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REVIEW ARTICLE

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

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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 possitive 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 enroling patients for PARP inhibitors clinical trials (van Osterweik, personal communication) as well as during peridiagnostic (presurgical) testing for a newly diagnozed 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 rearangements (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 ammenable 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:

6174delT) [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.5946delT) 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 c.5266dupC mutations (64% and 67% respectively), however is much lower for the c.5946delT 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>A)) 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: 5181delGTT) 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 *BRCA*2 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_3952delTAGinsAT 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_5064delGTT (BIC: 5181_5183delGTT/1688Val) variant of unknown significance (VUS) actually is a deleterious mutation with high frequency in North-East Italy [74]. The founder c.5062_5064delGTT 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: 3958delCTCAGinsAGGC) [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_3759del4 (BIC: 3875delGTCT), 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: c.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: 5374delTATG) 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: 3780G>T) and three *BRCA2* c.516+1G>A (BIC: IVS6+1G>A), c.6275_6276delTT (BIC: 6503_6504delTT), c.8904delC (BIC: 9132delC) alterations), which accounted 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 Braband 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.5946delT 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.8755delG (BIC: 8984delG) 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: 1538del4), 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 desribed 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: 3171ins5), 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, aslo 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 *BCRA1* 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]. The founder mutation, *BRCA1* c.3171_3175dup, may explains more than 80% of excess number of ovarian cancer after breast cancer in this region [115, 125].

Norway

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.8327T>G (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.8327T>G 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 *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].

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 (*BRCA1* c.2681_2682delAA (BIC: 2800delAA) and *BRCA2* c.6275_6276delTT (BIC: 6503delTT) [149]. The *BRCA1* c.2681_2682delAA, probably originated from the West-Central Scotland or Ireland [150]. *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 reccurent mutations (*BRCA1* c.4065_4068del4 and BRCA2 c.1929delG (BIC: 2157delG) accounted for 16% of identified *BRCA1* mutations in breast/ovarian cancer families and for 20% of *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 *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 *BRCA1* mutations in UK [4, 152]. It is distributed mainly in English-speaking countries or in countries with historical links with Britain.

Ireland

A single *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].

Poland

There is strong founder effect in Polish population for *BRCA1* gene mutations. In Poland 3 most common mutations (c.5266dupC, c.181T>G and c.4035delA (BIC: 4154delA) accounted for 91% (111/122) *BRCA1* mutations detected and for 86% of all detected mutations in *BRCA1/2* genes [40, 100]. The *BRCA1* c.5266dupC, c.181T>G and c.4035delA accounted for about 56%, 25% and 10% of all *BRCA1* mutations, respectively. Mutations in *BRCA2* gene comprises for about 5.4% of all *BRCA1/2* mutations identified [40]. One of three *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 *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 *BRCA*-mutated families and no c.4035delA was identified [156], what is in accordance with other studies [157]. By adding two other recurring *BRCA1* mutations (c.68_69delAG and c.3700_3704del5), the vast majority (87%) of mutation-positive families will be encompassed. At least 2 novel *BRCA1* LGRs were found in Poland and they are not so uncommon [157].

In fact, observed *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 *BRCA1/2* founder mutations.

Latvia

In Latvia two *BRCA1* mutations (c.5266dupC and c.4035delA) made up more than 80% of all mutations *BRCA1* identified [50, 158]. The 4154delA mutation is the second most abundant *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 *BRCA1* mutation in Lithuania [53, 54]. A common shared haplotype, with probable Lithuanian origin, was reported in these mutation carriers [159]. The *BRCA1* c.181T>G is the third recurrent mutation in Latvia, but is not very commonly found. There are no data present about *BRCA2* mutation profile in Latvia.

Lithuania

In Lithuania *BRCA1* gene mutations are influenced by significant founder effect, which is similar to that reported from Latvian (Baltic) population [50]. *BRCA1* c.4035delA and c.5266dupC attributes to 86% (53% and 33% respectively) of detected *BRCA1* mutations [53, 54, 160]. Two

Table 1 Most common and founder *BRCA1/2* mutations in European populations

Population	*BRCA1* mutation		*BRCA2* mutation	
	HGVS	BIC	HGVS	BIC
Ashkenazi Jews	*c.68_69delAG*	*185delAG*	*c.5946delT*	*6174delT*
	c.5266dupC	*5382insC*		
Austrian	c.181T>G	300T>G	c.8363G>A	8591G>A
	c.5266dupC	5382insC	c.8754+1G>A	IVS21-1G>A
	c.1687C>T	1806C>T	c.3860delA	4088delA
	c.3016_3019del4	3135del4		
	c.2676_2679del4	*2795del4*		
Slovenian	c.1687C>T	1806C>T	*c.7806-2A>G*	*IVS16-2A>G*
	c.181T>G	300T>G		
	c.5266dupC	5382insC		
	c.181T>A	300T>A		
Italian (Tuscany)	*c.3228_3229delAG*	*3347delAG*	*c.8537_8538delAG(Sardinia)*	*8765delAG*
	c.3285delA	*3404delA*		
	c.1380dupA	*1499insA*		
	c.5062_5064del3	*5181delGTT*		
Italian (Calabria)	*c.4964_4982del19*	*5083del19*		
Italian (North-East)	*c.5062_5064delGTT*	*5181_5183delGTT*		
French	*c.3481_3491del11*	*3600del11*		
	c.5128G>T	5247G>T		
Spanish	*c.68_69delAG*	*185delAG*	c.2808_2811del4 (Castilla-Leon)	3036_3039del4
	c.211A>G (Galicia)	*330A>G*	c.6629_6630delAA	c.6857delAA
	c.5117G>A	5236G>A	c.9026_9030del5	9254-9258del5
	c.5123C>A	5242C>A	c.9310_9311delAA	9538delAA
	c.470_471delCT	589_590delCT	*c.5146_5149del4*	*374delTATG*
	c.5153-1G>A	*5272-1G>A*		
Portuguese			*c.156_157insAlu*	*384insAlu*
Belgian	*c.212+3A>G*	*IVS5+3A>G*	*c.516+1G>A*	*IVS6+1G>A*
	c.2359dupG	*2478insG*	*c.6275_6276delTT*	*6503_6504delTT*
	c.3661G>T	*3780G>T*	*c.8904delC*	*9132delC*
Dutch	*c.2685_2686delAA*	*2804delAA*	*c.5351dupA*	*5579insA*
	c.2193del5	2312del5	*c.6275_6276delTT*	*6503delTT*
	c.1292dupT	1411insT		
	exon 13 deletion (3,8-kb)			
	exon 22 deletion (510-bp)			
German	*exon 17 deletion*		c.1813dupA	2041insA
	c.5266dupC	*5382insC*	c.4478del4	4706del4
	c.181T>G	300T>G	c.9098dupA	9326insA
	c.4065_4068del4	4184del4		
	c.2338C>T	2457C>T		
Czech	c.181T>G	300T>G	*c.7913_7917del5*	*8141del5*
	c.5266dupC	*5382insC*	*c.8537_8538del2*	*8765delAG*
	c.3700_3704del5	3819del5		
	exons 1–17 deletion			
	exons 5–14 deletion			
Hungarian	*c.5266dupC*	*5382insC*	c.9098dupA	9326insA
	c.181T>G	*300T>G*	*c.5946delT*	*6174delT*
	c.68_69delAG	185delAG		

Table 1 (continued)

Population	*BRCA1* mutation		*BRCA2* mutation	
	HGVS	BIC	HGVS	BIC
Greek	*c.5266dupC*	*5382insC*		
	c.5212G>A	5331G>A		
	c.5251C>T	5370C>T		
	c.5467G>A	5586G>A		
Cypriot			*c.8755delG*	*8984delG*
Danish	*c.2475delC*	*2594delC*	c.6373delA	6601delA
	c.3319G>T	3438G>T	c.1310_1013del4	1538del4
	c.5266dupC	5382insC	c.6486_6489del4	6714del4
	c.3710delT	3829delT	c.3847_3848delGT	4075delGT
	exons 3-16 deletion			
Swedish	*c.3171_3175dup*	*3171ins5*	c.4258delG	4486delG
	c.2475delC	*2594delC*		
	c.1082_1092del11	*1201del11*		
	c.1687C>T	1806C>T		
	c.3626delT (Northern)	*3745delT*		
	c.1016dupA	1135insA		
	exon 13 duplication (ins6kbEx13)			
Norwegian	c.1556delA	1675delA	*c.2808del4*	*3036del4*
	c.3228delAG	*3347delAG*	*c.3847delGT*	*4075delGT*
	c.697delGT	*816delGT*		
	c.1016dupA	1135insA		
	c.3178G>T	*3297G>T*		
	c.4745delA	*4864delA*		
	c.2351del7	*2470del7*		
	c.3084del11	*3203del11*		
	c.1A>C	120A>C		
	c.5075-2A>C	IVS17-2A>C		
	exons 1-13 deletion			
	exon 13 duplication (ins6kbEx13)			
Finnish	c.4097-2A>G	4216-2A>G	c.771_775del5	999del5
	c.3485delA	3604delA	*c.7480C>T*	*7708C>T*
	c.3626delT	3745delT	*c.8327T>G*	*8555T>G*
	c.4327C>T	4446C>T	c.9118-2A>G	9346-2A>G
	c.2684del2	2803delAA	*c.9117+1G>A*	*9345+1G>A*
	c.5251C>T	5370C>T		
	c.4096+3A>G	*IVS11+3A>G*		
Iceland			*c.771_775del5*	*999del5*
British	*c.2681_2682delAA (Scotland)*	*2800delAA*	c.6275_6276delTT *(Scotland)*	6503delTT
	c.4065_4068del4 (North-West)	4184del4	c.1929delG (North-West)	2157delG
	exon 13 duplication (ins6kbEx13)			
Irish	*c.427G>T*	*546G>T*		
Polish	*c.5266dupC*	*5382insC*		
	c.181T>G	*300T>G*		
	c.4035delA	4154delA		
Latvian	*c.4035delA*	*4154delA*		
	c.5266dupC	5382insC		

Table 1 (continued)

Population	*BRCA1* mutation		*BRCA2* mutation	
	HGVS	BIC	HGVS	BIC
Lithuanian	*c.4035delA*	*4154delA*		
	c.5266dupC	5382insC		
Belarusian	*c.5266dupC*	*5382insC*		
	c.181T>G	300T>G		
Russian	*c.5266dupC*	*5382insC*		

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

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 innitial 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 innitiated to confirm further the occurence 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.

Knowledge about mutation distibution 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, taken the profoud and broad impact of possitive 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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