Founder BRCA1/2 mutations in the Europe: implications for hereditary breast-ovarian cancer prevention and control

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Abstract Detection of mutations in hereditary breast and ovarian cancer-related BRCA1 and BRCA2 genes is an effective method of cancer prevention and early detection. Different ethnic and geographical regions have different BRCA1 and BRCA2 mutation spectrum and prevalence. Along with the emerging targeted therapy, demand and uptake for rapid BRCA1/2 mutations testing will increase in a near future. However, current patients selection and genetic testing strategies in most countries impose significant lag in this practice. The knowledge of the genetic structure of particular populations is important for the developing of effective screening protocol and may provide more efficient approach for the individualization of genetic testing. Elucidating of founder effect in BRCA1/2 genes can have an impact on the management of hereditary cancer families on a national and international healthcare system level, making genetic testing more affordable and cost-effective. The purpose of this review is to summarize current evidence about the BRCA1/2 founder mutations diversity in European populations.

Keywords BRCA genes · Oncogenetic testing · Breast and ovarian cancer · Founder mutations · European populations · Prediction and prevention

Introduction

The most significant and well characterized genetic risk factors for breast and/or ovarian cancer to date are germline mutations of the BRCA1 (MIM#113705; 17q chromosome; [1]) and BRCA2 (MIM#600185; 13q chromosome [2]) genes. In the general population, about 5–10% of all breast cancer and 10–15% of ovarian cancer cases can be attributed to these major genetic risk factors, which can explain around half of breast/ovarian cancer aggregation in some families [3, 4]. The prevalence of BRCA1/2 mutation carriers in the general population is around 0.2% (1/500) what accounts for BRCA1 mutation rate carriers of around 1/800 [5], however it can vary significantly among different countries or some ethnic groups due to founder effect [6].

The mutations in these high-penetrance genes confer a high life-time risk of breast and ovarian cancer. Women with an inherited BRCA1 mutation have a lifetime risk of 65–80% of developing breast cancer and 37–62% of developing ovarian cancer, while BRCA2 mutation carriers have a lifetime risk of 45–85% for breast cancer and 11–23% for ovarian cancer [7].

The identification of BRCA1 and BRCA2 mutation carriers and individualized risk assessment is an important procedure growing in clinical importance, since management protocols for mutation carriers become well established [8–10] and proven life-saving, risk-reducing preventive medical interventions exist [11–13]. Once mutation is identified in a given family, a very informative predictive (or presymptomatic) oncogenetic test can be offered virtually to all adult family members. Moreover, oncogenetic testing is becoming the powerful therapeutical predictive tool, as new targeted therapeutic opportunities, such as poly(ADP-ribose) (PARP) inhibitors [14, 15], emerge and chemosensitivity to platinum based therapy is constantly reported [16, 17].
Currently, in most countries clinical BRCA1/2 testing is offered after genetic counseling by clinical cancer geneticist (oncogeneticist) when mutation finding probability exceeds 10%, or even 20% (as in the UK) [18]. Various selection criteria, based on family history, age at onset and tumors clinicopathological features, as well as computational risk prediction models (Claus, BRCAPRO, BOADICEA, IBIS, Myriad and Manchester scoring system [19, 20]) are used. Unfortunately, these models often underestimate the probability of finding a mutation, are validated only in some countries, are not particularly helpful for daily use and no consensus exist regarding their common use [9, 21]. Moreover, familial history is also absent or unknown in at least half of all mutation positive families [22] and mutation detection methods varies between most centers.

It is now evident, that in a near future the uptake and demand for rapid BRCA1/2 mutations testing will increase and more flexible genetic counseling strategies will be needed. As new targeted therapies become available, more individuals will request testing to get access to specific treatments (i.e., PARP inhibitors), regardless of their a priori low risk and clinicians will force laboratories towards rapid testing results. This tendency is already seen in the centers enrolling patients for PARP inhibitors clinical trials (van Osterweik, personal communication) as well as during peridiagnostic (presurgical) testing for a newly diagnosed breast cancer patients [23].

However, a full BRCA1 and BRCA2 gene screening still remains labor and time consuming challenge due to large genes size, diverse mutations or variants of unknown significance (VUS) and complexity of large genomic rearrangements (LGRs), requiring special technical approach. This procedure still remains too complex and expensive to cover a broader target (e.g. all breast or ovarian cancer patients and their first degree relatives) and cannot be routinely applied in less privileged countries.

Fortunately, recent advances in high-throughput mutation detection and screening techniques, such as high resolution melting (HRM) analysis [24] and conformation-sensitive capillary electrophoresis (CSCE) [25] are especially promising rapid, sensitive, cost-efficient and amenable for automation screening approaches for the large genes, whereas decreased cost in genotyping methods offers affordable targeted testing option for predefined set of mutations.

Massively parallel next-generation sequencing platforms [26] provide another technological breakthrough, however they are still at a prohibited cost and complex data overload for routine use.

On the other hand, variation in the distribution of BRCA1 and BRCA2 mutations is well recognized worldwide [27] and several recent reviews already summarized the evidence, that in certain countries and ethnic communities the BRCA1/2 mutation spectrum is limited to a few founder mutations [3, 4, 6, 28]. Founder effects are most prominent in geographically, culturally or religiously isolated populations that undergo rapid expansion from a limited number of ancestors, when, as a consequence of low genetic diversity, some alleles become more frequent.

The purpose of this review is to summarize current evidence about the BRCA1/2 founder mutations diversity in European populations. For the current manuscript only the unequivocally deleterious mutations were considered, excluding as yet the unclassified variants that could not be clearly related with pathogenicity. For the consistency, the unequivocal term “founder” is used for those mutations where haplotype studies revealed shared polymorphic markers consistent with common ancestor, or when unrelated mutation carriers were repeatedly identified (at least 3 times). Some mutations previously described as founder mutations in one country, subsequently are found at a higher proportion in other countries/regions as true founders. These mutations in adjacent countries will likely reflect the gradient transition from the “epicenter” over the time due to historical co-existence of different populations in the same region. Mutations that do not segregate with the same alleles are referred as “recurrent”. They presumably occurred several times at unstable ‘mutational hot spots’ parts of the gene. The mutation nomenclature will be generally presented according to Human Genome Variation Society (HGVS) recommendations (http://www.hgvs.org/rec.html); only at the first mutation mention the older BIC database (http://research.nhgri.nih.gov/bic/) nomenclature will be used between the parentheses, where possible.

BRCA1 is numbered by GeneBank U14680 reference sequence; BRCA2 is numbered by GeneBank U43746 reference sequence.

For the mutations distribution in other geographic regions or more detailed prevalence, penetrance and contribution to unselected for family history cancer cases, readers are referred to other review sources [3, 4, 6, 27–30].

**Founder BRCA1 and BRCA2 mutations in European populations**

**Ashkenazi Jews**

The BRCA1/2 founder effect in Ashkenazi Jews population is very well described. About 10 millions Ashkenazi people living worldwide are descendants of ancestors from Eastern and Central Europe, such as Poland, Lithuania, Belarus, Germany, Hungary, Ukraine and Russia. The most well characterized three founder mutations are two in BRCA1 gene c.68_69delAG (BIC: 185delAG) and c.5266dupC (BIC: 5382insC) and one in BRCA2 c.5946delT (BIC:
6174delIT) [31–33]. Screening for these three founder mutations alone is now part of routine clinical practice for Ashkenazi Jewish individuals.

These 3 mutations \(BRCA1\) c.68_69delAG, c.5266dupC and \(BRCA2\) c.5946delIT account for 98–99% of identified mutations and are carried by about 2.6% (1/40) of the Ashkenazi Jewish population (1%, 0.13% and 1.52% respectively) [34–36]. There are differences between particular mutations and breast/ovarian cancer risk [37]. The average risk of breast cancer by the age of 70 years is similar for carriers of the \(BRCA1\) c.68_69delAG and \(BRCA2\) c.5266dupC mutations (64% and 67% respectively), however is much lower for the c.5946delIT mutation (43%). The corresponding values for ovarian cancer lifetime risk is respectively of 14%, 33% and 20% in carriers, respectively [6, 37, 38].

It is worth noting that \(BRCA1\) c.68_69delAG and c.5266dupC are not found exclusively in Ashkenazi patients. The c.68_69delAG mutation has been found in patients of Spanish ancestry (i.e. Hispanic) as well as other non-Ashkenazi ethnic groups, sometimes with frequencies similar to those in Ashkenazi populations [3], suggesting a common ancient ancestor or two independent mutational events [39].

The c.5266dupC mutation in \(BRCA1\) exon 20 is the second most frequently reported mutation in the BIC database, being very prevalent in Central and Eastern Europe. This single mutation is found in a various frequency in high risk breast and/or ovarian cancer families from Poland (34%) [40], Russia (14%) [41], Hungary (14%) [42], Slovenia (13%) [43], Ashkenazi Jews (10%) [44], Greece (8%) [45], Germany (4%) [46], Italy (3%) [47]. It is virtually absent in Spain and Portugal and is found at low frequency in the Netherlands, Belgium and Scandinavian countries [6]. In Russia, Belarus, Poland, Latvia, Czech Republic, Greece and Lithuania this mutation accounts for respectively 94% [48], 73% [49], 60% [40], 55% [50], 37–52% [51, 52], 46% [45], 34% [53, 54] of all \(BRCA1\) mutations.

Haplotype analysis points to the Baltic origin of this mutation approximately 38 generations ago during the medieval period [55], with a gradual decrease thereafter from East to the West and nearly worldwide spread. A common ancestor for c.5266dupC mutation families reported from Europe, Brazil and North America is evident [46, 56, 57].

Austria

In Austria the ratio of \(BRCA1\) mutations to \(BRCA2\) mutations is 2:1 (Rappaport, personal communication). There were initial reports for several apparently founder \(BRCA1\) mutations in Austria [58, 59], although they (c.181T>G (BIC: 300T>G/C61G), c.5266dupC, c.1687C>T (BIC: 1806C>T)) represent common mutations prevalent in other European countries. In Austria these alterations represent 15%, 10% and 6% of the \(BRCA1\) mutation families, respectively (Rappaport, personal communication). Of note, c.1687C>T is also frequent in Slovenia [43] and Sweden (BIC database). Haplotype analysis revealed a common ancestor for the Austrian and Swedish families, which may indicate Austrian origin of this mutation [59], although its even more common in Slovenia (26% of the \(BRCA1\) mutation families) [43].

Another common mutation is \(BRCA1\) c.3016_3019del4 (BIC: 3135del4) (8% of the \(BRCA1\) mutation families), which was also found in Italy [60]. One \(BRCA1\) mutation c.2676_2679del4 (BIC: 2795del4) was reported at least in three unrelated families in Austria only, what may represent founder effect [58, 59], however this mutation is uncommon. The most prevalent \(BRCA2\) mutations are c.8363G>A (BIC: 8591G>A/W2788X), c.8754+1G>A (BIC: IVS21-1G>A) and c.3860delA (BIC: 4088delA), representing 9%, 7% and 6% of the \(BRCA2\) mutation families respectively (Rappaport, personal communication).

Slovenia

In Slovenia five highly recurrent specific mutations were identified: four in the \(BRCA1\) gene (c.1687C>T, c.181T>G, c.5266dupC, c.181T> (BIC: 300T>G)) and one in the \(BRCA2\) gene (c.7806-2A>G (BIC: IVS16-2A>G)) [43, 61, 62]. Respectively, they accounted for 26%, 18%, 13% and 11% of \(BRCA1\) mutations and 56% of \(BRCA2\) mutations. The c.7806-2A>G in the \(BRCA2\) gene appears to be an unique founder mutation in the Slovenian population, found in 26% (10/38) of all \(BRCA1/2\) mutations harboring families. These 5 mutations account for 67% of the \(BRCA1/2\) positive families [43].

Italy

In Italy, 4–27% of the identified mutations recurred among apparently unrelated families, and significant regional founder effect has been demonstrated for few mutations [63–66].

Four distinct \(BRCA1\) founder mutations (c.3228_3229delAG (BIC: 3347delAG), c.3285delA (BIC: 3404delA), c.1380dupA (BIC: 1499insA), c.5062_5064del3 (BIC: 5181delGTG)) accounted for a large fraction (73%) of \(BRCA1\)-attributable hereditary breast/ovarian cancer in families originating from Tuscany (Central Italy) area [47, 66].

The \(BRCA1\) c.1380dupA mutation was reported in at least 14 families from Tuscany and originated here about 30 generations ago (~750 years) [65].
In Sardinia, contribution of BRCA1/2 mutations to breast cancer predisposition has been reported for populations from the Northern part of the island [67], where founder BRCA2 c.8537_8538delAG (BIC: 8765delAG) mutation comprises 28% for BRCA1/2 positive families [68, 69]. The ratio of BRCA2 mutations to BRCA1 mutations is approximately 2:1, although BRCA1 being more prevalent in South-West area [68]. Conversely, previously regarded as another founder mutation, BRCA2 3950_3952delTAAginsAT was found instead running in families belonging to a single extended pedigree [68].

The BRCA1 c.4964_4982del19 (BIC: 5083del19) is a founder mutation from the southern region of Calabria and accounted for 23% of all BRCA1 mutations [60, 63]. It was also recurrently found at least four times in Sicilia [70, 71]. Another BRCA1 c.4724delC (BIC: 4843delC) mutation could be a possible Sicilian founder mutation, although present evidence is scarce [71–73].

Using a number of independent approaches, Malacrida et al. [74] showed that previously reported BRCA1 c.5062_5064delGT (BIC: 5181_5183delGT/1688Val) variant of unknown significance (VUS) actually is a deleterious mutation with high frequency in North-East Italy [74]. The founder c.5062_5064delGT mutation accounts for 15% (9/61) of families with small BRCA1 mutations.

France

In France geographical clustering in North-Eastern part is evident for two recurrent BRCA1 mutations, suggesting a founder effect. The c.3481_3491del11 (BIC: 3600del11) in exon 11 accounts for 37% and the nonsense mutation c.5128G>T (BIC: 5247G>T/Gly1710X) in exon 18 for 15% of all BRCA1/2 mutations in that region (overall 52%) [4, 75].

The haplotype analysis of the families carrying the mutation c.3481_3491del11, all originating from Alsace–Lorraine, revealed the presence of a common allele, indicating a founder effect [75]. Although this mutation is found in many different geographical areas, it is more common in France. The BRCA1 mutation c.5128G>T would appear to be specific to the France, but the analysis of its haplotype is less conclusive and needs further confirmation [6].

The BRCA1 c.5030_5033delCTAA (BIC: 5149delCTAA) [76] and c.3839_3843delinsAGGC (BIC: 3958delCTCA/GinsAGGC) [77] mutations were reported in at least three independent families from France.

Well-described founder mutations are identified in French-Canadians population in Quebec, which originated from France during 17–18th century settlement period. In this region 4 BRCA1 gene mutations (c.4327C>T (BIC: 4446C>T/Arg1443X), c.3756_3759del14 (BIC: 3875del1GTCT), c.962G>A (BIC: 1081G>A), c.2834_2836delinsC (BIC: 2953delGTA/insC) and 3 BRCA2 mutations (c.3170_3174del5 (BIC: 3398del5), c.5857G>T (BIC: 6085G>T), c.8537_8538delAG (BIC: 8765delAG)) are now routinely included in early onset breast/ovarian cancer screening assays and represent up to 84% of the total BRCA1/2 mutations in the French-Canadian population in Quebec [78]. Among these, the most common founder mutations are BRCA1 c.4327C>T and BRCA2 c.8537_8538delAG and c.3170_3174del5, which are found in 1.7% of women affected by breast cancer diagnosed before age 41 and in 1.3% of women with ovarian cancer [6].

Spain

In Spain, five mutations in BRCA1 and other five in BRCA2 genes account for approximately half of the mutations detected in Spanish families. Specific mutations differ significantly in their frequencies and geographic distribution.

A compilation of BRCA test results from different laboratories shows that five mutations in the BRCA1 gene (c.68_69delAG, c.211A>G (BIC: 330A>G), c.5117G>A (BIC: 5236G>A), c.5123C>A (BIC: 5242C>A), c.470_471delCT (BIC: 589_590delCT) account for 46.6% of BRCA1 mutations and four mutations in BRCA2 (c.2808_2811del4 (BIC: 3036_3039del4), c.6629_6630delAA (BIC: 6857delAA), c.9026_9030del5 (BIC: 9254_9258del5), c.9310_9311delAA (BIC: 9538delAA)) account for 56.6% of the BRCA2 mutations [79].

Diez et al., [80] have reviewed the frequency of BRCA1 and BRCA2 recurrent mutations reported in seven geographic areas of Spain.

The founder mutation BRCA1 c.211A>G, that leads to aberrant splicing of the transcript, originates from North Western Spain (Galicia) and accounts up to 50% of all mutations in this region [81]. It was also found in French and British families of Spanish origin [82].

The BRCA1 c.68_69delAG and BRCA2 c.9026_9030del5 mutations accounted for the 30.4% (7/23) of the BRCA1 mutations and for the 18.5% (5/27) of the BRCA2 positive families respectively and were specific only to the Mediterranean areas. Indeed, haplotype studies indicated a common origin of c.68_69delAG mutation in Spanish (Sephardic Jewish) and Ashkenazi Jewish populations [83]. Some data indicate an unique origin of reported BRCA2 exon 23 mutation BRCA2 c.9026_9030del5 in Catalan families (North-East Spain) [84]. Likewise, the BRCA2 c.2808_2811del4 mutation was predominant only in the Castilla-Leon region (Central Spain), but it also has been described worldwide in many populations and is the second recurrent pathological mutation in the BIC database ranking with a presumable multiple different origins [85, 86].
Splicing mutation c.5153-1G>A (BIC: 5272-1G>A) of \(BRCA1\) and frameshift mutation c.5146_5149del4 (BIC: 5374delITATG) of \(BRCA2\) are also prevalent founder mutations in the Central Spain region, accounting for 18.4% and 13.6% of \(BRCA1\) and \(BRCA2\) positive families, respectively [80, 85, 87]. Such knowledge of the spectrum of mutations and their geographical distribution can allow a more effective detection strategy in countries with large Spanish population.

Conversely, in the Basque population, only 1.2% (1/81) of early onset breast cancer women unselected for family history had pathological mutations; no founder mutation was identified [88].

Portugal

An \(Alu\) sequence insertion in \(BRCA2\) exon 3 (c.156_157insAlu (BIC: 384insAlu)) is a founder mutation of Portuguese origin and accounts for more than one-fourth of deleterious \(BRCA1/2\) mutations in breast/ovarian cancer families in Northern/Central Portugal. This mutation creates \(BRCA2\) exon 3 skipping and is the most frequent large \(BRCA2\) rearrangement described to date [89, 90].

Belgium

Claes et al. [91] in a 49 \(BRCA1/2\) positive families found six major recurrent founder mutations (three \(BRCA1\) c.212+3A>(BIC: IVS5+3A>G), c.2359dupG (BIC: 2478insG), c.3661G>T (BIC: 3704del5) and three \(BRCA2\) c.516+1G>A (BIC: IVS6+1G>A), c.6275_6276delTT (BIC: 6503delTT), c.5351dupA accounts for nearly 60% of all mutations identified. \(BRCA1\) c.212+3A>G was previously reported as Belgian founder mutation [92, 93], later also found in a few German, Dutch and French families [91]. \(BRCA1\) c.2359dupG and \(BRCA2\) c.516+1G>A have not yet been reported in other populations.

The Netherlands (Holland)

Several founder mutations in \(BRCA1/2\) have been identified in Holland [94], where significant regional and cultural differences exist. The \(BRCA1\) c.2685_2686delAA (BIC: 2804delAA) founder mutation probably originated approximately 32 generations (~200 years) ago, was also reported few times in Belgium and accounted for 24% of all \(BRCA1/2\) mutations [92]. \(BRCA1\) c.2193del5 (BIC: 2312del5), and c.1292dupT (BIC: 1411insT) mutations were also commonly found [92, 94].

In the south-west of Holland two founder mutations: 3.8-kb deletion of \(BRCA1\) exon 13, also known as c.4186-1643_4357+2020del3835 (BIC: del exon 13del3835/IVS12-1643del3835), and \(BRCA2\) c.5351dupA (BIC: 5579insA) were found in families from two different geographical areas, and were prevalent respectively in Catholic (West Brabant clustering) and Protestant (South Beveland clustering) families, reflecting religious endogamy [95]. Together with another Dutch \(BRCA2\) founder mutation c.6275_6276delTT (BIC: 6503delTT), c.5351dupA accounts for 62% of hereditary breast/ovarian families [94, 95].

Slightly outdated (as of year 2002) list of published and unpublished \(BRCA1/2\) mutations in Netherlands and Belgium can be found at http://www.humgen.nl/lab-devilee/Lab/b1nlmuts.htm.

Large genomic rearrangements (LGRs) in \(BRCA1\) gene are surprisingly common in Dutch population and more than 30% of the \(BRCA1\) related cases of hereditary breast cancer are due to copy number changes of one or more exon in this gene. The majority of these (25%) are due to two frequently occurring founder mutations: already described 3.8-kb deletion of exon 13 or 510-bp deletion of exon 22 [96], which can be easily detected by multiplex-ligation dependent probe amplification (MLPA) method.

Germany

The \(BRCA1\) deletion of exon 17 accounts for 8% of all the \(BRCA1\) mutations and is the most frequent rearrangement in Germany, found in 3% of high-risk families and in 6% of families without point mutations [97]. Altogether, recurrent aberrations such as deletion of exon 17, duplication of exon 13 and deletion of exon 22, accounts for more than 50% of all \(BRCA1\) large genomic rearrangements in Germany [98].

There was a large number of recurrent mutations with a common haplotype identified in breast/ovarian cancer patients [99]. Eighteen \(BRCA1\) mutations, including the most common c.5266dupC, c.181T>G, c.4065_4068del4 (BIC: 4184del4) and c.2338C>T (BIC: 2457C>T), were found at least 3 times and comprised 66% of all \(BRCA1\) mutations. The 2 most common \(BRCA1\) c.5266dupC and c.181T>G mutations, also prevalent in other populations, accounted for 38% of \(BRCA1\) mutations [4, 99]. Seven distinct mutations accounted for 28% of \(BRCA2\) mutations, and most frequent c.1813dupA (BIC: 2041insA), c.4478del4 (BIC: 4706del4) and c.9098dupA (BIC: 9326insA) were associated with common alleles, suggesting a possible founder effect [99].

Czech Republic

Five mutations (\(BRCA1\): c.181T>G, c.5266dupC, c.3700_3704del5 (BIC: 3819del5), and \(BRCA2\): c.7913_7917del5 (BIC: 8141del5) and c.8537_8538del2 (BIC: 8765delAG)) represented 52% of all mutations detected in one study population [52]. There is evident strong Slavic founder
effect, particularly for two **BRCA1** mutations (c.181T>G and c.5266dupC) also regarded as founder mutations in Poland and some other Slavic countries [100]. The single **BRCA1** c.5266dupC mutation was detected in 51.4% of **BRCA1** mutation positive women in one study from Prague area [51]. The **BRCA1** c.3700_3704del5 mutation is also frequent mutation in Germany [99]. Three **BRCA1** Czech founder mutations (c.181T>G, c.3700_3704del5, and c.5266dupC) account for approximately 9%, 13% and 44% of the **BRCA1** mutations identified, respectively [51, 52].

**BRCA1** mutations appears to be about 2 times more frequent than **BRCA2** mutations in the Czech population [52].

A Czech founder effect is evident for two **BRCA2** mutations (c.7913_7917del5 and c.8537_8538del2), that are more frequent in Moravian (Eastern) rather than in Bohemian (Western) region [101]. These **BRCA2** mutations accounted for 15.6% and 16.7% of the **BRCA2** mutations identified in one study, respectively [52].

LGRs in **BRCA1** gene are relatively common in Czech population and account for 12.3% of all pathogenic **BRCA1** mutations. The deletions of exons 1–17 and 5–14, identified each in four families, represented Czech founder mutations [102]. No LGRs in **BRCA2** gene were described so far.

**Slovakia**

The ratio of **BRCA1** mutations to **BRCA2** is approximately 9:2 and the most common **BRCA1**/2 mutations in Slovak population are three common to the Ashkenazi mutations (Zajac, personal communication). However, as yet there are no convincing data about true **BRCA1/2** mutational spectrum in this population.

**Hungary**

In Hungarian patients from high-risk breast/ovarian cancer families, common **BRCA1** founder mutations c.5266dupC, c.181T>G and c.68_69delAG accounted for 80% of all **BRCA1** mutations and c.9098dupA (BIC: 9326insA) with c.5946delIT accounted for 50% of all **BRCA2** mutations [42, 103]. The **BRCA1** c.181T>G is the most frequent of founder mutations, representing 48% [103]. Breast cancer patients were more likely to carry the c.5266dupC mutation whereas ovarian patients were more likely to carry either the c.68_69delAG or the c.181T>G mutation [103]. Among unselected Hungarian male breast cancer patients, one third carried **BRCA2** mutations, including c.9098dupA [104].

**Greece**

In the Greek population four **BRCA1** mutations (c.5526dupC, c.5212G>A (BIC: 5331G>A/G1738R), c.5251C>T (BIC: 5370C>T/R1751X), c.5467G>A (BIC: 5586G>A), account for 54% of all mutations detected in **BRCA1/2** genes and for 73% of the **BRCA1** mutations positive families, whereas the rest are unique or low-frequency mutations, reflecting the population’s genetic heterogeneity.

The most frequent **BRCA1** mutation c.5526dupC accounts for 31% of the **BRCA1/2** mutations identified in Greek familial breast/ovarian cancer patients [45, 105].

Previously described as unclassified **BRCA1** missense variant G1738R was proved to be pathogenic founder mutation in Greece and accounts for about 12% of all carriers with deleterious mutations in **BRCA1/2** genes [106].

**Cyprus**

In Cypriot breast cancer women proportion of **BRCA2** to **BRCA1** gene mutations is approximately 2:1 [107]. The **BRCA2** c.8755delIG (BIC: 8984delIG) mutation was reported in three unrelated families and could represent Cypriot founder mutation [107, 108].

**Denmark**

**BRCA1** and **BRCA2** small scale mutations in Denmark are a mixture of Scandinavian founder mutations and other European mutations, including **BRCA1** c.5266dupC. The most common **BRCA1** mutations were c.2475delC (BIC: 2594delC), c.3319G>T (BIC: 3438G>T), c.5266dupC and c.3710delT (BIC: 3829delT), which accounted 16%, 9%, 8% and 5% of **BRCA1** positive families, respectively [109–111]. The c.2475delC **BRCA1** mutation was also reported in Sweden, Norway and Western Europe (BIC database) and the c.3319G>T **BRCA1** mutation was also reported in Norway (http://www.legeforeningen.no/id/153250.0).

The most common **BRCA2** mutations were c.6373delA (BIC: 6601delA), c.1310_1013del4 (BIC: 1538del14), c.6486_6489del4 (BIC: 6714del4) and c.3847_3848delGT (BIC: 4075delGT), found in 11%, 10%, 9% and 5% of **BRCA2** positive families, respectively [111]. Two of the recurrent **BRCA2** mutations (c.1310_1313del4 and c.6486_6489del4) have also been observed in many other populations, whereas the c.6373delA **BRCA2** mutation is less frequent. There was a slight tendency towards a higher frequency of **BRCA2** families in West Denmark (56%) compared to East Denmark (44%). Altogether 7 common **BRCA1/2** mutations (excluding c.5266dupC) accounts for around 35% of carriers [4].

LGRs in **BRCA1** and **BRCA2** are common in East Denmark and account for 9.2% (15/163) of the disease causing mutations. **BRCA1** exons 3–16 deletion represents Danish founder mutation, comprising 40% (6/15) of all **BRCA1/2** families with LGRs [112].
Recently a pathogenic founder BRCA1 mutation c.234T>G (BIC: 2466T>G/Cys39Gly) was described in Greenland (Inuit population), an autonomous country within the Kingdom of Denmark, with a high carrier frequency (1.6%) in this population [113, 114]. Therefore all women of Greenlandic origin are recommended to be counseled and screened for this mutation [113].

Sweden

In Sweden, many different mutations in the BRCA1 and BRCA2 genes have been detected. The most recurrent BRCA1/2 mutation in Sweden is the single BRCA1 mutation c.3171_3175dup (BIC: 3171insS), which originate from a limited geographic area along the west coast of Sweden [115]. Mutation carriers have a conserved haplotype of 3,7 cM which is thought to have originated about 50 generations ago. In the western part of Sweden this mutation accounts for 65–77% of identified mutations in these two genes [116, 117]. Other common BRCA1 mutations in Sweden, c.2475delC and c.1082_1092del11 (BIC: 1201del11), have been detected primarily in families from southern Sweden [118–120], Denmark and Norway (BIC database). Another BRCA1 mutation, c.1687C>T, occurs primarily in southern Sweden as well as other European countries (BIC database). Yet another BRCA1 mutation c.3626delT (BIC: 3745delT) apparently originates in northern Sweden and Finland [121].

The 6-kb duplication of BRCA1 exon 13, aso known as ins6kbEx13 (HGVS: c.4186-1787_4357+4122dup; BIC: 4305ins6000(dup_ex13) mutation, is quite common in Sweden and is apparently specific to English-speaking and related countries [122].

One BRCA2 mutation c.4258delG (BIC: 4486delG) is found repeatedly in Swedish breast cancer families [120, 123].

In the Western Sweden, six mutations, including the most common BRCA1 c.3171_3175dup, four other common Scandinavian BRCA1 mutations (c.1082_1092del11, c.2475delC, c.1687C>T, c.1016dupA (BIC: 1135insA)) and one BRCA2 mutation (c.4258delG) accounted for approximately 75% of all BRCA1/2 mutations [124].

Four Norwegian founder mutations in BRCA1 gene c.1556delA (BIC: 1675delA), c.3228delAG (BIC: 3347delAG), c.697delGT (BIC: 816delGT) and c.1016dupA make up 68% of the BRCA1 mutation carriers [126, 127], and these have their own specific geographic distribution. The first three originate from the south-western region of the country, while the fourth is from the south-east [127].

These four founder mutations together with other six most frequent BRCA1/2 mutations (BRCA1 c.3178G>T (BIC: 3297G>T), c.4745delA (BIC: 4864delA), c.2351del7 (BIC: 2470del7), c.3084del11 (BIC: 3203del11) and BRCA2 c.2808del4 (BIC: 3036del4), c.3847delGT (BIC: 4075delGT), account for about 60% BRCA1/2 carriers in Norway [128]. BRCA1 c.1A>C (BIC: 120A>C) and c.5075-2A>C (BIC: IVS17-2A>C) mutations are also locally frequent. The large deletion of BRCA1 exons 1–13 is frequently found as well as exon 13 duplication (ins6kb13Ex) (http://www.inherited-cancer.com).

The BRCA1 c.1016dupA mutation has also been reported in other countries (Italy, Germany, French-Canada), however allelotyping results indicated an independent origin of this mutation. That would justify the inclusion of this mutation into targeted BRCA1 mutation screening panels in any population, irrespective of ethnic origin [129].

Finland

In the Finnish population, at least 13 recurrent BRCA1/2 mutations with a founder effect have been identified (6 in BRCA1 and 7 in BRCA2 gene), and these represent majority (around 84%) of all BRCA1/2 mutations detected [130–138]. The most common BRCA1 mutations are c.4097-2A>G (BIC: 4216-2A>G), c.3485delA (BIC: 3604delA), c.3626delT (BIC: 3745delT), c.4327C>T (BIC: 4446C>T), c.2684del2 (BIC: 2803delAA) and c.5251C>T (BIC: 5370C>T). The c.5266dupC is also found relatively frequently.

The most recurrent mutation in BRCA2 is the Icelandic founder mutation c.771_775del5 (BIC: 999del5), three other (c.7480C>T (BIC: 7708C>T), c.8327G>T (BIC: 8555T>G), c.9118-2A>G (BIC: 9346-2A>G) and following (c.6384del2 (BIC: 6503delTT), c.3853dupA (BIC: 4081insA) and c.5569G>T (BIC: 5797G>T)). Some mutations are unique to the Finns, such as c.4096+3A>G (BIC: IVS11+3A>G) in BRCA1 and c.9117+1G>A (BIC: 9345+1G>A), c.7480C>T, c.8327G>T in BRCA2 genes.

The mutation spectrum in Eastern part slightly differs from those observed in the Northern and Southern parts of the country [139].

Large genomic alterations are uncommon in BRCA1 or BRCA2 gene in the Finnish population [140–142], and only one LGR was found so far in BRCA1 [143].

Iceland

In Iceland, the most common single founder mutation is c.771_775del5 in the BRCA2 gene [144, 145], which accounts for virtually all breast/ovarian cancer families and simplifies genetic testing. It occurs in 0.4% (1/250) of
the population, 8.5% of consecutive unselected breast cancer cases, 7.9% of ovarian cancer cases and 40% of male breast cancer cases [6, 146].

The \textit{BRCA1} c.5074G>A (BIC: 5193G>A) is another founder mutation recently identified in Icelandic population, however it is extremely rare and contributes only to 1% of breast/ovarian cancer cases [147].

The profound founder effect in Iceland can be traced to comparatively small number of women, mostly originating from Scandinavia and the British Isles [148].

\textbf{United Kingdom}

There is some evidence about specific recurrent mutations confined to particular geographic regions in the UK.

In one study from Scotland and Northern Ireland 10 specific recurring mutations (five in each gene) accounted for almost half of the total mutations detected, and almost one-quarter were accounted by just two founder mutations (\textit{BRCA1} c.2681_2682delAA (BIC: 2800delAA) and \textit{BRCA2} c.6275_6276delTT (BIC: 6503delTT) [149]. The \textit{BRCA1} c.2681_2682delAA, probably originated from the West-Central Scotland or Ireland [150]. \textit{BRCA2} c.6275_6276delTT has been found elsewhere in the UK as well as in Dutch, Swedish, Danish and Belgian families (BIC database).

In the North-west of England two recurrent mutations (\textit{BRCA1} c.4065_4068del4 and \textit{BRCA2} c.1929delG (BIC: 2157delG) accounted for 16% of identified \textit{BRCA1} mutations in breast/ovarian cancer families and for 20% of \textit{BRCA2} positive male breast cancer families, respectively, what is around 1 in 8 of every mutation identified in each gene [151].

A duplication of a 6-kb fragment including \textit{BRCA1} exon 13 (ins6kbEx13), which creates a frameshift in the coding sequence, is considered to be a common founder mutation originating from Northern Britain [152] and comprise for 9% of \textit{BRCA1} mutations in UK [4, 152]. It is distributed mainly in English-speaking countries or in countries with historical links with Britain.

\textbf{Ireland}

A single \textit{BRCA1} c.427G>T (BIC: 546G>T/E143X) mutation accounts for about 22% of all hereditary breast cancer patients from relatively homogenous Irish population and presumably is due to the founder effect [153].

\textbf{Poland}

There is strong founder effect in Polish population for \textit{BRCA1} gene mutations. In Poland 3 most common mutations (c.5266dupC, c.181T>G and c.4035delA (BIC: 4154delA) accounted for 91% (111/122) \textit{BRCA1} mutations detected and for 86% of all detected mutations in \textit{BRCA1/2} genes [40, 100]. The \textit{BRCA1} c.5266dupC, c.181T>G and c.4035delA accounted for about 56%, 25% and 10% of all \textit{BRCA1} mutations, respectively. Mutations in \textit{BRCA2} gene comprises for about 5.4% of all \textit{BRCA1/2} mutations identified [40]. One of three \textit{BRCA1} founder mutations was identified in 13.5% (49/364) consecutive ovarian cancer cases and in 32.8% (58/177) women with familial ovarian cancer in Western Poland, therefore its reasonable to recommend genetic testing to all invasive ovarian cancer cases regardless the age [154].

Data from other groups indicate, that mutational \textit{BRCA1/2} spectrum in Poland is more dispersed and different in various subregions [155, 156]. In North-Eastern Poland two common mutations (c.5266dupC and c.181T>G) accounted for more than half (up to 70%) of all \textit{BRCA}-mutated families and no c.4035delA was identified [156], what is in accordance with other studies [157]. By adding two other recurring \textit{BRCA1} mutations (c.68_69delAG and c.3700_3704del5), the vast majority (87%) of mutation-positive families will be encompassed. At least 2 novel \textit{BRCA1} LGRs were found in Poland and they are not so uncommon [157].

In fact, observed \textit{BRCA1} founder mutations are by no means unique for Poland but rather of global or European distribution [156] and its necessary to extend analysis, including LGR, among patients negative for \textit{BRCA1/2} founder mutations.

\textbf{Latvia}

In Latvia two \textit{BRCA1} mutations (c.5266dupC and c.4035delA) made up more than 80% of all mutations \textit{BRCA1} identified [50, 158]. The 4154delA mutation is the second most abundant \textit{BRCA1} gene mutation after the c.5266dupC in Latvia [50] and is especially common for patients of Baltic (Latvian and Lithuanian) origin. It was also reported several times from Russia, Poland, has been predominantly detected in individuals of Eastern European and also is the most characteristic \textit{BRCA1} mutation in Lithuania [53, 54]. A common shared haplotype, with probable Lithuanian origin, was reported in these mutation carriers [159]. The \textit{BRCA1} c.181T>G is the third recurrent mutation in Latvia, but is not very commonly found. There are no data present about \textit{BRCA2} mutation profile in Latvia.

\textbf{Lithuania}

In Lithuania \textit{BRCA1} gene mutations are influenced by significant founder effect, which is similar to that reported from Latvian (Baltic) population [50]. \textit{BRCA1} c.4035delA and c.5266dupC attributes to 86% (53% and 33% respectively) of detected \textit{BRCA1} mutations [53, 54, 160]. Two
<table>
<thead>
<tr>
<th>Population</th>
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<th>BRCA2 mutation</th>
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<tr>
<td>Irish</td>
<td>c.427G&gt;T</td>
<td>546G&gt;T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polish</td>
<td>c.5266dupC</td>
<td>5382insC</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>c.181T&gt;G</td>
<td>300T&gt;G</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.4035delA</td>
<td>4154delA</td>
<td></td>
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<tr>
<td>Latvian</td>
<td>c.4035delA</td>
<td>4154delA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c.5266dupC</td>
<td>5382insC</td>
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</table>
other mutations, *BRCA1* c.181T>G and recently proved to be pathogenious c.5258G>C (BIC: 5377G>C/R1753T) were also found in more than one family; together with two founder mutations they comprise around 90% of *BRCA1* gene mutations and around 85% of all *BRCA1/2* mutations identified (Janavičius, unpublished data). Rapid screening of three *BRCA1* amplicons by HRM analysis now is the initial procedure for breast/ovarian cancer patients in our hospital.

The most frequently observed is *BRCA1* c.4035delA mutation, which is more frequent in families of Baltic (Lithuanian) origin rather than Slavic [53, 54, 161], and was detected in 16.3% (7/43) of unrelated ovarian cancer patients unselected for family history in one study [159]. Among *BRCA1* positive patients in a single population, this particular mutation has the highest proportion identified to date (53%), where in neighbouring countries (Latvia, Poland, Belarus and Russia) it accounts for around 40% [Tihomirova, personal communication], 10% [40], 9% [49] and 9% [41] respectively of all *BRCA1* mutations. This distribution is in agreement with geographic area of ancient Baltic people. Currently haplotype studies have been initiated to confirm further the occurrence and timing of this mutation in Lithuania.

**Estonia**

Newly published data from Estonia about *BRCA1/2* mutations structure showed significant involvement of *BRCA1* c.5266dupC and to a lesser extent *BRCA1* c.4035delA [162], what could be also expected projecting data from adjacent countries.

**Belarus**

Only one small study in West Belarus for targeted *BRCA1* mutations identified similar spectrum of 3 common mutations as in Poland, and c.5266dupC accounted here for 73% of all *BRCA1* mutations [49].

Russia

In Russia the most common *BRCA1* gene mutation in c.5266dupC, comprising around 90% of all *BRCA1* mutations [41, 163–167]. Other less common mutations found in Western Russia are c.4035delA, c.181T>G, and c.68_69delAG. In Siberian region of Russia there is seen preponderance of individual *BRCA2* gene mutations [164].

**Other countries**

In some countries, such as Romania, Bulgaria, Ukraine, Malta, Albania and most previous Yugoslavian countries (Serbia, Bosnia and Herzegovina, Macedonia and Montenegro) it seems no surveys on *BRCA1* and *BRCA2* mutations have been yet conducted and no data are available. From Croatia no conclusive data about founder *BRCA1/2* mutations pattern is available, since only some individual mutations and harmless variants were reported in one study [168].

**Conclusions**

The distribution of mutations in a European populations is characterized by the genetic homogeneity or heterogeneity of particular populations (Table 1). A stepwise mutation screening protocol, based on initial screening for the common mutations, is possible in populations with a high proportion of founder mutations, allowing for a more rapid, less expensive and hence, more affordable first-line genetic testing strategy. However, subsequent full *BRCA1/2* testing is mandatory in most populations, probably with the exception for Ashkenazi and Icelandic individuals, where effect of few founder mutations is nearly absolute. The contribution of LGRs should be also acknowledged for most populations and specific techniques must be considered to achieve full coverage of *BRCA1/2* genes. It is possible that common founder mutations remain to be identified in some populations.

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**Table 1**

<table>
<thead>
<tr>
<th>Population</th>
<th><em>BRCA1</em> mutation</th>
<th><em>BRCA2</em> mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HGVS</td>
<td>BIC</td>
</tr>
<tr>
<td>Lithuanian</td>
<td>c.4035delA</td>
<td>4154delA</td>
</tr>
<tr>
<td></td>
<td>c.5266dupC</td>
<td>5382insC</td>
</tr>
<tr>
<td>Belarusian</td>
<td>c.5266dupC</td>
<td>5382insC</td>
</tr>
<tr>
<td>Russian</td>
<td>c.5266dupC</td>
<td>5382insC</td>
</tr>
</tbody>
</table>

Apparently true founder mutations are written in italic. Nomenclature is given according HGVS (Human Genetic Variation Society) recommendations and BIC (Breast Cancer Information Core) database. *BRCA1* numbered by GeneBank U14680 reference sequence; *BRCA2* numbered by GeneBank U43746 reference sequence.
Knowledge about mutation distribution diversity is important not only for the consideration of country specific cost-efficient strategy for mutation screening, but also for the breast-ovarian cancer control and prevention through more liberal, yet rational, genetic testing and counseling in a globalized landscape of postmodern Europe. Common genetic variation (e.g. single nucleotide polymorphisms (SNPs)) might also influence disease risks in BRCA1/2 carriers and this subject is being addressed on a larger scale by the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA) which aims to identify genetic modifiers of breast and ovarian cancer risk in BRCA1 and BRCA2 carriers [169]. This information might be useful for more precise risk estimation in the near future.

Personalized treatment era, based on comprehensive and rapid BRCA1/2 genetic test result is nearly here. However, taking the profound and broad impact of positive genetic testing result for patients and their relatives, the importance of pre- and post-test oncogenetic counseling still remain essential.

Conflict of interest  No conflicts of interest to be disclosed. The author have full control of all primary data, if such are presented in text, and agree to allow the journal to review their data if requested.

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