Founder mutations in \textit{BRCA1} and \textit{BRCA2} genes

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\textit{BRCA1} and \textit{BRCA2} germline mutations contribute to a significant number of familial and hereditary breast and/or ovarian cancers. The proportion of high-risk families with breast and/or ovarian cancer cases due to mutations in these tumor suppressor genes varies widely among populations. In some population, a wide spectrum of different mutations in both genes are present, whereas in other groups specific mutations in \textit{BRCA1} and \textit{BRCA2} have been reported with high frequency. Most of these mutations are prevalent in restricted populations as consequence of a founder effect. The comparison of haplotypes between families with the same mutation can distinguish whether high-frequency alleles derive from an older or more recent single mutational event or whether they have arisen independently more than once.

Here, we review some of the most well-known and significant examples of founder mutations in \textit{BRCA} genes found in European and non-European populations.

In conclusion, the identification of the ethnic group of families undergoing genetic counseling enables the geneticist and oncologist to make more specific choices, leading to simplify the clinical approach to genetic testing carried out on members of high-risk families. Furthermore, the high frequency of founder mutations, allowing to analyze a large number of cases, might provide accurate information regarding their penetrance.

\textbf{Key words:} \textit{BRCA1}, \textit{BRCA2}, founder mutation

\section*{Introduction}

About 5\%–10\% of breast cancer (BC) and ovarian cancer (OC) are hereditary and 30\%–50\% of these are due to mutations, inherited in a dominant autosomal manner, in the susceptibility genes, \textit{BRCA1} (MIN 113705) and \textit{BRCA2} (MIN 600185), localized respectively on chromosomes 17q21 and 13q12 [1].

In both cases the variants are distributed uniformly along the entire coding region and intronic sequences flanking each exon; in order to identify such mutations it is therefore necessary to examine the whole sequence of both the genes.

Since most of the mutations involved are at high penetrance, women carriers have an 80\%–90\% lifetime risk of developing these neoplasias [2, 3].

Women who carry \textit{BRCA1} mutations are particularly susceptible to the development of a BC before age 35–40 and also of an OC with a probability rate of, respectively, 45\%–60\% and 20\%–40\%, whereas women who inherit a \textit{BRCA2} mutation present a 25\%–40\% risk of developing a BC and a 10\%–20\% risk of an OC [4–6].

The presence of a mutation in the gene \textit{BRCA2} in men leads to a risk of BC of 5\%–10\% and an increased risk of developing prostatic or pancreatic tumors, while there is a much lower risk in male carriers of \textit{BRCA1} mutations [7, 8].

The incidence of mutations in high-risk families varies widely among different populations; some present a wide spectrum of different mutations, while in particular ethnic groups specific mutations show a high frequency due to a ‘founder’ effect. ‘Founders’ are small groups of people who have remained isolated with consequent interbreeding and the result that a normally rare mutation continues to be present and becomes more common within the population.

The comparison of haplotypes between families with the same mutation can distinguish whether high-frequency alleles derive from an older or more recent single mutational event or whether they have arisen independently more than once [9].

The aim of this review is to examine several populations where founder mutations have been identified in the \textit{BRCA1} and \textit{BRCA2} genes (Tables 1 and 2). The identification of the ethnic group of families undergoing genetic counseling enables the geneticist and oncologist to make more specific choices, leading to simplify the clinical approach to genetic testing carried out on members of high-risk families.
founder effect among the Ashkenazi Jews

The well-known example of a founder effect is that of the Ashkenazi Jews population. Ashkenazi is the term used to describe Jews who have ancestors from Eastern and Central Europe, such as Germany, Poland, Lithuania, Ukraine and Russia. Today, most of the world’s 10 million Ashkenazi Jews live in the United States, Israel, South America, South Africa, Australia and New Zealand.

Although only 10% of cases of BC/OC is due to genetic predisposition, the hereditary proportion of such tumors is much higher in Ashkenazi Jews since they often carry one of three founder mutations [5–10]. The BRCA1-185delAG mutation is found in 1% of these and contribute to 16%–20% of BC diagnosed before age 50 [3–11]. A second founder mutation in the BRCA1 gene, 5382insC, is found in 0.13% of this population [11].

The third founder mutation, 6174delT in the BRCA2 gene, has a frequency of 1.52% in Ashkenazi Jews [11]. Eight percent of Ashkenazi women with BC diagnosed before age 42 and 7% of those with BC at age 42–50, with a strong family history of BC or OC, are carriers of this mutation [12].

The overall rate of these three founder mutations is 2.6% (1/40) compared with the rate of 0.2% (1/500) of mutation carriers in BRCA1/2 in the general population [11, 12].

A combined analysis of several studies based on 22 different Ashkenazi populations has shown that BC lifetime risk is similar in carriers of the 185delAG and 5382insC mutations (respectively of 64% and 67%), whereas it is much lower for the 6174delT mutation (43%). This difference is particularly marked at age 50 (8% versus 36% when the first two mutations are combined) [13].

With regard to other neoplasias, although several studies have reported that founder mutations in BRCA1 lead to a higher risk of developing colorectal cancer and that there exists an association between the presence of the founder mutation 6174delT and the risk of developing a lymphoma and prostate cancer [15, 16], there is still considerable discordance between the different published data (Table 1) [17, 18].

The 5382insC mutation has been identified in several countries, as Russia, Poland, Czech Republic and Lithuania, where it accounts, respectively, 94%, 60%, 33% and 50% of the BRCA1/2 gene mutations [19–24]. In subjects with a family history of BC/OC, the frequency in Russia is of 11%, in Hungary of 14% [25], in Greece of 8% [26], in Germany of 4%, in France [27], in Italy of 3% [28] and in Canada of 13% [29]. On the contrary, a low frequency has been found in the Scandinavian countries, in Belgium and in Holland. It is thought that this mutation probably originated in the Baltic area 38 generations ago, with a gradual decrease going from east to west. A haplotype analysis indicates the likelihood of a single founder both in Europe and in North America for 5382insC mutations [30].

### Table 1. BRCA1/2 founder mutations in European populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Mutation</th>
<th>BRCA1 Reference</th>
<th>BRCA2 Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jews</td>
<td>185delAG</td>
<td>[3, 11]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5832insC</td>
<td>[11, 19–26, 30]</td>
<td></td>
</tr>
<tr>
<td>Icelandians</td>
<td>6174delT</td>
<td>[11, 12]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>995delG</td>
<td>[31]</td>
<td></td>
</tr>
<tr>
<td>Norwegians</td>
<td>1675delA</td>
<td>[35, 36]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>816delGT</td>
<td>[35, 36]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3347delAG</td>
<td>[35, 36]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1135insA</td>
<td>[35–37]</td>
<td></td>
</tr>
<tr>
<td>Finns</td>
<td>IVS11 + 3A&gt;G</td>
<td>[38]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9345 + 1G&gt;A</td>
<td>[38]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C7708T</td>
<td>[38]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T8555G</td>
<td>[38]</td>
<td></td>
</tr>
<tr>
<td>Swedes</td>
<td>3171ins5</td>
<td>[39–41]</td>
<td></td>
</tr>
<tr>
<td>French</td>
<td>3600del11</td>
<td>[42]</td>
<td></td>
</tr>
<tr>
<td>Dutch</td>
<td>2804delAA</td>
<td>[49]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVS12-1643del3835</td>
<td>[48]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5579insA</td>
<td>[48]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6503delTT</td>
<td>[48]</td>
<td></td>
</tr>
<tr>
<td>Italians (Calabria)</td>
<td>5083del19</td>
<td>[64, 65]</td>
<td></td>
</tr>
<tr>
<td>Italians (Sardinia)</td>
<td>8765delAG</td>
<td>[68, 69]</td>
<td></td>
</tr>
</tbody>
</table>

The table describes the most significant examples of founder mutations in European populations reported in the text.

### Table 2. BRCA1/2 founder mutations in non-European populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Mutation</th>
<th>BRCA1 Reference</th>
<th>BRCA2 Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>French-Canadians</td>
<td>C4446T</td>
<td>[43–45]</td>
<td></td>
</tr>
<tr>
<td>(Quebec)</td>
<td>8765delAG</td>
<td>[43–45]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3398delAAAG</td>
<td>[43–45]</td>
<td></td>
</tr>
<tr>
<td>Icelanders</td>
<td>R1443X</td>
<td>[46]</td>
<td></td>
</tr>
<tr>
<td>Hispanics (South)</td>
<td>S995X</td>
<td>[32]</td>
<td></td>
</tr>
<tr>
<td>California</td>
<td>2553delC</td>
<td>[32]</td>
<td></td>
</tr>
<tr>
<td>Hispanics (Columbia)</td>
<td>3450delCAAG</td>
<td>[53]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A1708E</td>
<td>[53]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3034delACAA</td>
<td>[53]</td>
<td></td>
</tr>
<tr>
<td>Afro-Americans</td>
<td>943ins10</td>
<td>[54]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1832del5</td>
<td>[54]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5296del4</td>
<td>[54]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVS13 + 1G&gt;A</td>
<td>[55]</td>
<td></td>
</tr>
<tr>
<td>South Africans</td>
<td>E881X</td>
<td>[56]</td>
<td></td>
</tr>
<tr>
<td>Iraqi/Iranian Jews</td>
<td>Tyr978X</td>
<td>[57]</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>1081delG</td>
<td>[58]</td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>Q934X</td>
<td>[59, 60]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L63X</td>
<td>[59, 60]</td>
<td></td>
</tr>
<tr>
<td>Malaysians</td>
<td>2846insA</td>
<td>[61]</td>
<td></td>
</tr>
<tr>
<td>Filipinos</td>
<td>4265delCT</td>
<td>[62]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4859delA</td>
<td>[62]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5454delC</td>
<td>[62]</td>
<td></td>
</tr>
<tr>
<td>Pakistanian</td>
<td>S1503X</td>
<td>[63]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R1835X</td>
<td>[63]</td>
<td></td>
</tr>
</tbody>
</table>

The table describes the most significant examples of founder mutations in non-European populations reported in the text.
founder mutations in Europe

Founder mutations are found in several European populations. In Iceland, the most common founder mutation is 999del5 in the BRCA2 gene [31]. It occurs in 0.4% of this population and is found in 8.5% and 7.9%, respectively, of BC and OC patients, but does not appear to contribute to the development of other tumor types [32]. Another founder mutation identified in this population is G5193A in BRCA1 gene, although this is extremely rare and is present in only 1% of cases of BC/OC [33, 34].

In Norway, hereditary forms of BC and OC involve four main founder mutations, 1675delA, 816delGT, 3347delAG and 1135insA. The first three originate from the southwestern region of the country, while the fourth is from the south-east. Overall, they represent 68% of BRCA1 mutations [35]. All four mutations are at high penetrance with regard to both diseases in Norwegian population [36].

The 1135insA mutation has also been reported in other ethnic groups; nevertheless, allelotyping of Norwegian, French-Canadian, Italian and German families has led to different results, which would indicate an independent origin of this mutation in each of the examined populations [37].

In Finland, 11 recurrent mutations with a founder effect have been identified and these represent 84% of all the mutations found in the BRCA1/2 genes. Some of these are exclusive to the Finnish population, such as IVS11 + 3A>G in BRCA1 and 9345 + 1G>A, C7708T, T8555G in BRCA2 genes. Others have been found in other countries, although in some of these haplotype analysis has shown an independent origin (C4446T-BRCA1, 3604delAA-a BRCA2) [38].

The most common mutation found in Sweden is BRCA1-3171insS; in the western region of the country it accounts for 70% of the mutations in the BRCA1/2 genes. Mutation carriers have a conserved haplotype of 3.7 cM which is thought to have originated about 50 generations ago [39, 40]. Penetrance for BC/OC at age 70 is estimated between 59% and 93% [41].

In 2004, a study carried out in France involving high-risk families showed the presence of two particularly frequent mutations in BRCA1: 3600del11 and G1710X, which represent 37% and 15%, respectively, of all the mutations identified.

The haplotype analysis of the families carrying the mutation 3600del11, all originating from Alsace–Lorraine, revealed the presence of a common allele, indicating a founder effect. Although this mutation is found in many different geographical areas, it is more common in France. The mutation G1710X would appear to be specific to the French but the analysis of its haplotype has less conclusive and needs further confirmation [42].

The large number of founder mutations identified in the population of Quebec originate from France since the 6.5 million French-Canadian are descendants of the groups who colonized ‘La Nouvelle France’ between 1608 and 1795. Among these, the most common founder mutations are BRCA1-C4446T, BRCA2-8765delAG and BRCA2-3398delAAAAG, which is found in 1.7% of women affected by BC diagnosed before age 41 and in 1.3% of women with OC [43–45].

In 2005, Vezina et al. [46] described for the first time not only the molecular but also the genealogical features of the nonsense mutation BRCA1-R1443X, recurrent in French-Canadians. A highly conserved haplotype was identified in 18 families, indicating that this is a founder mutation within the Quebec population. Furthermore, reconstruction of the genealogy of these families has made it possible to identify the founder couple with the highest probability of having introduced the mutation into the population and also to detect the presence of a geographical concentration in its diffusion pattern (Table 2).

In 2001, the ‘German Consortium for Hereditary Breast and Ovarian Cancer’ identified a large number of recurrent mutations with a common haplotype [47]. A deletion of exon 17 was found in 3% of high-risk families and in 6% of families without mutations. This accounted for 8% of all the BRCA1 mutations, indicating that it might be a founder mutation within the German population [48].

Several founder mutations in BRCA1/2 have been identified in Holland [49]. These include BRCA1-2804delAA, also found in Belgium, which accounts for 24% of all BRCA1/2 mutations and which probably originated ~200 years ago (32 generations); its frequency has increased as a result of the isolation of these two countries immediately after the second World War [50].

The mutations IVS12-1643del3835 in BRCA1 and 5579insA in BRCA2 are found in families from two different geographical areas, limited to the southwest region of Holland, which became repopulated as a result of religious conflicts. It is no coincidence that these two mutations are mainly found respectively in Catholic and Protestant families [49].

Another Dutch founder mutation is 6503delTT, which, together with 5579insA in BRCA2 accounts for 62% of hereditary BC and OC linked to this gene (Table 1) [49].

The founder mutation A339G (R71G) originates from Spain and is also found in French and British families of Spanish origin [51]. Several other founder mutations have been identified in Lithuania and in Poland (4153delA and C61G in BRCA1) [21–24].

founder mutations in other countries

In America, Hispanic people constitutes 14% of the total population. A study conducted in South California on high-risk families showed several recurrent mutations indicated as founder mutations by allelotyping. Some of these, such as 5995X and 2552delC in BRCA1, are present only in families of Latin-American, Caribbean or Spanish origin [52]. These results, however, cannot be applied to the Hispanic population of Colombia, which presents three different founder mutations (3450delCAAG and A1708E in BRCA1 and 3034delACAA in BRCA2), indicating that different strategies of risk evaluation are needed for Hispanic populations of South America and for those of the United States [53].

Among Afro-Americans, the mutational spectrum of BRCA1/2 is not been well characterized than that of Caucasian peoples, but is nevertheless unique. Several recurrent mutations have been found and in three of these (943ins10, 1832del5 and 5296del14 in BRCA1), haplotype analysis has shown a common origin [54]. The first of these, in fact, is extremely
old and comes from West Africa. Recently, a fourth recurrent mutation, IVS13 + 1G>A, has been found in BRCA1 and identified as a potential Afro-American founder [55].

The mutation E881X in BRCA1 gene is a founder mutation in South African families. Genealogical studies have identified three possible founder couples, who arrived in the area from France in ~1600 [56].

BRCA1-Tyr978X is a founder mutation detected in 1% of non-Ashkenazi Jews of Iraqi or Iranian origin. The limited ethnic occurrence of the Tyr978X-BRCA1 mutation in Jews indicates that it originated from a common Jewish ancestor, which is not so in the case of the French-Canadian families in which it has been found [57].

With regard to the Far East, several recurrent mutations have been identified in the Chinese population and one of these, 1081delG in BRCA1, has a founder effect. It is interesting to note that carriers of these mutations all come from South China (Hong Kong), indicating that there may well be a different genetic background between the north and the south of the country [58].

In Japan, the cumulative frequency of BRCA1 and BRCA2 mutations is of 32%, similar to that of Caucasian populations. Two founder mutations have been identified in BRCA1, Q934X and L63X, the latter exclusively in the eastern region of the country and one in BRCA2, 5802delAATT [59, 60]. Founder mutations have been also identified in Malaysia (BRCA1-2846insA), Philippines (BRCA2-4265delCT and 4859delA, BRCA1-5454delC) and Pakistan (BRCA1-S1503X and R1835X); of all the Asian countries, the latter has the highest rate of BC/OC [61–63] (Table 2).

founder mutations in Italy

In 2004, the ‘Italian Consortium of Hereditary Breast and Ovarian Cancer’ (nine Units) has established that the prevalence of BRCA1/2 mutations in Italy is 23%, following an analysis of 1758 families, 405 of which carries pathohiological mutations, 251 in BRCA1 and 154 in BRCA2. The genetic screening of this group of families showed different expressivity according to the type of tumor considered and allelic heterogeneity in both genes. Only a few of these mutations resulted to be recurrent in particular geographical areas [64].

In 2001, Baudi et al. [65] described for the first time an example of founder mutation in the Italian population. The screening of the whole BRCA1 gene was carried out on 24 patients with BC and/or OC who belonged to unrelated families and showed a high rate of the 5083del19 mutation (four of 24 cases). All the families with this mutation originated from Calabria and haplotype analysis carried out on the probands and on the healthy family members showed a common allele. This indicated a possible founder effect, in concordance with the genetic background of the Calabrian population, which is homogeneous and associated with negligible immigratory phenomena. A North American study carried out on 116 women of Italian origin with primary BC or OC showed this mutation in five of the families involved, three of which of Calabrian origin [66].

These data confirm that this is a founder mutation of the Italian population, most probably originating in Calabria, although the presence of four families carrying the mutation identified in the genetic screening of 106 patients of Sicilian origin indicates that it might well be of Southern Italian origin. Only a haplotype analysis will make it possible to understand if all these families originating from two close regions of the south of Italy (Calabria and Sicily) have a common ancestor [67].

Another regional founder effect has been demonstrated in Italy for the mutation BRCA2-8765delAG. In 2002, Palmieri et al. found this mutation in four Sardinian families with the same haplotype, at the rate of 1.7% in a group of patients with BC. This founder mutation was identical to that observed in French-Canadian families [69], but involved a different haplotype (Table 1) [68].

In Tuscany, the analysis of 11 families carrying the mutation 1499insA in BRCA1 showed a specific haplotype associated with this mutation, also found fairly frequently in the rest of the population. It has therefore been indicated that this is probably due to a founder effect [70].

Several other recurrent mutations have been identified in other limited areas of Italy, but only genetic screening carried out on a larger number of cases within the various regions of the country will make it possible to reach more definite conclusions regarding the presence of a founder effect.

conclusions

Identification of founder mutations in the various ethnic groups is an extremely important step towards the improvement of genetic counseling since it makes possible to use a more specific approach to molecular testing that would also be cheaper and quicker. A less expensive mutation detection strategy might also allow to extend genetic counseling and testing to families with a low hereditary history.

The high frequency of founder mutations, allowing to analyze a large number of cases, might provide accurate information regarding their penetrance. Furthermore, the evidence of differences in susceptibility and in age onset of cancer among carrier of a specific mutation could make it possible to define the role and importance of risk-modifying factors with the resulting improved disease management.

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