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Founder mutations in *BRCA1* and *BRCA2* genes

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BRCA1 and *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 *BRCA1* and *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 *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. Futhermore, the high frequency of founder mutations, allowing to analyze a large number of cases, might provide accurate information regarding their penetrance.

Key words: *BRCA1*, *BRCA2*, founder mutation

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 autosomic manner, in the susceptibility genes, *BRCA1* (MIN 113705) and *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 *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 *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 *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 *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 *BRCA1* and *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.

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

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

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

Population	Mutation *BRCA1*	*BRCA2*	Reference
French-Canadians	C4446T		[43–45]
(Quebec)		8765delAG	[43–45]
		3398delAAAAG	[43–45]
	R1443X		[46]
Hispanics (South	S995X		[52]
California)	2552delC		[52]
Hispanics (Columbia)	3450delCAAG		[53]
	A1708E		[53]
		3034delACAA	[53]
Afro-Americans	943ins10		[54]
	1832del5		[54]
	5296del4		[54]
		IVS13 + 1G>A	[55]
South Africans	E881X		[56]
Iraqi/Iranian Jews	Tyr978X		[57]
Chineses	1081delG		[58]
Japaneses	Q934X		[59, 60]
	L63X		[59, 60]
		5802delAATT	[59, 60]
Malaysians	2846insA		[61]
Filipinos		4265delCT	[62]
		4859delA	[62]
	5454delC		[62]
Pakistanis	S1503X		[63]
	R1835X		[63]

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

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 [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]. The corresponding OC lifetime risk is respectively of 14%, 33% and 20% in carriers of the 185delAG, 5382insC and 6174delT mutations, respectively [13, 14].

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].

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, 3604delTT-BRCA2) [38].

The most common mutation found in Sweden is BRCA1-3171ins5; 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 descendents 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 S995X 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 5296del4 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 carriers of pathological 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 the 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.

references

1. Szabo CI, King MC. Inherited breast and ovarian cancer. Hum Mol Genet 1995; 4: 1811–1817.
2. Neuhausen S, Gilewski T, Norton L et al. Recurrent BRCA2 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. Nat Genet 1996; 13: 126–128.
3. Struewing JP, Abeliovich D, Peretz T et al. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nat Genet 1995; 11: 198–200.
4. Brose MS et al. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Nat Cancer Inst 2002; 9418: 1365–1372.
5. Robles-Diaz L, Goldfrank DJ, Kauff ND et al. Hereditary ovarian cancer in Ashkenazi Jews. Fam Cancer 2004; 3: 259–264.
6. Antoniou A, Pharoah PD, Narod S et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003; 72: 1117–1130.

7. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol 2004; 22: 735–742.
8. Giordano SH. A review of the diagnosis and management of male breast cancer. Oncologist 2005; 10: 471–479.
9. Friedman LS, Szabo CI, Ostermeyer EA et al. Novel inherited mutations and variable expressivity of BRCA1 alleles, including the founder mutation 185delAG in Ashkenazi Jewish families. Am J Hum Genet 1995; 57: 1284–1297.
10. Rubinstein WS. Hereditary breast cancer in Jews. Fam Cancer 2004; 3: 249–257.
11. Roa BB, Boyd AA, Volcik K et al. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. Nat Genet 1996; 14: 185–187.
12. Neuhausen S, Gilewski T, Norton L et al. Recurrent BRCA2 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. Nat Genet 1996; 13: 126–128.
13. Antoniou AC, Pharoah PD, Narod S et al. Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies. J Med Genet 2005; 42: 602–603.
14. Satagopan JM, Boyd J, Kauff ND et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clin Cancer Res 2002; 8: 3776–3781.
15. Kadouri L, Hubert A, Rotenberg Y et al. Cancer risks in carriers of the BRCA1/2 Ashkenazi founder mutations. J Med Genet 2007.
16. Kirchhoff T, Kauff ND, Mitra N et al. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clin Cancer Res 2004; 10: 2918–2921.
17. Kirchhoff T, Satagopan JM, Kauff ND et al. Frequency of BRCA1 and BRCA2 mutations in unselected Ashkenazi Jewish patients with colorectal cancer. J Natl Cancer Inst 2004; 96: 68–70.
18. Hamel N, Kotar K, Foulkes WD. Founder mutations in BRCA1/2 are not frequent in Canadian Ashkenazi Jewish men with prostate cancer. BMC Med Genet 2003; 4: 7.
19. Sokolenko AP, Mitiushkina NV, Buslov KG et al. High frequency of BRCA1 5382insC mutation in Russian breast cancer patients. Eur J Cancer 2006; 42: 1380–1384.
20. Gorski B, Byrski T, Huzarski T et al. Founder mutations in the BRCA1 gene in Polish families with breast-ovarian cancer. Am J Hum Genet 2000; 66: 1963–1968.
21. Grzybowska E, Sieminska M, Zientek H et al. Germline mutations in the BRCA1 gene predisposing to breast and ovarian cancers in Upper Silesia population. Acta Biochim Pol 2002; 49: 351–356.
22. Pohlreich P, Zikan M, Stribrna J et al. High proportion of recurrent germline mutations in the BRCA1 gene in breast and ovarian cancer patients from the Prague area. Breast Cancer Res 2005; 7: 728–736.
23. Ciernikova S, Tomka M, Kovac M et al. Ashkenazi founder BRCA1/BRCA2 mutations in Slovak hereditary breast and/or ovarian cancer families. Neoplasma 2006; 53: 97–102.
24. Gronwald J, Elsakov P, Gorski B et al. High incidence of 4153delA BRCA1 gene mutations in Lithuanian breast and breast-ovarian cancer families. Breast Cancer Res Treat 2005; 94: 111–113.
25. Ramus SJ, Kote-Jarai Z, Friedman LS et al. Analysis of BRCA1 and BRCA2 mutations in Hungarian families with breast or breast–ovarian cancer. Am J Hum Genet 1997; 60: 1242–1246.
26. Ladopoulou A, Kroupis C, Konstantopoulou I et al. Germ line BRCA1 & BRCA2 mutations in Greek breast/ovarian cancer families: 5382insC is the most frequent mutation observed. Cancer Lett 2002; 185: 61–70.
27. Stoppa-Lyonnet D, Laurent-Puig P, Essioux L et al. BRCA1 sequence variations in 160 individuals referred to a breast/ovarian family cancer clinic. Am J Hum Genet 1997; 60: 1021–1030.
28. Caligo MA, Ghimenti C, Cipollini G et al. BRCA1 germline mutational spectrum in Italian families from Tuscany: a high frequency from novel mutations. Oncogene 1996; 13: 1483–1488.
29. Simard J, Tonin P, Durocher F et al. Common origins of BRCA1 mutations in Canadian breast and ovarian cancer families. Nat Genet 1994; 8: 392–398.
30. Backe JMD, Hofferbert SMD, Skawran B et al. Frequency of BRCA1 mutation 5382insC in German breast cancer patients. Gynecol Oncol 1999; 2: 402–406.
31. Thorlacius S, Olafsdottir G, Tryggvadottir L et al. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nat Genet 1996; 13: 117–119.
32. Johannesdottir G, Gudmundsson J, Bergthorsson JT et al. High prevalence of the 999del5 mutation in Icelandic breast and ovarian cancer patients. Cancer Res 1996; 56: 3663–3665.
33. Bergthorsson JT, Jonasdottir A, Johannesdottir G et al. Identification of a novel splice-site mutation of the BRCA1 gene in two breast cancer families: screening reveals low frequency in Icelandic breast cancer patients. Hum Mutat 1998; (Suppl 1): 195–197.
34. Rafnar T, Benediktsdottir KR, Eldon BJ et al. BRCA2, but not BRCA1, mutations account for familial ovarian cancer in Iceland: a population-based study. Eur J Cancer 2004; 40: 2788–2793.
35. Moller P, Heimdal K, Apold J et al. Genetic epidemiology of BRCA1 mutations in Norway. Eur J Cancer 2001; 37: 2428–2434.
36. Heimdal K, Maehle L, Apold J et al. The Norwegian founder mutations in BRCA1: high penetrance confirmed in an incident cancer series and differences observed in the risk of ovarian cancer. Eur J Cancer 2003; 39: 2205–2213.
37. Rudkin TM, Hamel N, Galvez M et al. The frequent BRCA1 mutation 1135insA has multiple origins: a haplotype study in different populations. BMC Med Genet 2006; 7: 15.
38. Sarantaus L, Huusko P, Eerola H et al. Multiple founder effects and geographical clustering of BRCA1 and BRCA2 families in Finland. Eur J Hum Genet 2000; 8: 757–763.
39. Bergman A, Einbeigi Z, Olofsson U et al. The western Swedish BRCA1 founder mutation 3171ins5; a 3.7 cM conserved haplotype of today is a reminiscence of a 1500-year-old mutation. Eur J Hum Genet 2001; 9: 787–793.
40. Bergman A, Flodin A, Engwall Y et al. A high frequency of germline BRCA1/2 mutations in western Sweden detected with complementary screening techniques. Fam Cancer 2005; 4: 89–96.
41. Einbeigi Z, Bergman A, Kindblom LG et al. A founder mutation of the BRCA1 gene in western Sweden associated with a high incidence of breast and ovarian cancer. Eur J Cancer 2001; 37: 1904–1909.
42. Muller D, Bonaiti-Pellié C, Abecassis J et al. BRCA1 testing in breast and/or ovarian cancer families from northeastern France identifies two common mutations with a founder effect. Fam Cancer 2004; 3: 15–20.
43. Tonin PN, Mes-Masson A-M, Narod SA et al. Founder BRCA 1 and BRCA 2 mutations in French Canadian ovarian cancer cases unselected for family history. Clin Genet 1999; 55: 318–324.
44. Tonin PN, Perret C, Lambert JA et al. Founder BRCA1 and BRCA2 mutations in early-onset French Canadian breast cancer cases unselected for family history. Int J Cancer 2001; 95: 189–193.
45. Oros KK, Leblanc G, Arcand SL et al. Haplotype analysis suggest common founders in carriers of the recurrent BRCA2 mutation, 3398delAAAAG, in French Canadian hereditary breast and/ovarian cancer families. BMC Med Genet 2006; 7.
46. Vezina H, Durocher F, Dumont M et al. Molecular and genealogical characterization of the R1443X BRCA1 mutation in high-risk French-Canadian breast/ovarian cancer families. Hum Genet 2005; 117: 119–132.
47. German Consortium for Hereditary Breast and Ovarian Cancer. Comprehensive analysis of 989 patients with breast or ovarian cancer provides brca1 and brca2 mutation profiles and frequencies for the german population. Int J Cancer 2002; 97: 472–480.
48. Hartmann C, John AL, Klaes R et al. Large BRCA1 gene deletions are found in 3% of German high-risk breast cancer families. Hum Mutat 2004; 24: 534.
49. Zeegers MPA, van Poppel F, Vlietinck R et al. Founder mutations among the Dutch. Eur J Hum Genet 2004; 12: 591–600.
50. Peelen T, van der Vliet M, Petrij-Bosch A et al. A high proportion of novel mutations in BRCA1 with strong founder effects among Dutch and Belgian hereditary breast and ovarian cancer families. Am J Hum Genet 1997; 60: 1041–1049.

51. Vega A, Campos B, Bressac-de-Paillerets B et al. The R71G BRCA1 is a founder spanish mutation and leads to aberrant splicing of the transcript. Hum Mutat 2001; 419: 1–6.
52. Weitzel JN, Lagos V, Blazer KR et al. Prevalence of BRCA mutations and founder effect in high-risk Hispanic families. Cancer Epidemiol Biomarkers Prev 2005; 14: 1666–1671.
53. Torres D, Usman Rashid M, Gil F et al. High proportion of BRCA1/2 founder mutations in Hispanic breast/ovarian cancer families from Colombia. Breast Cancer Res Treat .
54. Olopade OI, Fackenthal JD, Dunston G et al. Breast cancer genetics in African Americans. Cancer 2003; 97 (Suppl): 236–245.
55. Pal T, Permuth-Wey J, Holtje T et al. BRCA1 and BRCA2 mutations in a study of African American breast cancer patients. Cancer Epidemiol Biomarkers Prev 2004; 13: 1794–1799.
56. Reeves MD, Yawitch TM, van Der Merwe NC et al. BRCA1 mutations in South African breast and/or ovarian cancer families: evidence of a novel founder mutation in Afrikaner families. Int J Cancer 2004; 110: 677–682.
57. Quintana-Murci L, Gal I, Bakhan T et al. The Tyr978X BRCA1 mutation: occurrence in non-Jewish Iranians and haplotype in French-Canadian and non-Ashkenazi Jews. Fam Cancer 2005; 4: 85–88.
58. Khoo US, Chan KY, Cheung AN et al. Recurrent BRCA1 and BRCA2 germline mutations in ovarian cancer: a founder mutation of BRCA1 identified in the Chinese population. Hum Mutat 2002; 486.
59. Ikeda N, Miyoshi Y, Yoneda K et al. Frequency of BRCA1 and BRCA2 germline mutations in japanese breast cancer families. Int J Cancer 2001; 91: 83–88.
60. Sekine M, Nagata H, Tsuji S et al. Mutational analysis of BRCA1 and BRCA2 and clinicopathologic analysis of ovarian cancer in 82 ovarian cancer families: two common founder mutations of BRCA1 in Japanese population. Clin Cancer Res 2001; 7: 3144–3150.
61. Lee ASG, Ho GH, Oh PC et al. Founder mutation in the BRCA1 gene in Malay breast cancer patients from Singapore. Hum Mutati 2003; 633.
62. De Leon Matsuda ML, Liede A, Kwan E et al. BRCA1 and BRCA2 mutations among breast cancer patients from the Philippines. Int J Cancer 2002; 98: 596–603.
63. Rashid MU, Zaidi A, Torres D et al. Prevalence of BRCA1 and BRCA2 mutations in Pakistani breast and ovarian cancer patients. Int J Cancer 2006; 119: 2832–2839.
64. Cipollini G, Tommasi S, Paradiso A et al. Genetic alterations in hereditary breast cancer. Ann Oncol 2004; 15 (Suppl 1): I7–I13.
65. Baudi F, Quaresima B, Grandinetti C et al. Evidence of a founder mutation of BRCA1 in a highly homogeneous population from southern Italy with breast/ovarian cancer. Hum Mutat 2001; 18: 163–164.
66. Nedelcu R, Liede A, Aube J et al. BRCA mutations in Italian breast/ovarian cancer families. Eur J Hum Genet 2002; 10: 150–152.
67. Russo A, Calo V, Agnese V et al. BRCA1 genetic testing in 106 breast and ovarian cancer families from southern Italy (Sicily): a mutation analyses. Breast Cancer Res Treat 2007.
68. Pisano M, Cossu A, Persico I et al. Identification of a founder BRCA2 mutation in Sardinia. Br J Cancer 2000; 82: 553–559.
69. Tonin PN, Mes-Masson AM, Futreal PA et al. Founder BRCA1 and BRCA2 mutations in French Canadian breast and ovarian cancer families. Am J Hum Genet 1998; 63: 1341–1351.
70. Caligo MA, Ghimenti C, Cipollini G et al. BRCA1 germline mutational spectrum in Italian families from Tuscany: a high frequency of novel mutations. Oncogene 1996; 13: 1483–1488.