Prevalence of specific and recurrent/founder pathogenic variants in BRCA genes in breast and ovarian cancer in North Africa

Oubaida Elbiad (✉ obdo90@gmail.com)
Laboratoire de Biodiversité, Ecologie et Génome, Faculté des Sciences, Université Mohammed V, Rabat

Abdellah Laraqui
Laboratoire de Recherche et de Biosécurité P3, Hôpital Militaire d'Instruction Mohammed V, Rabat

Fatima Boukhrissi
Laboratoire de Biochimie-Toxicologie, Hôpital Militaire Moulay Ismail Meknès, Faculté de Médecine et de Pharmacie, Université Sidi Mohamed Ben Abdellah, Fès

Chaimae Mounjid
Laboratoire de Recherche et de Biosécurité P3, Hôpital Militaire d'Instruction Mohammed V, Rabat

Meryam Lamsissi
Laboratoire de Virologie, Microbiologie, Qualité, Biotechnologies/Ecotoxicologie et Biodiversité, Faculté des sciences et techniques, Mohammadia, Université Hassan II, Casablanca

Hicham Elannaz
Unité de séquençage, Centre de virologie, des maladies infectieuses et tropicales, Hôpital militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Université Mohammed V, Rabat

Amine Idriiss Lahou
Unité de séquençage, Centre de virologie, des maladies infectieuses et tropicales, Hôpital militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Université Mohammed V, Rabat

Jaouad Kouch
Service d'Oncologie Médicale, Hôpital Militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Rabat

Khadija Benchechkroune
Service d'Oncologie Médicale, Hôpital Militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Rabat

Mohammed Ouakabi
Laboratoire d'Anatomopathologie, Hôpital Militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Rabat

Yassir Sbitti
Service d'Oncologie Médicale, Hôpital Militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Rabat

Hafsa Chahdi
Laboratoire d'Anatomopathologie, Hôpital Militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Rabat

Moulay Mustapha Ennaji
Laboratoire de Virologie, Microbiologie, Qualité, Biotechnologies/Ecotoxicologie et Biodiversité, Faculté des sciences et techniques, Mohammadia, Université Hassan II, Casablanca

Rachid Tanz
Service d'Oncologie Médicale, Hôpital Militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Rabat

Mohammed Ichou
Service d'Oncologie Médicale, Hôpital Militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Rabat

Khalid Ennibi
Laboratoire de Virologie, Centre de virologie, des maladies infectieuses et tropicales, Hôpital militaire d'Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Université Mohammed V, Rabat

Bouabid Badaoui
Laboratoire de Biodiversité, Ecologie et Génome, Faculté des Sciences, Université Mohammed V, Rabat

Yassine Sekhsokh
Laboratoire de Recherche et de Biosécurité P3, Hôpital Militaire d'Instruction Mohammed V, Rabat
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Abstract

Background

Elucidation of specific and recurrent/founder pathogenic variants (PVs) in BRCA (BRCA1 and BRCA2) genes can have an impact on breast cancer (BC) and/or ovarian cancer (OC) risk, making genetic testing affordable and accessible.

Methods

To establish the knowledge about BRCA PVs and to determine the prevalence of the specific and recurrent/founder variants in BRCA genes in BC and/or OC women in North Africa, a systematic review was conducted in Morocco, Algeria, and Tunisia.

Results

Search of the databases yielded 25 relevant references, including eleven studies in Morocco, five in Algeria, and nine in Tunisia. Overall, 15 studies investigated both BRCA1 and BRCA2 genes, four studies examined the entire coding region of the BRCA1 gene, and six studies in which the analysis was limited to a few BRCA1 and/or BRCA2 exons. Overall, 76 PVs (44 in BRCA1 and 32 in BRCA2) were identified in 196 BC and/or OC patients (129 BRCA1 and 67 BRCA2 carriers). Eighteen of the 76 (23.7%) PVs [10/44 (22.7%) in BRCA1 and 8/32 (25%) in BRCA2] were reported for the first time and considered to be novel PVs. Among those identified as unlikely to be of North African origin, the BRCA1 c.68_69del and BRCA1 c.5266dupC Jewish founder alleles and PVs that have been reported as recurrent/founder variants in European populations (ex: BRCA1 c.181T > G, BRCA1 c1016dupA). The most well characterized PVs are four in BRCA1 gene [c.211dupA (14.7%), c.798_799delTT (14%), c.5266dup (8.5%), c.5309G > T (7.8%), c.3279delC (4.7%)] and one in BRCA2 [c.1310_1313delAAGA (38.9%)]. The c.211dupA and c.5309G > T PVs were identified as specific founder variants in Tunisia and Morocco, accounting for 35.2% (19/54) and 20.4% (10/49) of total established BRCA1 PVs, respectively. c.798_799delTT variant was identified in 14% (18/129) of all BRCA1 North African carriers, suggesting a founder allele. A broad spectrum of recurrent variants including BRCA1 3279delC, BRCA1 c.5266dup and BRCA2 c.1310_1313delAAGA was detected in 42 patients. BRCA1 founder variants explain around 36.4% (47/129) of BC and outnumber BRCA2 founder variants by a ratio of ≈ 3:1.

Conclusion

Testing BC and/or OC patients for the panel of specific and recurrent/founder PVs might be the most cost-effective molecular diagnosis strategy.

Introduction

Breast cancer (BC) became the most common cancer globally as of 2021, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases [1]. According to the GLOBOCAN Cancer Tomorrow prediction tool, incident cases are expected to increase by more than 46% by 2040. The increasing global BC burden is mainly observed in low- and middle-income countries, particularly women under the age of fifty [2]. The rapid changes in diets and lifestyles, built and social-cultural environments brought by growing economies and an increase in the proportion of women in the industrial workforce have had an impact on the prevalence of factors associated with increased BC risk - postponed pregnancy, having fewer number of children, excessive total and abdominal body fat and physical inactivity - have resulted in a convergence toward the risk factor profile of countries in Western Europe and narrowing international gaps in BC morbidity [1].

BC incidence rates uniformly increased rapidly in transitioning countries. Some of the most rapid increases are occurring in North Africa, including Morocco, Algeria, Tunisia, Libya, and Mauritania. The incidence of BC among North African women aged 15 to 49 is lower than in Western countries, but the very low incidence among women aged more than 50, combined to the young age pyramid of North Africa, makes the relative proportions of young patients substantially higher (50 to 60% versus 20% in France) [3]. The size and grade of breast tumors in North Africa are increased, while the median age of onset (48) is more than ten years younger than the European/North American median of 61 [4], and is often diagnosed in premenopausal women. The relative frequency of triple-negative and inflammatory BC is also higher [3]. The combination of lower incidence and lower age of onset of BC in North Africa suggests that
genetic factors such as pathogenic variants (PVs) in \textit{BRCA} (\textit{BRCA1} and \textit{BRCA2}) genes may contribute to a larger proportion of BC overall.

Prevalence and PV distribution of \textit{BRCA} genes can vary in different regions and among different ethnic groups due to specific and recurrent/founder variants. Founder variants originated from an ancestor population and maintained over time, were observed in specific geographic areas \cite{5}. Significant evidence from founder mutation has been described in Ashkenazi Jewish, Icelandic, French-Canadian, Brazilian and Italian populations \cite{5}. Traditionally, well-documented founder \textit{BRCA} PVs have been instrumental to informed prioritization strategies for time- and cost-effective genetic testing and prompt identification of carrier individuals \cite{61}. Given the high rates of consanguinity and endogamy marriage culture among the North African populations, it seems plausible that specific and recurrent/founder \textit{BRCA} PVs may be detected in the region. Rebbeck et al. investigated 1650 and 1731 unique PVs in \textit{BRCA1} and \textit{BRCA2} genes, respectively, from 29,700 families worldwide and observed distinct variation in PV type or prevalence by geographical region and race/ethnicity \cite{7}. Racial and ethnic differences can play an important role in hereditary breast carcinomas through its associations with specific and recurrent/founder variants. The purpose of this review is to establish the knowledge about \textit{BRCA} PVs and to determine the prevalence of the specific and recurrent/founder variants in \textit{BRCA} genes in BC and/or OC women in Morocco, Algeria and Tunisia. It seems that no surveys on \textit{BRCA} PVs have yet been conducted in Libya and Mauritania, therefore no data are available.

**Methods**

We conducted a systematic review of all literature published on the \textit{BRCA} PVs spectrum and frequencies in BC women in North Africa. PubMed, Science Direct and Google Scholar were searched up to June 2021 for eligible studies using the following keywords: “breast cancer”, or “breast tumor”, or “adenocarcinoma of the breast”, or “\textit{BRCA} genes”, or “\textit{BRCA1} gene”, or “\textit{BRCA2} gene”, or “\textit{BRCA} pathogenic variant”, or “\textit{BRCA} mutation”, or “\textit{BRCA} prevalence” or “\textit{BRCA} frequency”, or “\textit{BRCA} rate” or “\textit{BRCA} incidence”. An additional literature search was also conducted using North Africa and specific country names belonging to the considered region and any other variant names for any of North Africa countries (ex: Mediterranean countries, Maghreb, Arab population). We manually checked reference lists of the included studies and relevant reviews to identify additional studies. We also searched relevant abstracts reported in the most important multi-disciplinary societies of medical oncology such as the American Society of Clinical Oncology (ASCO) meetings to identify unpublished studies.

Original research articles were identified from Morocco, Algeria, and Tunisia. The included studies had to meet the following criteria: the study must relate to the role of \textit{BRCA1} and/or \textit{BRCA2} genes in BC and/or OC, it should analyze all the coding regions, test for known mutations, or select exons of \textit{BRCA} genes; the study must provide sufficient information on the \textit{BRCA1} and/or \textit{BRCA2} PV frequencies. Likely pathogenic variants or variants of unknown/uncertain significance (VUS) were excluded from this study. The prevalence of any variant was included regardless of whether the variant was specific or recurrent/founder. Also, where study authors did not clearly state that variant was germline or somatic and/or pathogenic, or clinically relevant, the variant was classified as not reported/unclear in order to avoid any misinterpretation. Details of the study methods, population characteristics, and prevalence of \textit{BRCA} PVs were extracted and summarized in Table 1.
Table 1
Details of studies examining BRCA1 and BRCA2 genes in North Africa

| Number of patients | BRCA carriers | Mean age | Methods | Covered gene region |
|--------------------|---------------|----------|---------|---------------------|
| Morocco            |               |          |         |                     |
| Laarabi et al. (2011) | 8             | 6        | NA      | Direct sequencing   | All |
| Tazzite et al. (2012) | 40            | 10       | 38      | Direct sequencing   | All |
| Laraqui et al. (2013) | 121           | 7        | 44      | Direct sequencing   | BRCA1 |
| Elkhachibi et al. (2015) | 71           | 2        | 41      | HRM, Direct sequencing | Exon11(BRCA1) |
| Jouali et al. (2016) | 15            | 6        | 47      | NGS                 | All |
| Quiles et al. (2016) | 11            | 8        | 36.5    | Direct sequencing   | Exon20 (BRCA1) |
| Laarabi et al. (2017) | 122           | 14       | Direct sequencing (51 patients), NGS (23 patients), Target screening (BRCA2 exon 10, 48 patients) | All, Exon10 (BRCA2) |
| El Ansari et al. (2020) | 64            | 18       | 42      | NGS                 | All |
| Bakkach et al. (2020) | 33            | 4        | 35      | NGS                 | All |
| Mansouri et al. (2020) | 32            | 7        | 45      | NGS                 | All |
| Jouali et al. (2020) | 39            | 1        | 46      | NGS                 | All |
| Algeria            |               |          |         |                     |
| Uhrhammer et al. (2008) | 51           | 5        | 31.5    | Direct sequencing, MLPA | BRCA1 |
| Cherbal et al. (2010) | 86            | 10       | NA      | Direct sequencing, MLPA | All |
| Henouda et al. (2016) | 40            | 8        | 36.6    | Direct sequencing, MLPA | All |
| Boulenouar et al. (2018) | 50           | 4        | NA      | Direct sequencing, MLPA | All |
| Mehemmai et al. (2019) | 113           | 7        | 44      | Direct sequencing, NGS | Exon3, 4, and 10 (BRCA1), Exon10 (BRCA2) |
| Tunisia            |               |          |         |                     |
| Troudi et al. (2007) | 36            | 7        | 56.8    | Direct sequencing   | All |
| Troudi et al. (2008) | 32            | 5        | 46.5    | Direct sequencing   | BRCA1 |
| Mahfoudh et al. (2011) | 24            | 6        | 41      | Direct sequencing   | BRCA1 |

HRM: High Resolution Melt, MLPA: Multiplex Ligation-dependent Probe Amplification, NGS: Next generation sequencing, NA: not available
| Number of patients | Number of BRCA carriers | Mean age | Methods                          | Covered gene region                                      |
|--------------------|-------------------------|----------|----------------------------------|----------------------------------------------------------|
| Riahi et al. (2013)| 48                      | 12       | NA                               | Direct sequencing                                         |
|                    |                         |          |                                  | All                                                      |
| Fourati et al. (2014)| 66                    | 12       | 45                               | Direct sequencing                                         |
|                    |                         |          |                                  | BRCA1 (5,20, and part of 11), BRCA2 (10,11)              |
| Msolly et al. (2015)| 17                     | 1        | 45.8                             | Direct sequencing                                         |
|                    |                         |          |                                  | All                                                      |
| Mahfoudh et al. (2019)| 33                  | 2        | 53.8                             | Direct sequencing                                         |
|                    |                         |          |                                  | All                                                      |
| Mighri et al. (2020)| 112                    | 9        | NA                               | Direct sequencing, NGS                                     |
|                    |                         |          |                                  | All                                                      |
| Guerfali et al. (2021)| 134                 | 19       | NA                               | NGS                                                      |
|                    |                         |          |                                  | All                                                      |

HRM: High Resolution Melt, MLPA: Multiplex Ligation-dependent Probe Amplification, NGS: Next generation sequencing, NA: not available

Reinterpretation of sequence variant was conducted by following the classification system recommended by the American College of Medical Genetics and Genomics-Association for Molecular Pathology (ACMG-AMP) Standards and Guideline for the Interpretation of Sequence Variants [8]. The 2015 ACMG-AMP guidelines were a major step toward establishing a common framework for variant classification. The ACMG-AMP suggests that the clinical pathogenicity of a variant can be evaluated using multiple lines of evidence from available literature, structural/functional data, population frequencies, and statistical analyses of clinical data. The process can result in 1 of 5 classifications: benign (class 1), likely benign (2), VUS (class 3), likely pathogenic (class 4), and pathogenic (class 5). Likely benign and benign variants were not clinically reported.

Variants were considered to be “founder” if they were described as such in the primary literature, based on confirmatory haplotype analysis or population frequency.

Results

The search of the databases yielded 25 relevant references which are closely related to defining the inclusion criteria and was included in this review. The retrieved articles describe studies conducted in Morocco (n = 11) [9–19], Algeria (n = 5) [20–24], and Tunisia (n = 9) [25–33]. Overall, 15 studies investigated both BRCA1 and BRCA2 genes [9, 10, 13, 16–19, 21–23, 25, 28, 30–33], four studies examined the entire coding regions of the BRCA1 gene [9, 10, 13, 16–19, 21–23, and BRCA2] [25, 28, 30–33], and six studies in which the analysis was restricted to a few BRCA1 and/or BRCA2 exons [12, 14, 15, 24, 29].

Overall, we observed 76 distinct BRCA PVs (44 in BRCA1 and 32 in BRCA2). The identified variants are current in 196 BC and/or OC patients (129 BRCA1 carriers and 67 BRCA2 carriers). A total of 18 of the 76 (23.7%) PVs [10/44 (22.7%) in BRCA1, 8/32 (25%) in BRCA2] were reported for the first time and were considered to be novel PVs in the North African populations. Among them, four PVs were reported in Morocco (c.3453delT in BRCA1 [19], and c.3381delT, c.7110delA, c.7234_7235insG in BRCA2 [10], three in Algeria (deletion of exon2 in BRCA1 [21], c.2805delA and c.6450del in BRCA2 [22], and eleven in Tunisia (c.211dupA [25, 26], c.296_297delTG [33], c.2418dupA [32], c.3254delG [33], c.3364_3370delACAGATT [33], c.3751dup [29], c.4067_4071delAAGAA in BRCA1 [33] and c.1313dupT [28], c.1976_1800delCTTAT [28], c.2095C > T [33], c.7654dupT [28] in BRCA2). The reported PVs in BRCA genes from North African studies are presented in Table 2.
| Exon     | Mutation type | Protein consequence | Number of cases | Country  | Cancer site | Familial Cases | References |
|----------|---------------|---------------------|-----------------|----------|-------------|----------------|------------|
| BRCA1 Pathogenic variants |               |                     |                 |          |             |                |            |
| c.46_74del29 | 2 FS          | p.Asn16fs           | 2               | Algeria  | BC          | 1 Familial 1 Sporadic | [20]      |
| c.66_67delAG | 2 FS          | p.Glu23fs           | 2               | Morocco  | BC          | Familial      | [16]      |
| c.68_69delAG | 2 FS          | p.Glu23fs           | 4               | Morocco  | 3 BC, 1 OC | Familial      | [9]       |
| Del exon 2 | 2 LGR         | -                   | 2               | Algeria  | 1 BOC, BC  | Familial      | [21],[22] |
| c.83_84delTG | 3 FS          | p.Arg28fs           | 2               | Algeria  | BC          | 1 Familial 1 Sporadic | [20],[21] |
| c.116G > A | 3 MS          | p.Cys39Tyr          | 1               | Morocco  | BC          | Familial      | [18]      |
| c.181T > G | 5 MS          | p.Cys61Gly          | 3               | Morocco, Algeria | BC          | Familial [8],[19] |
| c.211dupA  | 5 FS          | p.Arg71fs           | 19              | Tunisia  | 3 BC, 2 BOC | Familial [25],[26],[28],[29],[32] |
| c.212 + 2insG | 5 Splicing    | -                   | 1               | Tunisia  | BC          | Familial      | [31]      |
| Del exon 8 | 8 LGR         | -                   | 1               | Algeria  | BC          | Familial      | [21]      |
| c.2338C > T | 10 NS         | p.Gln780Ter         | 2               | Tunisia  | OC          | 1 Familial 1 Sporadic | [33]      |
| c.798_799delTT | 11 FS        | p.Ser267LysfsX19    | 18              | Morocco, Algeria, Tunisia | BC          | 16 Familial 2 Sporadic [10],[11],[13],[16],[17],[18],[20],[21],[30],[31] |
| c.1016dupA | 11 FS         | p.Val340LysfsX6     | 3               | Morocco  | BC          | Familial      | [11],[16] |
| c.1504_1508delTTAAA | 11 FS     | p.Leu502fs          | 1               | Tunisia  | BC          | Familial      | [28]      |
| c.1817delC  | 11 FS         | p.Pro606Leufs6      | 2               | Algeria  | BC          | 1 Familial 1 Sporadic | [20],[22] |
| c.202 + 1G > A | 11 FS        | -                   | 1               | Algeria  | BC          | Familial      | [20]      |
| c.296_297delTG | 11 FS     | p.V99fs*9           | 1               | Tunisia  | BC          | Familial      | [33]      |

FS: frameshift mutation, LGR: Large genomic rearrangement, MS: missense mutation, BC: breast cancer, OC: ovarian cancer, BOC: breast and ovarian cancer, NS: Nonsense mutation
| Exon | Mutation type | Exon | Mutation type | Protein consequence | Number of cases | Country | Cancer site | Familial | Sporadic | References |
|------|---------------|------|---------------|---------------------|----------------|---------|-------------|----------|----------|------------|
| c.2125_2126insA | 11 | FS | p.Phe709Tyrfs | 4 | Morocco, Algeria | BC | 3 Familial | Familial | [17],[18], [19], [23] |
| c.2418dupA | 11 | MS | p.Ala807Serfs | 1 | Tunisia | BC | Familial | [32] |
| c.2551delG | 11 | FS | p.Glu851fs | 2 | Tunisia | BC | Familial | [25],[26] |
| c.2745dupT | 11 | NS | p.Ser915fs | 1 | Algeria | BC | Familial | [20] |
| c.2805delA | 11 | FS | p.Asp936Ilefs | 2 | Morocco | BC | Familial | [10],[12] |
| c.3254delG | 11 | FS | p.Arg1085Asnfs2 | 1 | Tunisia | BC | Familial | [33] |
| c.3279delC | 11 | FS | p.Tyr1094Ilefs | 6 | Morocco | BC | Familial | [10],[12],[16] |
| c.3331_3334delCAAG | 11 | FS | p.Gln1111fs | 1 | Tunisia | BC | Familial | [31] |
| c.3364_3370dupACAGATT | 11 | FS | Stop1115 | 1 | Tunisia | BC | Familial | [33] |
| c.3453delT | 11 | FS | p.Asp1151Glufs | 1 | Morocco | BC | Familial | [19] |
| c.3715delT | 11 | FS | p.Ser1239fs | 1 | Algeria | BC | Sporadic | [20] |
| c.3751dup | 11 | FS | p.Thr1251fs | 1 | Tunisia | DC | Familial | [29] |
| c.4041_4042delAG | 11 | FS | p.Gly1348fs | 4 | Tunisia | BC | Familial | [25],[26], [29],[33] |
| c.4065_4068del | 11 | FS | p.As1355Lysfs10 | 1 | Algeria | BC | Familial | [22] |
| c.4067_4071delAAGAA | 11 | FS | p.Gln1356Argfs8 | 1 | Tunisia | BC | Familial | [33] |
| c.5095C>T | 14 | MS | p.Arg1699Trp | 2 | Morocco | BC | Familial | [11] |
| c.4676-?_4986 + ? Del/p. ? | 15 | ? | - | 2 | Algeria | BC | Familial | [24] |
| c.5030_5033delCTAA | 15 | NS | p.Thr1677Ilefs2 | 3 | Tunisia | 1 BC, 1 BOC | Familial | [33] |
| c.4823C>G | 16 | NS | p.Ser1608Ter | 1 | Morocco | BC | Familial | [16] |
| c.4942A>T | 16 | NS | p.Lys1648X | 1 | Morocco | BC | Familial | [11] |
| c.5062_5064delGTT | 17 | FS | p.Val1688del | 1 | Morocco | BC | Familial | [10] |
| c.5117G>C | 18 | MS | p.Gly1706Ala | 1 | Algeria | BC | Familial | [23] |
| c.5158C>T | 18 | MS | p.Arg1720Trp | 1 | Morocco | BC | Familial | [16] |
| c.5266dupC | 20 | FS | p.Gln1756Profs | 11 | Tunisia | BC, 2 BOC | Familial | [25],[26],[27],[28],[29],[31] |

FS: frameshift mutation, LGR: Large genomic rearrangement, MS: missense mutation, BC: breast cancer, OC: ovarian cancer, BOC: breast and ovarian cancer, NS: Nonsense mutation
| Exon   | Mutation type | Protein consequence | Number of cases | Country    | Cancer site | Familial | Sporadic | References |
|--------|---------------|---------------------|-----------------|------------|-------------|----------|----------|------------|
| c.5309G > T | 20 | MS | p.Gly1770Val | 10 | Morocco | 9BC, 1OC, 8 Familial | 2 Sporadic | [14],[18] |
| c.5332 + 1G > A | 20 | Splicing | - | 2 | Algeria | 1 BC, 1 OC | Familial | 22],[24] |
| c.5390C > A | 22 | NS | p.Ser1797Ter | 1 | Morocco | BC | Familial | [18] |

**BRCA2 Pathogenic variants**

| Exon   | Mutation type | Protein consequence | Number of cases | Country    | Cancer site | Familial | References |
|--------|---------------|---------------------|-----------------|------------|-------------|----------|------------|
| c.17_20delAAGA | 2 | FS | p.Lys6Argfs17 | 2 | Tunisia | BC | Familial | [33] |
| c.250C > T | 3 | NS | p.Gln84Ter | 1 | Algeria | BC | Familial | [33] |
| c.289G > T | 3 | NS | p.Glu97Ter | 1 | Morocco | BC | Familial | [23] |
| c.517_1G > A | Intron 6 | SA | - | 1 | Morocco | BC | Sporadic | [10] |
| c.632_1G > A | 7 | Splicing | - | 2 | Tunisia | BC | Familial | [33] |
| c.1302_1305delAAGA | 10 | FS | p.Lys437fs | 1 | Morocco | OC | Familial | [16] |
| c.1309del4 | 10 | FS | Stop459 | 1 | Tunisia | BC | Familial | [26] |
| c.1310_1313delAAGA | 10 | FS | p.Lys437ilefsX22 | 26 | Morocco, Algeria, Tunisia | 25 BC, 1MBC | Familial | [15],[21],[29],[33] |
| c.1313dupT | 10 | FS | Stop451 | 2 | Tunisia | BC | Familial | [28] |
| c.1528G > T | 10 | NS | p.Glu510 | 1 | Algeria | BC | Familial | [22] |
| c.1813dupA | 10 | FS | p.Ile605Asnfs11 | 1 | Algeria | BC | Familial | [24] |
| c.1976_1800delCTTAT | 10 | FS | p.Ser599 | 1 | Tunisia | BC | Familial | [33] |
| c.2095C > T | 10 | NS | p.Gln699Ter | 1 | Tunisia | BC | Familial | [33] |
| c.5116_5119delAATA | 11 | FS | p.Arg2108Cys | 2 | Morocco | BC | Familial | [17],[18] |
| c.3381delT | 11 | FS | p.Phe1127Leufs | 1 | Morocco | BC | Familial | [17] |
| c.3847_3848delGT | 11 | FS | p.Val1283fs | 1 | Morocco | OC | Familial | [10] |
| c.3860delA | 11 | FS | p.Asn1287fs | 1 | Morocco | BOC | familial | [16] |
| c.5073dupA | 11 | FS | p.Trp1692Metfs | 2 | Morocco | BC | Familial | [9] |
| c.5576_5579delTTAA | 11 | FS | p.I1859fs | 1 | Morocco | OC | familial | [16] |
| c.5682insA | 11 | FS | - | 1 | Tunisia | BC | familial | [26] |
| c.5722_5723delCT | 11 | FS | p.Leu1908Argfs2 | 1 | Algeria | BC | familial | [21] |
| c.6450del | 11 | FS | p.Val2151Phefs17 | 1 | Algeria | BC | familial | [22] |
| c.7110delA | 14 | FS | p.Lys2370Asnfs | 2 | Morocco | 1 OC, 1BC | familial | [10],[16] |
| c.7234_7235insG | 14 | FS | p.Thr2412fs | 3 | Morocco | BC | Familial | [10],[19] |
| c.7235_7236insG | 14 | FS | p.Lys2413fs | 1 | Morocco | OC | Familial | [16] |

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| Exon | Mutation type | Protein consequence | Number of cases | Country | Cancer site | Familial status | References |
|------|---------------|---------------------|-----------------|---------|------------|----------------|-------------|
| c.7654dupA | 16 | FS | p.Ile2552Asnfs2 | 2 | Algeria | BC | Familial | [22], [24] |
| c.7654dupT | 16 | FS | p.Ile2552fs | 2 | Tunisia | BC | Familial | [28] |
| c.8485C>T | 19 | NS | p.Gln2829 | 1 | Algeria | BC | familial | [24] |
| Del exons 19–20 | 19/20 | LGR | - | 1 | Algeria | BC | familial | [22] |
| c.8940delA | 22 | FS | p.Glu2981Lysfs7 | 1 | Algeria | BOC | Familial | [24] |
| c.9097delA | 22 | FS | p.Thr3033Leufs | 1 | Tunisia | BC | Familial | [33] |
| c.9364G>A | 25 | MS | p.Ala3122Thr | 1 | Algeria | BC | familial | [23] |

FS: frameshift mutation, LGR: Large genomic rearrangement, MS: missense mutation, BC: breast cancer, OC: ovarian cancer, BOC: breast and ovarian cancer, NS: Nonsense mutation

Among those identified as unlikely to be of North African origin including the BRCA1 c.68_69del and BRCA1 c.5266dupC Jewish founder variants, as well as PVs that have been reported as founder variants in European populations (ex: BRCA1 c.181T>G in Poland).

Furthermore, other PVs have been described worldwide and represented as common PVs in several populations (ex: BRCA1 c.1016dupA in Italy, Germany, Scandinavian countries and French-Canadians, BRCA1 c.2125_2126insA in French-Canadians, BRCA1 c.2338C>T and BRCA2 c.1813dupA in Germany, BRCA1 c.5030_5033delCTAA in France, BRCA2 c.3860delA in Austrian population, and BRCA2 c.3847_3848delGT in Denmark).

The most well characterized five PVs are four in BRCA1 gene including c.211dupA (19/129, 14.7%) [25, 26, 28, 29, 32], c.798_799delTT (18/129, 14%) [10, 11, 13, 16–18, 21, 26, 27, 30], c.5266dup (11/129, 8.5%) [25–29, 31], c.5309G>T (10/129, 7.8%) [14, 18], c.3279delC (6/129, 4.7%) [10, 12, 16] and one in BRCA2 including c.1310_1313delAAGA (26/67, 38.9%) [15, 19, 21, 29, 33]. The BRCA1 c.798_799delTT was identified in 18 North African patients, accounting for 14% (18/129) of total identified BRCA1 PVs [10, 11, 13, 16–18, 20, 21, 26, 27, 30]. Microsatellite markers in and anking the BRCA1 locus showed a common haplotype in Algerian and Tunisian carriers, suggesting the first non-Jewish founder variant to be described in Northern Africa [20]. The c.798_799delTT variant, located in exon 11, is a frame-shift variant including two small deletions, two bases (TT) deletion, that cause truncated protein signal at codon 285.

The other frequent recurrent PVs c.211dupA [25, 26, 28, 29, 32] and c.5266dupC [25–29, 31] were found in 55.6% (30/54) of BRCA1-related hereditary breast and ovarian cancer (HBOC) in Tunisian families but neither in Algerian nor in Moroccan families with BC and/or OC. The c.211dupA variant seems to be the most frequent BRCA PVs in Tunisia, accounting for 35.2% (19/54) of all identified BRCA1 PVs [25, 26, 28, 29, 32]. It seems to be specific to Tunisia since it has never been previously described in any other population. Haplotype analysis supported the founder effect of c.211dupA in Tunisia and showed its recent origin. The frameshift variant c.211dupA results in a premature protein termination at codon 79 at the level of the splicing donor site of exon 5.

The c.5266dupC variant in BRCA1 exon 20 was detected in most Tunisian series, accounting for 20.4% (11/54) of all BRCA1 PVs [25, 26, 27, 28, 31]. Haplotype analysis indicates the likelihood of a single founder origin both in Europe and in North America for the c.5266dupC variant [34]. Haplotype analysis may be useful in establishing whether or not it has a common founder origin for all BRCA1 c.5266dupC variant in Tunisia. The BRCA1 c. 5266dupC variant results in a frameshift, which alters the protein's amino acid sequence beginning at position 1756 and leads to a premature termination codon 73 amino acids downstream.

The BRCA1 c.5309G>T variant was identified in ten patients of which 9 BC and 1 OC, two of the BC patients were sporadic cases [14, 18]. A haplotype linked to c.5309G>T, constructed from five microsatellite markers and spanning 1.54 Mb, was defined in one family. The alleles found in the other families are consistent with this haplotype, supporting the founder effect of c.5309G>T in Morocco [14, 35, 36]. This mutation was first reported in Spain in two families of Moroccan origin and was classified as probably pathogenic on the basis of a combination of functional and structural analyses [18]. The c.5309G>T variant in BRCA1 is located in the functionally important BRCA1 carboxyl-terminal domain, a domain known to harbor missense substitutions associated with increased risk of BC and/or OC. The c.5309G>T variant should be treated as a disease-causing variant despite a lack of evolutionary conservation at glycine at position 1770 [35].
The BRCA1 c.3279delC variant mutation is a recurring PV in the Moroccan population. Its accounts for 12.2% (6/49) of the BRCA1 mutations [10, 12, 16], suggesting a possible founder effect. The c.3279delC variant in exon 9 is a frame shift variant including one small deletion, one base (C) deletion. The deletion causes a frame-shift which changes a tyrosine to isoleucine at codon 1094 and creates a premature stop codon at position 15 of the new reading frame.

The BRCA2 c.1310_1313delAAGA frameshift PV is considered as a North African recurrent mutation since it has been identified in Moroccan [15, 19], Algerian [21], and Tunisian [29] BC patients. Interestingly, geographical clustering in the North-Eastern area of Morocco is evident for the c.1310_1313delAAGA mutation, suggesting a founder effect [15]. c.1310_1313delAAGA incidence rate is higher and accounts for 50% (17/34) of all BRCA2 PVs in North-East of Morocco [15]. This sequence change deletes four nucleotides from exon 10 of the BRCA2 mRNA, causing a frameshift after codon 437 and the creation of a premature translational stop signal 22 amino acid residues.

**Discussion**

BRCA genes remain the primary inherited causes of BC and OC, accounting for 30–70% of hereditary BC families and approximately 90% of hereditary OC families. BRCA PV carriers are linked with an increased lifetime risk of developing BC and/or OC. Current investigations have reported several differences and significant heterogeneity in the incidence and geographic distribution of PVs [7, 37]. In North Africa, BRCA PVs frequency varies widely from ≈ 1% (Morocco) in sporadic BC [11] to 37.5% (Tunisia) in HBOC [26]. The spectrum and prevalence of BRCA PVs vary mainly due to population-specific recurrent/founder variants. Some of which have documented a founder effect of such recurrent or unique variants through haplotype analysis. Prevalence studies of BRCA gene variants suggest that these genetic alterations can explain a high-frequency BC in some populations than others and may contribute to differences in cancer risk between populations and racial/ethnic minorities [5–7]. Accurate identification of the population-specific variant spectrum is therefore the first step towards incorporating appropriate BRCA genetic testing into clinical practice in certain populations and racial/ethnic groups [38].

In North Africa, BRCA1 founder variants explain around 36.4% (47/129) of BC and outnumber BRCA2 founder variants by a ratio of ≈ 3:1. Clear founder effects have been reported in Morocco (BRCA1 c.5309G > T) and Tunisia (BRCA1 c.211dupA). Furthermore, the BRCA1 c.798_799delTT was identified in 14% (18/129) of BRCA1 carriers in North African populations. It was initially thought to be specific to Algeria (5/26, 19.23%) [20, 21], but later found to be prevalent in Tunisia (4/54, 7.4%) [26, 27, 30] and Morocco (9/49, 18.4%) [10, 11, 13, 16–18]. Haplotype analysis of some families carrying this PVs revealed the presence of a common allele [20]. The BRCA1 c.798_799delTT frame-shift variant is cited twice in the Breast Cancer Information Core (BIC) database, without any ethnic origin indicated. Interestingly, the c.798_799delTT and c.5309G > T variants in BRCA1 have been identified in sporadic BC patients in North Africa, and hence their presence in patients without a history of BC and/or OC cannot be attributed to the de novo mutational event. To our knowledge, the c.798_799delTT variant has been identified in Spain [39], in southern Italy [40, 41], and in France [42]. This restricted geographical distribution to close Mediterranean countries could be explained by geographical proximity and migration flow history. The c.1310_1313delAAGA variant in BRCA2 represents another common PV in North African populations which founder effect through haplotype analysis is required for confirmation in this region. According to the BIC database, the BRCA2 c.1310_1313delAAGA variant was found in different European patients and was recorded several times in the French Universal Mutation database-BRCA2 (UMD-BRCA2) and classified as founder variant [43]. In addition, it is important to highlight that one of the three Ashkenazi Jewish founder variants (BRCA1 c.5266dup) is frequently observed in Tunisian BRCA1 carriers (11/54, 20.38%) and is in agreement with data from several variant databases, which have suggested that this is one of the most common PVs ever described in BRCA1 [44]. Though being often referred to as a Jewish founder variant, BRCA1 c.5266dupC is common in Central and Eastern Europe with a high frequency among different ethnic populations [44]. The BRCA1 c.5266dupC variant is the second most frequently reported PV in the BIC database. Besides recurrent/founder variants, two BRCA1 variants (c.211dupA and c.5309G > T) were not reported previously. The c.211dupA and c.5309G > T PVs in the BRCA1 gene were identified as unique to the Tunisian and Moroccan populations, respectively [25, 26, 28, 29, 32].

Several founder variants as they have common ancestral haplotypes have been identified in various areas and races. For example, the well-known founder variants are c.68_69delAG, c.5266dupC in BRCA1, and c.5946_5946delT in BRCA2 in the Ashkenazi Jewish population [45, 46]. The c.824_825ins10, c.1713_1717delAGAAAT, c.5177_5180del4, c.4357 + 1G > A variants in BRCA1 and c.4471_4474delCTGA variant in BRCA2 have been identified as a potential Afro-American founder variant [47–49]. A high frequency of founder c.771_775del5 BRCA2 PV was identified in Iceland. The founder BRCA2 c.771_775del5 variant was reported to cause the familial clustering of both female and male BC cases [50, 51]. The c.2685_2686del variant in BRCA1 and c.9672dup variant in BRCA2 have been reported as founder mutations for the Dutch population [52]. A French-Canadians founder status is evident for c.4327C > T in
The founder effect of c.68_69delAG, c.181T > G, c.676delT, c.1687C > T, c.3700_3704delGTAA, c.3756_3759delGTCT, c.4035delA, c.5251C > T, c.5266dupC in BRCA2 and c.658_659delGT, c.3847_3848delGT, c.5946delT, c.7913_7917delTTTCT in BRCA2 are characteristic for Central European population [44]. Three large genomic deletions (deletion of exon 20, exon 24, and exons 23 and 24) and the c.5212G > A PV have been characterized as population-specific founder variants by haplotype analysis in the Greek population [54]. The c.1140dupG and c.4136_4137delCT variants in BRCA1 were identified as novel putative founder variant in Middle Eastern patients [55]. In addition to c.2641G > T, c.68_69delAG, c.5266dupC, and c.1374delC variants in BRCA1, haplotype analysis confirmed the founder status of c.5771_5774del and c.7934del variants in BRCA2 and revealed an additional founder variant in BRCA2, c.582G > A, in South African families [56]. In Latin America, clear founder effects have been reported in Mexico (BRCA1 del exons 9–12), Brazil (BRCA1 c.5266dupC and BRCA2 c.156_157insA), and Colombia (BRCA1 c.3331_3334delCAAG, BRCA1 c.5123C > A, and BRCA2 c.2808_2811delACAA) [57]. In the Middle Eastern population, nine PVs were recurrent in epithelial OC and founder mutation analysis revealed only two mutations (BRCA1 c.4136_4137delCT and BRCA1 c.1140dupG) sharing the same haplotypes thus representing founder mutations [58]. Studying the founder effect of these variants can provide a comprehensive analysis of a population's evolution and its migration pathways.

Identification of recurrent/founder variants is an extremely important step towards the improvement of genetic counseling since molecular testing can be targeted to the recurrent/founder variant allowing for a more rapid and less expensive test [27]. The high frequency of recurrent/founder variants, allowing for analyzing a large number of cases, might provide accurate information regarding their penetrance and distinguish factors that affect them. Once a risk factor is identified in one subgroup of PV carriers it would need to be tested across other PV carriers. Subsequently, it would need to be tested in a large population-based case-control study of patients with BC and/or OC, in order to determine how important the risk factor is in the general population [59]. Furthermore, the evidence of differences in susceptibility and in age onset of cancer and in the type of cancers that develop among carriers of a founder variant could make it possible to define the role and importance of risk-modifying factors with the resulting improved disease management [5].

Furthermore, a specific variant in BRCA genes has been found with high prevalence in restricted populations as a consequence of a founder effect. The specific founder variant of c.303T > G and c.2641G > T in BRCA1 were reported in the Yoruba population from Nigeria [60], and in the Afrikaner population from South Africa [56], respectively. Geographical clustering of c.3481_3491del11 and c.5128G > T mutations in BRCA1 in the Alsace-Lorraine region at the North-East and in the north-east of France, respectively, suggests a founder effect [42, 61]. In the southwest of Netherlands, the founder effect of c.4186_1643_4357 + 2020del3835 variant in BRCA1 and c.5351dupA variant in BRCA2 were prevalent in Catholic (West Brabant clustering) and Protestant (South Beveland clustering) families, respectively, reflecting religious endogamy [62]. The c.4964_4982del19 variant in BRCA1 has been identified as a founder variant in a geographically and historically homogeneous population from Calabria, a south Italian region [63]. Significant regional founder effect has been demonstrated for c.3228_3229delAG, c.3285delA, c.1380dupA, and c.5062_5064del3 variants in BRCA1 in Tuscany in central Italy [64]. The c.5062_5064delGT variant in BRCA1 and c.8537_8538delAG variant in BRCA2 have been described as founder variants in Middle Sardinia and in South and Middle Sardinia, respectively [65]. Fimgioli et.al., showed that the BRCA1 c.190T > C is a founder variant in BC families from Bergamo province in the Northern Italian region [6]. The c.3048_3052dupA variant in BRCA2 was prevalent in Catholic (West Brabant clustering) and Protestant (South Beveland clustering) families, respectively, reflecting religious endogamy [62]. The c.4964_4982del19 variant in BRCA1 has been identified as a founder variant in a geographically and historically homogeneous population from Calabria, a south Italian region [63]. Significant regional founder effect has been demonstrated for c.3228_3229delAG, c.3285delA, c.1380dupA, and c.5062_5064del3 variants in BRCA1 in Tuscany in central Italy [64]. The c.5062_5064delGT variant in BRCA1 and c.8537_8538delAG variant in BRCA2 have been described as founder variants in Middle Sardinia and in South and Middle Sardinia, respectively [65]. Fimgioli et.al., showed that the BRCA1 c.190T > C is a founder variant in BC families from Bergamo province in the Northern Italian region [6].

The identification of specific BRCA variants could allow us to identify new founder effects for some of these and to quantify the degree of homogeneity within a population. Moreover, it was essential for promoting and potentially advancing to rapid founder-based BRCA point-of-care technology as a time- and cost-effective alternative. This discovery can surely help oncologists and cancer genetics professionals to simplify their choices in the genetic screening on high-risk families, on the basis of their ethnic origin, through more accurate estimation of carrier probabilities of BRCA variants. Understanding the contribution of specific variants to BC risk in such a population will help to examine the possibility of conducting population-wide genetic testing for candidate variants that are over-represented in this population [69]. The most well-known and significant examples of recurrent/founder mutations in BRCA genes found worldwide are presented in Table 3.

The high rates of specific and recurrent/founder PVs have led to a scientifically valid initiative to offer limited genotyping platforms. Establishing a founder effect lies mainly in the reduction of costs. Cost remains a frequently mentioned barrier to genetic testing in some populations such as North Africa. If we manage to decrease costs, screening could be offered more widely and cover a larger number of women, and could offer the benefits of early or pre-symptomatic diagnosis. The complete evaluation of BRCA genes is necessary only in cases where there is a strong family history and none of the corresponding founder variants is identified. This
The approach requires previous knowledge of the prevalence of the PVs in the population of interest [70]. The three Ashkenazi-Jewish founder PVs (c.66_67del, c.5266dup in \textit{BRCA1}, and c.5946del in \textit{BRCA2}) are offered as a variant testing panel for self-reported Ashkenazim. This approach is much less expensive than comprehensive gene sequencing. With advances in sequencing technologies, testing women for the panel of population-specific recurrent/founder variants may be a valuable advance for therapy decisions in BC and OC patients. A panel of \textit{BRCA1} and \textit{BRCA2} variants, including close to 100 recurrent variants (HiSPANEL), has been constructed with diverse variants from Hispanic women with BC from the USA, based on the information in manuscripts describing variants in \textit{BRCA} genes from Latin American countries and data bases [71]. In Poland, Łukomska et al., recommend that all women with OC and first-degree female relatives should be tested for the panel of 18 founder variants in \textit{BRCA1}, \textit{BRCA2}, \textit{PALB2}, and \textit{RAD51C} [72]. In addition to the known founder deleterious variants in the Chinese population, Jiang et al., highlight that the recurrent PVs in BC patients could be taken as candidate genetic screening loci for a more efficient genetic screening of this population [73]. Studies from Egypt suggest wider screening of the founder PVs (c.68_69del and c.5266dupC in \textit{BRCA1}) among high-risk families using pyrosequencing techniques that could be an excellent platform for \textit{BRCA} founder PVs analysis [74]. Identification of specific and recurrent/founder variants that could be included in a low-cost PV panel, used as a first line screening approach, would be useful in the North African region. The PV panel can also include other recurrent worldwide PVs such as \textit{BRCA1} c.1016dupA which has also been reported in other countries (Italy, Germany, and French-Canada), however allelotyping results indicated an independent origin of this PV. That would justify the inclusion of the \textit{BRCA1} c.1016dupA into targeted variant screening panels in any population, irrespective of ethnic origin [44].

### Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| ACMG-AMP     | American College of Medical Genetics and Genomics-Association for Molecular Pathology |
| ASCO         | American Society of Clinical Oncology |
| BC           | Breast cancer |
| BIC database | Breast Cancer Information Core database |
| BRCA         | BReast CAner |
| HBOC         | Hereditary breast and ovarian cancer |
| OC           | Ovarian cancer |
| PVs          | Pathogenic variants |
| UMD          | Universal mutation database |
| VUS          | Variant(s) of unknown/uncertain significance |

### Declarations
| Ethics approval and consent to participate | Not applicable |
| Consent for publication | Not applicable |
| Availability of data and materials | The datasets generated and analysed during the current study are available in the [ Breast and ovarian cancer in North Africa (tables) repository. ] |
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| Authors' information | - Full Name (first, family): Ouabida Elbad |
| | - Affiliation: |
| | • Laboratoire de Recherche et de Biosécurité P3, Hôpital Militaire d'Instruction Mohammed V, Rabat, Maroc |
| | • Unité de séquençage, Centre de virologie, des maladies infectieuses et tropicales, Hôpital militaire d’Instruction Mohammed V, Faculté de Médecine et de Pharmacie, Université Mohammed V, Rabat, Maroc |
| | • Laboratoire de Biodiversité, Ecologie et Génome, Faculté des Sciences, Université Mohammed V, Rabat, Maroc |

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**Tables**

Due to technical limitations, Table 3 is only available as a download in the Supplemental Files section.

**Supplementary Files**

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