite low [17]. In recent years, other rare moderate penetrance genes and common alleles with low penetrance have also been identified [18]. The majority of family cases are due to genes of high penetrance but are rare genes [18].

Up to now, a limited number of BRCA1/2 germline mutations have been reported in hereditary breast and/or ovarian cancer (HBOC) in the Moroccan population. The involvement of genes implicated in BC development within Moroccan women is not well known. Understanding the mechanisms underlying the pathogenesis of these diseases should improve their prevention, prognosis, and management. The objective of this article is to review current knowledge on the identified variants of hereditary and sporadic BC in Morocco and on a known familial mutation in healthy Moroccan females with a high risk of developing BC. Thus, the purpose of this study was to summarize all Moroccan genetic studies conducted on genetic alterations associated with BC that should be further studied to improve the prognosis and treatment of Moroccan patients, to reduce BC mortality, and to establish a national genetic database for BC.

MATERIALS & METHODS

Literature search and selection criteria

We conducted a literature review of all articles published on Moroccan patients who presented any form of BC or healthy individuals belonging to families with an elevated risk of developing BC. Five databases were consulted (PubMed, Science Direct, Embase, Scopus, and Google scholar) from the time of inception until August 31, 2021. We used a combination of search terms such as BRCA OR gene OR genetic OR polymorphism OR variant OR SNP OR BRCA1 OR BRCA2 AND (Morocco OR Moroccan) AND (Breast cancer), and Breast cancer AND (Morocco OR Moroccan) AND (gene or genetic) AND (polymorphism or variant or SNP).

For the current paper, all studies conducted on Moroccan patients who presented with any form of BC or healthy individuals belonging to families with an elevated risk of developing BC were considered eligible and all mutations (deleterious and non-deleterious) were also considered. Moreover, we searched the data concerning other continents in order to compare and discuss African results. Mutations are referred according to the BC Information Core (BIC) (http://research.nhgri.nih.gov/bic/) nomenclature.

Data extraction

Two independent investigators extracted data using a standard data collection form. The data were extracted from each study using the following standardized form: first author, publication year, study design, sample size, disease incidence, age, method of mutation detection, mutated genes, type of mutation, hazard ratio or odds ratio, and 95% confidence intervals (CIs).

Results

We made a systematic search of articles published from the time of inception until August 31, 2021, we included any Moroccan study studying the genetic

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mutations involved in BC in Moroccan women (figure 1). Our literature search has captured 23 published reports comprising 1858 cases for analysis and listed in tables 1, 2, and 3. While direct sequencing was the most used technique for BRCA1/BRCA2 (Whole genome sequencing or whole exome sequencing or targeted exon sequencing) , TaqMan SNP (single-nucleotide polymorphism) Genotyping Assay was the most commonly employed method for other genetics polymorphisms. All mutations announced in our analysis were examined over diverse mutation databases as indicated in the methods to estimate the pathogenicity of these mutations and to determine whether they are distinctive to the Moroccan population or not.

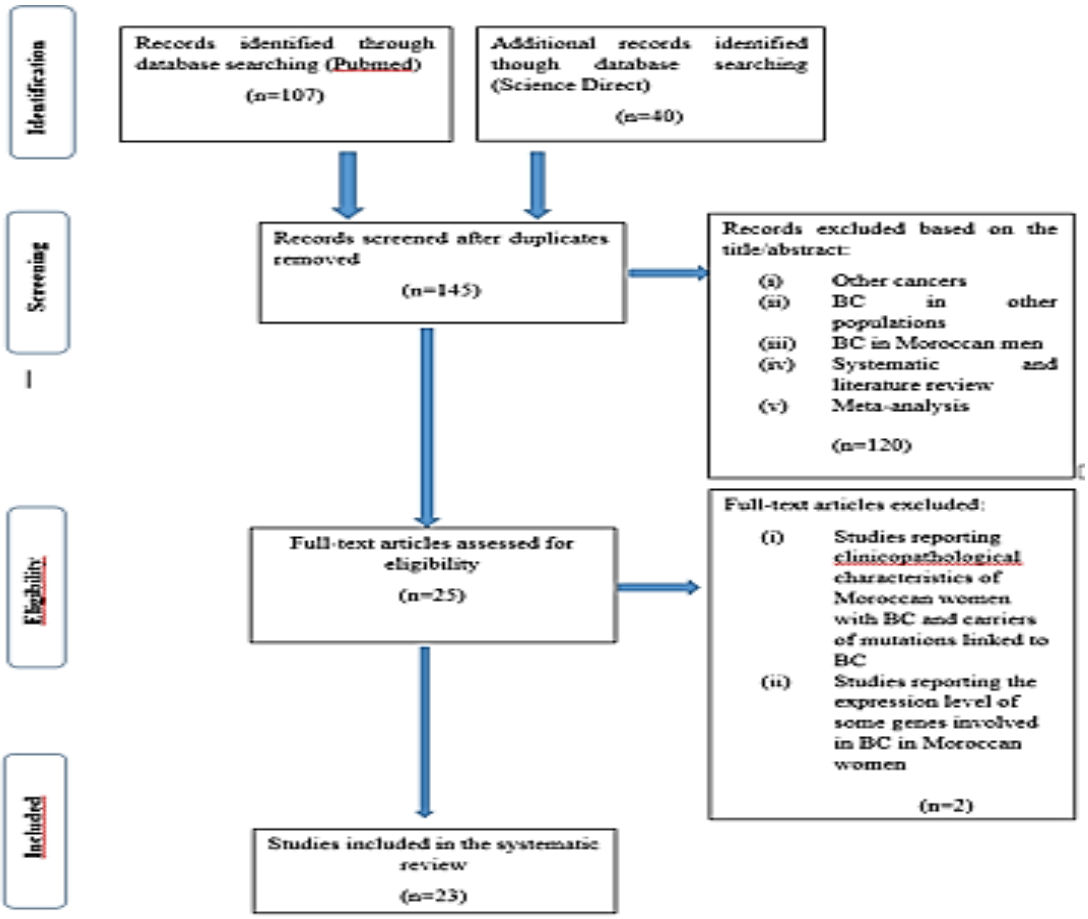

Figure 1: Flow diagram for identifying studies for assessment of breast cancer mutations in Moroccan women

Deleterious BRCA1 mutations among Moroccan women:

Our search strategy captured eighteen mutations located on BRCA1 among Moroccan women with BC [14, 19-27] (Table 1).

The first non-Jewish founder mutation described in North Africa, c.798_799delTT, is the most frequent BRCA1 mutation in Moroccan women and has been investigated in four studies. In the first one performed by Laraqui et al. [19], a total of 121 patients diagnosed with BC were included. The c.798_799delTT mutation was identified in two unrelated cases with HBOC family history. The second one was conducted by Taazite et al. [20] on 40 BC patients with an increased risk of carrying a mutation. The result revealed one familial case from 11 mutated patients who was positive for the c.798_799delTT.The third one was conducted by El Ansari et al. [21] on 49 breast tumors and 18 ovarian tumors. The c.798_799delTT was detected in three unrelated patients (3/49) suffering from BC with an HBOC family history. The last one was performed by Bekkach et al. [22] on 33 cases diagnosed with BC at the age of ≤40 years recruited irrespective of breast and/or ovarian cancer family history. They found that one sporadic case was positive for the c.798_799delTT.

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Table 1: BRCA1 mutation spectrum among Moroccan women with breast cancer.

Genetic variant	Affected Exon	Mutation type	Amino acid change	Number of mutations carriers	Age at diagnosis (years)	Familial (F) or sporadic (S)	References
c.68_69delAG	2	FS	p.Glu23Valfs*17	3	48,42,ni	F	[23, 21]
c.116G > A	3	MS	p.Cys39Tyr	1	≤35	F	[22]
c.181T>G	5	MS	p.Cys61Gly	1	34	F	[20]
c.798_799delTT	11	FS	p.Ser267Lysfs*19	7	44, 40, 42, ni, ≤35	F, S	[19-22]
c.3279delC		FS	p.Tyr1094Ilefs*15	6	32, 49, ni	F	[20,21]
c.2805delA		FS	p.Asp936Ilefs*64	1	41	F	[20]
c.1016dupA		FS	p.Val340Glyfs*6	3	44,46, ni	F	[19, 21]
c.2126insA		FS	p.Phe709TyrfsX3	2	ni, ≤35	F	[27,22]
c.3453delT		FS	p.Asp1151Glufs	1	ni	F	[27]
c.2884C>T		MS	p.Glu962Lys	1	46	F	[26]
c.2596C>T		MS	p.Arg866Cys	1	36	F	[26]
c.2612C>T		MS	p.Pro871Leu	22	[26-65]	F,S	[20, 26, 25]
c.1186A>G	11b	MS	p.? (Q356R)	4	28, 31 ,36, 39	S	[14]
c. 1100A>G		SM	p.? (T327T)	2	36,30	S	[14]
c.4942A>T	16	NS	p.Lys1648X	1	45	S	[19]
c.5062-5064delGTT	17	IFD	p.Val1688del Ilefs*15	1	25	F	[20]
c.5095C>T	18	MS	p.Arg1699Tr	2	44,45	F	[19]
c.5309G>T	20	SNV	p.Gly1770Val	5	30,31,ni	ni	[24]

FS: frame shift, MS: missense, SM: silent mutation, NS: nonsense, IFD: in frame deletion, SNV: single-nucleotide variants, ni: No Information.

The second known founder mutation is the pathogenic mutation BRCA1: c.68_69delAG (formerly 185delAG). In Morocco and for the first time, Laarabi et al. [23] were interested in analyzing BRCA1/2mutations in five healthy women. This investigation revealed that three asymptomatic women were found to be carriers of BRCA1/2 mutations, among them, two sisters with HBOC family history were positive for the BRCA1-185delAG mutation. Recently, this pathogenic variant has been identified in one patient with BC and with an HBOC family history [21].

Besides these founder mutations, Quiles et al. [24] have reported a new founder mutation specific to the Moroccan population by sequencing Five BRCA1 flanking microsatellites. They identified the variant c.5309G>T in 8/11 individuals belonging to five unrelated high-risk families from the north coast of Morocco, and described it as a Moroccan founder variant to be treated as "probably pathogenic."

The BRCA1 c.181T>G (300T>G) mutation was investigated in two studies. The first one was performed by Taazite et al. [20] and was focused on analyzing BRCA1/2 mutations in 40 patients. A total of nine BRCA1 and BRCA2 mutations were found in ten unrelated families, among which two cases with HBOC family history were found to be carriers of the BRCA1-c.181T>G mutation.

Another two small frameshift deletions (c.2805delA/ 2924delA and c.3279delC/ /3398delC) were identified. The first mutation (c.2805delA) was identified for the first time in the study of Taazite et al. [20] in an early onset woman with BC and with HBOC family history. Besides, the second mutation (c.3279delC) was detected in both the proband and her mother of Berber origin diagnosed with BC at ages 32 and 49 respectively, with HBOC family history [20]. In the same context, El khachibi et al. [25], confirmed the presence of these two mutations in one previously sequenced positive control (c.2805delA and c.3279delC) and demonstrate that the HRM approach, which is very sensitive, specific, and cost-effective. In addition, a recent study has identified the c.3279delC in four patients with BC, all with HBOC family history [21].

Taazite et al., [20] have identified for the first time a missense variant (SNP): The c.2612C>T in one familial BC case. Then, El khachibi et al., [25] have identified this SNP in two sporadic samples by the screening of exon 11 of BRCA1 gene. Later, it was found in 70.4% (19/27) of cases with a family history of BC by the screening of exon 11 of the BRCA1 gene [26].

The c.1016dupA BRCA1 missense mutation has been reported in two studies. First, by Laraqui et al. [19] in two unrelated cases (2/121) both diagnosed with invasive ductal carcinoma and with HBOC family history and one of them presented also one variant of unknown significance: The c.1941T>G (p.Ser647Arg). Second, by El Ansari et al. [21] in one patient suffering from BC with HOBC family history.

Another missense mutation; the c.5095C>TBRCA1, has been detected in two unrelated cases, with both invasive ductal carcinoma and both with HBOC family history [19].

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Interestingly, Taazite et al. [14] were the first to identify two mutations for the first time in the Moroccan population by screening exon 2 and exon 11a/b of BRCA1 gene. The first missense mutation is the c.1186A>G (Q356R) was detected in four sporadic cases (04/50). The second one is a silent mutation c. 1100A>G (T327T) and was detected in two sporadic young patients (<40 years old).
A study was conducted by Jouali et al. [27] on 15 Moroccan women with HBOC family history. In BRCA1, they reported two mutations in two unrelated families; the c.2126insA, a frameshift mutation, already listed in the BIC, and the mutation c.3453delT reported for the first time in this study. Then, they concluded that the NGS (next-generation sequencing) approach based on Ampliseq library and Ion Torrent PGM sequencing was efficient, fast, and cheap high-throughout mutation detection method that can be integrated into the public health program for the molecular testing of BRCA genes and the management of genetic counseling of relatives at risk [27]. Moreover, the c.2126insA mutation was detected recently in one familial case with BC [22].
Others BRCA1 mutations were found: c.2805delA, c.5062_5064delGTT, c.4942A>T, c.2884C>T, c.116G > A and c.2596C>T, c.4823C>G and detected only once in a BC case [20, 19, 22, 26 and 21].

BRCA2 mutation spectrum

Our search strategy captured eleven mutations located on BRCA2 among Moroccan patients with BC [19-22, 27, 28] listed in Table 2.
In Morocco, the c.1310_1313delAAGA mutation was investigated in two studies. The first one was performed by Jouali et al. [27] three unrelated patients with HOBC family history (3/15) from the North-East of Morocco were found positive for this mutation. The second one was performed by Laarabi et al. [28] to assess the c.1310_1313delAAGA frequency and its geographic distribution. This frameshift mutation was detected in 14/122 BC patients analyzed for at least exon 10 of the BRCA2 gene. All patients had BC diagnosed at age 50 or younger and/or positive family history. Moreover, they noticed that the c.1310_1313delAAGA mutation was frequent in patients from the North-East region of Morocco and absent in any of the other patients originated from other regions, suggesting a founder effect of this mutation in this restricted geographic area of the country. In the same region, a recent study was conducted on 33 BC cases from the North of Morocco and detected for the first time the c.5116_5119delAATA-BRCA2 mutation in one BC patient with a family history of cancer [22]. In addition, they suggested that this mutation has a founder effect in North Africa.
The BRCA2 c.7235insG has been described for the first time by Taazite et al. [20] in two unrelated families with a frequency of 5.12% (2/39) with a positive family history of BC. In the same context, Jouali et al. [27] have identified this pathogenic mutation in one BC patient from a high-risk family.
Another frameshift mutation in the BRCA2 gene: the c.7110delA/7338delA, reported for the first time by Taazite et al. [20] and recently by El Ansari et al. [21]. This mutation was unique and detected only once in a BC case with an HBOC family history.
The c.3381delT/3609delT (p.Phe1127Leufs*23) has been reported for the first time by Taazite et al. [20] and has been detected only once in an early onset BC case with HBOC family history. The investigators of the same study have identified another BRCA2 mutation (c.517-1G>A/IVS6-1G>A) in a sporadic BC case [20]. Besides these mutations, an unknown variant (UV) was detected in a BC case (c.7462A>G (7690A>G)) and was predicted to be possibly damaging with a score of 1.000, and thus, this variant may be pathogenic [20].
Recently, two studies have identified for the first time three single mutations that were not previously reported in BIC, but have already been described in the literature. The c.5576-5579delTTAA [21], the c.3847_ 3848delGT [21], and the c.289G> T [22]. These pathogenic mutations were unique and detected only once in a BC patient with an HBOC family history. Another BRCA2 polymorphism: c.6322C > T with conflicting interpretations of pathogenicity was also identified in one Moroccan familiar BC case [22].

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Table 2: BRCA2 mutation spectrum among Moroccan women with breast cancer.

Genetic variant	Affected Exon	Mutation type	Amino acid change	Number of mutations carriers	Age at diagnosis (years)	Familial (F) or Sporadic (S)	References
c.289G > T	3	NS	p.Glu97Ter	1	[28-35]	F	[22]
c.1310_1313delAAGA	10	FS	p.Lys437IlefsX22	17	ni	F	[27, 28]
c.3381delT	11	FS	p.Phe1127Leufs*23	1	38	F	[20]
c.5073dupA		FS	p.Trp1692Metfs*3	1	48	F	[19]
c.5116_5119delAATA		FS	p.Asn1706Leufs	1	[36-40]	F	[22]
c.6322C > T		MS	p.Arg2108Cys	1	[36-40]	F	[22]
c.3847_3848delGT		FS	p.Val1283fs	1	ni	F	[21]
c.5576-5579delTTAA		FS	p.I1859fs	1	ni	F	[21]
c.7110delA	14	FS	p.Lys2370Asnfs*6	2	38, ni	F	[20, 21]
c.7235inG		FS	p.Thr2412Serfs	3	40, 45, ni	F	[20,27]
c.517-1G>A	Intron 6	SS	p.Arg2484His	1	38	S	[20]

NS: nonsense, FS: frame shift, MS: missense, SS: splice site substitution, ni: No Information.

The last mutation is the BRCA2-c.5073dupA, identified by Laarabi et al. [23] in one asymptomatic woman belonging to a high-risk family.

Other variants detected in Moroccan women with BC:

For the other genetic variants detected in Moroccan women with BC, our search strategy captured twelve studies [29-40] listed in Table 3.

For the first time, a Moroccan case-control was conducted by Rahoui et al. [29] to investigate the association of four studied SNPs of the vascular endothelial growth gene (VEGF-A), with BC susceptibility in Moroccan women. They demonstrated that three of the SNPs studied (-1154A/G, -2578C/A, -634G/C, -460T/C) might have a protective effect against BC in Moroccan women: -1154A/G (p=0.018), -2578C/A (p=0.022) and -460T/ (0.043) [29].

Another case-control study was performed by Diakite et al. [30] to examine if the MTHFR C677T polymorphism modulates the risk of developing BC in Moroccan women. They found a significant association between the MTHFR 677T allele with the risk of developing BC in Moroccan women with OR= 1.59, which suggested that women with T allele have a higher risk of BC. Interestingly, they reported a significant association between MTHFR C677T polymorphism and the expression status of progesterone receptors (p = 0.04) [30]. The same result was confirmed later by Hardi et al. [31] (p=0,017). Moreover, this last study genotyped another MTHFR polymorphism (rs1801131 (A1298C)) and ERCC2 polymorphisms (rs1799793 (G934A) and rs13181 (A2251C)). They are the first to assign an increased BC risk to ERCC2-rs1799793 (Asn312Asn) polymorphism (OR: 2.90, 95% CI: 1.34–6.26, p = 0.0069). For the two other SNPs, they found that they had a small influence that can be identified in a larger number of participants [31].

Interestingly, It was shown for the first time a significant association between the homozygous genotype of TP53 72Pro variant and a higher BC risk (OR 2.2, 95% CI 1.07-4.54, p = 0.03) [32] in the Moroccan population. On the contrary, they showed that the Arg/Arg homozygous genotype was associated with a protective effect against BC (OR 0.45, 95% CI 0.22-0.93, p=0.03) [32].

Considering the potential function of CHEK2, Maarouf et al. [33] conducted a case-control study and they observed an absence or rarity of the variant CHEK2*1100delC heterozygosity among Moroccan women with BC.

A population-based case-control Moroccan study has examined 36 SNPs in 13 genes (APOBEC3A, APOBEC3B, ARID1B, ATR, MAP3K1, MLL2, MLL3, NCOR1, RUNX1, SF3B1, SMAD4, TBX3, and TTN) [34]. They revealed 12 SNPs in eight driver genes, four SNPs in APOBEC3B (Apolipoprotein B Editing Complex), and one SNP in APOBEC3A that were significantly associated with BC risk and/or clinical ($p \leq 0.05$). RUNX1_rs8130963 (p= 0.0005), TBX3_rs8853 (p = 0.0003), TBX3_rs1061651 (p = 0.0002), TTN_rs12465459 (p = 0.0009), were the most significantly associated SNPs with BC risk, conversely to the other driver gene that did not reveal an important role in BC risk. Moreover, they observed a strong association with clinical outcomes for SMAD4_rs3819122 with tumor size (p = 0.009) [34]. However, no significant association between APOBEC3 deletion polymorphism and BC risk was confirmed in the Moroccan population [34].

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Table 3: Panel of genes studied in the Moroccan women with breast cancer.

Genes	Variants	Studies	Detection Methods	Cases (n)	Controls (n)	OR	95% CIs	P-value	References
VEGFA	-1154A/G -2578C/A -634G/C -460T/C	Rahoui et al	TaqMan assay	70	70	2,25 2 ,26 2,63 2,12	[1.14–4.42] [1.12–4.58] [1.19–5.84] [1.01–4.43]	0,018 0,022 0,045 0,043	[29]
MTHFR	C677T	Diakite et al. Hardi et al.	PCR-RFLP TaqMan assay	96 151	117 156	1,59 2,49	[1.04-2.44] [1.17-5.29]	0,030 0,017	[30] [31]
ERCC2	rs1799793-AA	Hardi et al.	TaqMan assay	151	156	2.90	[1.34-6.26]	0,00069	[31]
TP53	PIN3 Ins16bp c.215G>C 72Pro c.215G>C Arg72	Maarouf et al Ayoubi et al.	PCR assay PCR-RFLP assay	105 126	114 126	1,07 2,2 0,45	[0,58-1,97] [1,07-4,54] [0,22-0,93]	0,830 0,03 0,03	[38] [32]
CHEK2	1100delC	Maarouf et al.	ASO-PCR	134	114				[33]
ATM	c.7271T > G c.1066–6T > G	Maarouf et al.	PCR-RFLP assay	163	150				[39]
APOBEC3A APOBEC3B ARID1B ATR MAP3K1 NCOR1 RUNX1 SMAD4 TBX3 TTN	rs17370615 rs6001376 rs28401571 rs1065184 rs73013281 rs2227928 rs832583 rs178831 rs8130963 rs17227210 rs12456284 rs8853 rs2242442 rs10616551 rs12465459 rs12463674	Maarouf et al.	TaqMan Assay	226	200	1,63 2,15 0,54 1,88 1,62 1,68 3,37 2,22 2,25 1,80 2,04 2,04 1,47 2,14 2,02 1,65	[0,67-3,95] [1,16-4,00] [0,32-0,91] [1,03-3,42] [1,05-2,50] [1,14-2,49] [1,20-9,47] [1,00-4,95] [1,42-3,56] [1,18-2,74] [1,32-3,15] [1,38-3.01] [1,18-2,55] [1,43-3,18] [1,33-3,07] [1,11-2,47]	0,2826 0,0148 0,0212 0,0385 0,0293 0,0090 0,0210 0,0500 0,0005 0,0066 0,0013 0,0003 0,0050 0,0002 0,0009 0,0140	[34]
ABCB1	C3435T	Taazite et al.	PCR-RFLP assay	60	68	0,7	[0,35-1,41]	0,370	[40]
PIK3CA AKT1 PTEN	Hot spot regions	Jouali et al.	Ion Torrent Ampliseq	39					[35]
CYP2C19	*CYP2C19*2* *CYP2C19*3* *CYP2C19*17*	Elouilamine et al.	PCR-RFLP assay	220	220	1,00 1,00 1,00	[0,64-1,59] [0,54-2,24] [0,81-2,40]	0,945 0,77 0,226	[36]
CYP2D6	*CYP2D6*3* *CYP2D6*4* *CYP2D6*10*	Elouilamine et al.	PCR-RFLP assay	220	220	2,08 1,22 1,15	[1,28-3,39] [0,72-2,07] [0,68-1,94]	0,003 0,447 0,594	[37]

PCR: polymerase chain reaction, PCR-RFLP: Polymerase chain reaction-Restriction Fragment Length Polymorphism, ASO-PCR: Allele-specific oligonucleotide polymerase chain reaction, Ampliseq: Amplification of sequence

A retrospective study conducted by Jouali et al. [35] analyzed the clinicopathological and molecular characteristics of the PI3K/AKT/PTEN pathway in Moroccan triple-negative BC (TNBC) patients. PIK3CA hotspot mutations were detected in five patients with TNBC (13%); one somatic mutation c.1633G > A p.E545K located in exon 9 which were found in 1/39 TNBC (2.5%) and 4/39 in exon 20 (10.26%). Moreover, no association between the mutational status of PIK3CA, clinical data, and clinicopathological features were detected [35].

Two Recent case-control studies were performed to assess the association of CYP2C19 polymorphisms (CYP2C19*2(rs4244285), CYP2C19*3(rs4986893) and CYP2C19*17(rs12248560)) [36] and CYP2D6 polymorphisms (CYP2D6*3 (A2549del), CYP2D6*4 (G1934A), and CYP2D6*10 (C100T) [37] with BC risk in Moroccan women. On the one hand, none of the CYP2C19 polymorphisms was significantly associated with BC risk [37]. However, they suspected a possible association between the CYP2C19*3 variant and triple-negative BC (P=0.02) [36]. On the other hand, a significant association between CYP2D6*3 (A/del) genotype and BC risk was detected in Moroccan women with BC (P =0.003) [36].

Finally, The PIN3 Ins16 bp polymorphism of the TP53 gene, the c.7271T > G, and c.1066–6T > G (IVS10–6T > G) ATM variants and the ABCB1 C3435T polymorphism were investigated in other Moroccan studies [38-40], however, no significant association was revealed between these polymorphisms and BC risk in Moroccan women.

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DISCUSSION:

According to the literature, the c.798_799delTT BRCA1mutation was found the most frequent and has been investigated in four studies [19-22] (Table 1). To our knowledge, **t**he BRCA1 c.798_799delTT mutation was also found recurrent in two North African countries, Algeria [41,42] and Tunisia [43] but absent in the other African regions, suggesting the first non-Jewish founder mutation to be described in this area [44]. This mutation was also observed in some close Mediterranean countries, in particular, Spain [45], Italy [46], and France [47]. The migration flow history and geographical proximity could explain this result [14]. The second most common mutation is the pathogenic mutation BRCA1: c.68_69delAG, which contributes to 16-20% of BC cases diagnosed before the age of 50 [48]. This mutation was identified first in two asymptomatic sisters with an elevated risk of BC [23] and second in one patient with BC [21]. This mutation was found also in two independent screening tests of the Jewish and non-Jewish Moroccan populations [49]. Moreover, the c.68_69delAG/185delAG mutation is one of the three founder mutations including the 5382insC in the BRCA1 gene and 6174delT in the BRCA2 gene, which have been identified in Ashkenazi Jews [50] and were identified in Egyptian women [51,52]. It was also described in many other ethnicities including Asian, American, African, and European populations [53]. Thus, further investigations with larger sample cohorts with this mutation are going to confirm the presence or absence of the founder aspect.

A Spanish follow-up study [24] has reported a new founder mutation in five Moroccan families, the c.5309G>Tp. (Gly1770Val) located in the BRCT tandem domain of the BRCA1 gene specific to the Moroccan population. In another study, it was illustrated that both segregation and tumor histopathological data demonstrate that BRCA1 c.5309G>T p. (Gly1770Val) portrayed the clinical characteristics of a high-risk pathogenic BRCA1 variant [54]. However, comprehensive studies of this mutation in a large series of Moroccan BC patients are needed to assess the real prevalence [24].

The fourth variant is the BRCA1 c.181T>G (300T>G) mutation that was investigated in one study [20] (Table 1). Our literature review revealed that this mutation is one of the most frequent founder mutations identified in Central Europe populations [55] and has been also identified in Algerian [42] and Egyptian studies [51]. In addition, haplotype analysis of Maghrebian and central European carriers of the BRCA1mutation c.181T>G may reveal whether the origin of this mutation in Maghrebian populations is linked to the Vandals, an East Germanic tribe, who invaded and established a kingdom in North Africa during antiquity [56]. We captured another founder mutation, the c.1016dupABRCA1that has been described as one of four founder mutations originating from the Eastern population of Norway [57]. This mutation has been reported for the first time in a Moroccan cohort [19], and then in a recent study [21]. According to the BIC database, this pathogenic mutation is the 12th most common frame-shift mutation occurring in BRCA1 [53].

The BRCA1 c.5062_5064delGTT mutation (5181delGTT) was identified in Moroccan families [20]. It represents the most frequent mutation in Northeast Italy and has been confirmed to be pathogenic using several independent approaches [58]. The c.5095C>TBRCA1mutation was identified in two unrelated cases [19]. Interestingly, functional and cosegregation data strongly suggested that this mutation is deleterious and predisposes carriers to breast and ovarian cancers [59-61]. Consequently, we can conclude that the c.5095C>T mutation can explain some of the BC cases in the Moroccan population [19].

The c.1186A>G (Q356R); a single nucleotide mutation (A>G) was detected in four Moroccan cases [14]. In the same study, another silent mutation, c.1100A>G (T327T), was detected for the first time in two young Moroccan cases. This last mutation is a single mutation that does not affect the BRCA1 protein composition but might play a role in exon skipping, as reported by Anczukow et al. [62]. Further studies with a large number of patients are needed to assess whether these two mutations (Q356R and T327T) have a founder aspect in the Moroccan population because of their high frequency (4-8% of patients) found in this study [14]. Interestingly, another BRCA1 variant: c.3279delC, was detected for the first time in Morocco in two women of Berber origin [20] and second identified in 4 Moroccan cases with BC [21]. In the world, this mutation was first reported in 2005 by van der Hout et al. in the Netherlands [63], and then in the USA by Strom et al. [64] in 2015. The high prevalence of this variant in the recent Moroccan cohort [21] and the fact that it has been reported many times in Morocco state the probability of whether it is a founder mutation in our population [21]. Therefore, more studies with a large number of Moroccan patients are needed to assess its founder

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aspect. The most common SNP in this series was the c.2612C>T, identified in the majority of familial cases (19/27) [26] and was described previously in Moroccan women with familial and sporadic BC [20, 25]. In Algeria, this variation was detected in 30.2% of cases [65]. As mentioned in the literature, the heterozygote form was more frequent in the African population while the homozygous form was the most frequent in the European [66].

Moreover, the c.3453delT mutation was reported for the first time in the first Moroccan study to use NGS for the BRCA1 and BRCA2 genes. In addition, this mutation was predicted to be deleterious in silico [27]. Our search strategy revealed that the most common BRCA2 mutation in the Maghreb region (Algeria, Morocco, and Tunisia) is the c.1310_1313delAAGA. In Morocco, this mutation was identified first in 3 unrelated patients [27], and second in 14 BC patients [28]. Interestingly, the two studies showed that the c.1310_1313delAAGA mutation was frequent in patients from the North-East region of Morocco. According to these findings, it was proposed to screen firstly, in public health strategies, the c.1310_1313delAAGA mutation in patients originated from the North of Morocco. However, this mutation was classified as a founder mutation in Europe [67] and the Tunisian population [68]. In Algeria, it was detected in one family among 10 with BRCA mutations [42]. The common genetic inheritance of Moroccans and Europeans suggests a common founder ancestor for this mutation between those populations [69].

The BRCA2c.7235insG (7463insG) has been revealed in two unrelated families with a frequency of 5.12% (2/39) (20) and in one BC patient [27]. However, other studies with a large number of BC cases are needed to determine whether it is a recurrent mutation in our population.

For the other BRCA2 mutations (c.5116_5119delAATA, c.3381delT, c.7110delA, c.517-1G>A, the c.5576-5579delTTAA, c.3847_3848delGT, c.289G >T and c.5073dupA) found in one individual each [20-22], other studies with a large number of Moroccan BC cases are needed to assess their prevalence.

A few case-control studies have focused on the association of SNPs with the genetic susceptibility of developing BC in Moroccan cases in other genes (Table 3). For the first time, the analysis of four SNPs of VEGF-A gene with BC susceptibility in Moroccan women showed that 3 of the SNPs studied might have a protective effect against BC in Moroccan women: -1154A/G (p=0.018), -2578C/A (p=0.022), and -460T/ (0.043) [69]. These SNPs may be considered as a low-penetrance BC risk gene that can be used as genetic biomarkers of BC susceptibility [69]. In addition, the VEGF-A appeared recently as the best candidate for cancer diagnostics (higher than the commonly used tumor marker: CA 15-3) specifically in stages I and II of BC [70].

A significant association between MTHFR C677T polymorphism with the risk of developing BC in Moroccan women with OR= 1.59, which suggests that women with T allele have a higher risk of BC [30]. Interestingly, they are the first to assign an increased BC risk to ERCC2-rs1799793 (Asn312Asn) polymorphism; an essential gene involved in the DNA damage repair pathway. However, other international studies reported that there was no significant association regarding populations from China, North America, or Europe [71-76], which suggests a probable role of the environment, ethnic diversity, and variable genetic background in cancer development [31].

It is known that The CHEK2 1100delC mutation has been reported to confer a high risk of BC among carriers [77,78]. An absence or rarity of the variant CHEK2*1100delC heterozygosity was observed among patients with BC in the Moroccan population [33]. However, the highest frequency has been described in Northern and Eastern European countries [74,76] and a very low frequency of CHEK2 1100delC mutation in North American populations was reported [77]. This difference can be explained by ethnic or geographic variations, which underlines the importance of considering the ethnic background before offering a genetic test [33].

For the first time, it was shown that there is a strong association between the RUNX1_rs8130963 (p= 0.0005), TBX3_rs8853 (p = 0.0003), TBX3_rs1061651 (p = 0.0002), TTN_rs12465459 (p = 0.0009) and BC risk [34].The study suggested a potential role of APOBEC3A and APOBEC3B in BC susceptibility. However, to verify the influence of these polymorphisms, other large studies are needed.

In Morocco, No significant association between ABCB1 C3435T polymorphism and BC was confirmed [40]. The ABCB1 gene encodes the P-gp protein; an ATP-dependent efflux pump that grants cells to eliminate toxins and carcinogenic elements [79]. However, In Egypt, Fawzy et al. [80] screened 190 Egyptian women with BC and reported that the frequency of the TT genotype (OR = 1.45; 95 % CI = 1.09–1.94; P = 0.01) and T allele (OR = 2.41; 95 % CI = 1.27–4.56; P = 0.0006) were significantly higher in BC patients compared to controls. Moreover, they demonstrated that the implication of the C3435T variant on the risk of BC

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risk is influenced by ethnicity. Thus, a large case-control study (at least 340 BC cases and 340 controls) including more polymorphisms in the ABCB1 gene implicated in the development of BC in Moroccan women may show more reliable results [40].

On the one hand, It was shown for the first time in Morocco a high positive correlation between the Pro/Pro homozygous genotype of TP53 variant and BC risk (OR 2.2, 95% CI 1.07-4.54, p= 0.03) [32]. Similarly, this variant is associated with BC in many populations [81-91]. Moreover, a meta-analysis from 41 studies conducted by Gonçalves et al., [92], reported an increased BC risk due to the TP53Pro allele variant dominant model. On the other hand, a decreased BC risk was noted in correlation with TP53 Arg/Arg homozygous genotype (OR0.45, 95% CI 0.22-0.93, p=0.03) [32]. These results are in agreement with a Tunisian study [93] suggesting a protective effect of the TP53 Arg72 variant against BC. Therefore, further studies with a larger sample size are recommended to confirm if the p. (Arg72Pro) polymorphism can be considered as a genetic marker for predisposition to BC in the Moroccan population [32].

A recent study found that carriers of CYP2D6*3delA; a CYP2D6 polymorphism, look to be at high risk of developing BC in Moroccan women (OR= 1.90, 95% CI (1.20 -3.00), P = 0.005) [37]. In this previous study, the prevalence of CYP2D6*3 was higher compared to other ethnicities [94], hence the need for further Moroccan studies to confirm this finding.

No significant association between PIN3 Ins16bp; polymorphism of the TP53 gene and BC risk (OR=1.07) was observed [38], that may be due to the small sample size because an association between this variant and BC risk was observed in studies with larger samples counting more than 500 subjects [95]. The same results were observed for the c.7271T > G and c.1066–6T > G (IVS10–6T > G) ATM variants in Moroccan BC cases [39]. Moreover, no risk variation was found in CYP2D6*4, CYP2D6*10, CYP2C19*2, CYP2C19*3, and CYP2C19*17 variants [36]. Finally, there is a crucial need to perform larger or/and combined association studies to analyze genes mutations implicated in BC in Moroccan women instead of only BRCA1/2.

CONCLUSION

This literature review will allow for an update of the Moroccan Human Mutation Database that lists mutations reported in the Moroccan population. We can conclude from the analysis of the genetic studies in our country reported in this review search that the screening of genes and mutations related to BC in Morocco is not well illustrative. Therefore, more comprehensive studies of a large series of BC Moroccan patients are needed to determine the exact prevalence of these mutations in the Moroccan population and their geographical distribution. Given That the frequency of BC is still increasing, we are asking for the introduction of genetic counselling to deal with this global burden. It is also crucial to support researchers in Morocco to identify other recurrent mutations that could facilitate the genetic testing procedure for the Moroccan population by targeting these mutations as a first step. This could be very beneficial to guide specific and more effective therapeutic strategies.

LIST OF ABBREVIATIONS:

- APOBEC3: Apolipoprotein B Editing Complex.
- BC: Breast cancer.
- BIC: BC Information Core.
- BRCA1: Breast cancer 1.
- BRCA2: Breast cancer 2.
- BRCT: BRCA1 COOH terminus.
- CASP-3: Caspase-3.
- CHEK2: Checkpoint kinase 2.
- CIs: confidence intervals
- CYP2C19: Cytochrome P450 2C19
- CYP2D6 : Cytochrome P450 2D6
- HBOC: Hereditary breast and ovarian cancer.
- MDM2: Murine double minute 2.
- MTHFR: Methylenetetrahydrofolatereductase.
- NGS: Next generation sequencing.
- PGM: Personal Genome Machine.
- PTEN: Phosphatase and TENsin homolog.
- SNP: Single-nucleotide polymorphism.
- TNBC: Triple negative breast cancer.
- TP53: Tumor protein 53.
- UV: Unknown variant.
- VEGF-A: Vascular endothelial growth A.

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