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Prevalence of the most frequent *BRCA1* mutations in Polish population

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Abstract The purpose of our study was to establish the frequency and distribution of the four most common *BRCA1* mutations in Polish general population and in a series of breast cancer patients. Analysis of the population frequency of 5382insC (c.5266dupC), 300T >G (p.181T >G), 185delAG (c.68_69delAG) and 3819del5 (c.3700_3704del5) mutations of the *BRCA1* gene were performed on a group of respectively 16,849, 13,462, 12,485 and 3923 anonymous samples collected at birth in seven Polish provinces. The patient group consisted of 1845 consecutive female breast cancer cases. The most frequent *BRCA1* mutation in the general population was 5382insC found in 29 out of 16,849 samples (0.17%). 300T >G and 3819del5 mutations were found in respectively 11 of 13,462 (0.08%) and four of 3923 (0.1%) samples. The population prevalence for combined Polish founder 5382insC and 300T >G mutations was 0.25% (1/400). The frequencies of 5382insC and 300T >G carriers among consecutive breast cancer cases were, respectively, 1.9% (35/1845) and 1.2% (18/1486). Comparing these data with the population frequency, we calculated the relative risk of breast cancer for 5382insC mutation at OR = 17 and for 300T >G mutation at OR = 26. Our results, based on large population studies, show high frequencies of founder 5382insC and 300T >G *BRCA1* mutations in Polish general population. Carriage of one of these mutations is connected with a very high relative risk of breast cancer.

Keywords *BRCA1* mutations · *BRCA1* in Poland · Hereditary breast cancer

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Introduction

Germline mutations in *BRCA1* gene are transmitted in an autosomal dominant manner with high penetrance, which predisposes individuals to breast and ovarian cancer. The carrier frequency in general populations ranges between 1/40 and 1/800 and depends on founder effect specific for distinct populations. In Poland, the founder *BRCA1* mutations are 5382insC, originated in the Baltic area, and 300T >G, widely spread throughout Central Europe.

These two DNA changes accounted for 60–80% *BRCA1* mutations in Poland (Gorski et al. 2000; Grzybowska et al. 2000; Jasinska and Krzyzosiak 2001; Perkowska et al. 2003; Ratajska et al. 2008; Van Der Looij et al. 2000a). The same two founder mutations were described in Germans, Latvians and Czechs (Csokay et al. 1999; Elsakov et al. 2010; Meindl et al. 2002). Other recurrent mutations in Polish population were described as founders in some European populations: 3819del5 (founder in Czech Republic), 185delAG (Ashkenazi Jews), 4153delA (Lithuania) and their distribution is variable in different historical regions of Poland.

The highest frequency of *BRCA1/2* founder mutations is recorded in Ashkenazi Jews (2–2.5%) and Icelanders (0.6%) (Neuhausen et al. 2009; Struewing et al. 1997). Even though founder effect was also recorded in other populations, in most European and American countries *BRCA1/2* mutations occur with the lower frequency of 0.06–0.24% (Antoniou et al. 2002; Ford et al. 1995; Whittemore et al. 1997, 2004). So far, only a few works were based on direct measurements of mutation occurrence but they were usually provided in ethnically and genetically distinct small populations (Gorski et al. 2005; Malone et al. 2006; Metcalfe et al. 2010; Struewing et al. 1997; Van Der Looij et al. 2000b). To date, most investigators estimated *BRCA1/2* gene mutation frequency indirectly by combining data from population-based series of breast and ovarian cancer patients with estimates of the cumulative risk of these cancers in carriers and non-carriers or on the basis of cancer mortality among relatives of affected women (Ford et al. 1995, Risch et al. 2006, Whittemore et al. 1997 and 2004).

The purpose of our study was to establish the frequency and spectrum of *BRCA1* mutations in Polish general population and consecutive breast cancer cases. Our choice of the four *BRCA1* alleles analysed in the present study reflects their high prevalence among Polish breast and/or ovarian cancer families and is based on the results of previous research (Brozek et al. 2009; Gorski et al. 2000; Grzybowska et al. 2000; Janiszewska et al. 2003; Jasinska and Krzyzosiak 2001; Perkowska et al. 2003; Ratajska et al. 2008; Van Der Looij et al. 2000a, b).

Materials and methods

Analysis of the frequency of 5382insC (c.5266dupC), 300T >G (p.181T >G), 185delAG (c.68_69delAG), and 3819del5 (c.3700_3704del5) mutations of *BRCA1* gene were performed on groups of respectively 16,849, 13,462, 12,485 and 3923 anonymous samples collected at birth. We made use of dried blood spots on filter paper applied for neonatal screening for phenylketonuria. The samples were collected from hospitals spread over the area of seven voivodeships of Poland. The population of these voivodeships equals 58% of the whole Polish population.

Consecutive, newly diagnosed female breast cancer cases were collected without regard to age or family history of breast and ovarian cancer in two voivodeships, Malopolska and Mazowsze. The patient study group included 1845 breast cancer patients.

Dried blood spots on filter paper were fragmented into 2 mm pieces. After their denaturation at 95°C in 25 µl H_2O, samples were subjected to 20 cycles of PCR reaction. Next, PCR product was centrifuged and 40 cycles nested PCR amplification were performed. The PCR primer sequences were: exon 2 Forward GAAGTTGTCATTTTA TAAACCTTT, Reverse TGTCTTTTCTTCCCTAGTATGT, exon 5 Forward GTTGTGAGATTATCTTTTCATGGC, Reverse CTTCCAACCTAGCATCATTACCA, exon 11 Forward GAGTCCTAGCCCTTTCACCCATAC, Reverse GTGATGTTCCTGAGATGCCTTTG, exon 20 Forward ATATGACGTGTCTGCTCCACC, Reverse AAT GAAGCGGCCCATCTC. Details concerning amplification conditions are available upon request.

In the groups of consecutive breast cancer cases DNA was extracted from peripheral blood lymphocytes in accordance with standard procedure. The contributions the mutation detection methods made to analysis pathogenic allels and representative examples of mutations detected by various methods are shown in Fig. 1. Mutation analyses were done using a combination of different screening methods. For detection of mutation 185delAG located in exon two and 3819del5 located in exon 11 of *BRCA1* gene single strand conformation polimorphism (SSCP) and denaturing high performance liquid chromatography (DHPLC) technique were used. For identification of change T >G in position 300 (exon 5) the restriction fragment length polymorphism (RFLP) or DHPLC were taken. For the last mutation tested within this study (5382insC, exon 20) an Allele Specific Oligonucleotide PCR (ASO-PCR) or DHPLC techniques were carried out. The sensitivity of applicated techniques ranges from 70% for SSCP to 98% for DHPLC.

The prevalence of each mutation was derived from the ratio of positive samples to the total number of tested samples. Comparisons between groups for statistical significance were performed by the use of χ^2 and Fisher's exact tests, as appropriate. P values less than 0.05 were considered statistically significant. For breast cancer relative risk estimation, we compared the proportions of the prevalence of the most common *BRCA1* founder mutations in consecutive breast cancer cases with the population controls. The results are presented as odds ratios (ORs) generated from two-by-two tables. Confidence intervals (CIs) are reported at the 95% significance level.

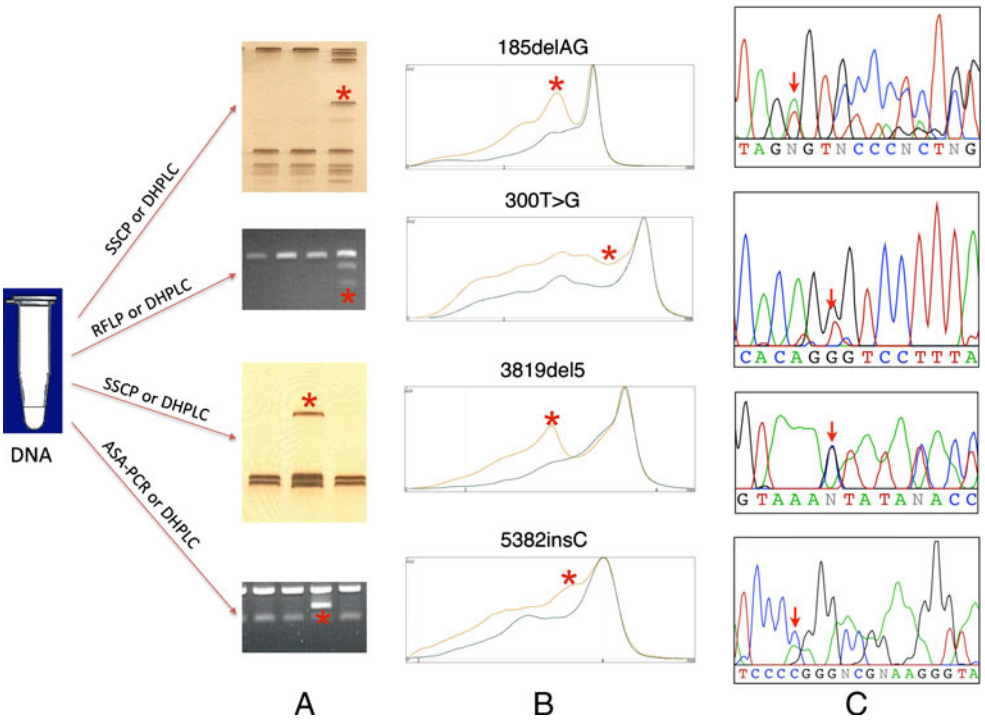

Fig. 1 The contributions the mutation detection methods made to analysis pathogenic allels and representative examples of detected mutations. **a** - representative gels showing PCR products, **b** - representative DHPLC chromatograms, **c** - representative sequencing results confirming the presence of the mutations, RFLP - restriction fragment length polymorphism, SSCP - single-strand conformation polymorphism, ASA-PCR - allele-specific PCR, DHPLC - denaturing high performance liquid chromatography

Results

The most frequent *BRCA1* mutation in the analysed population, without the division into provinces, was 5382insC found in 29 out of 16,849 samples (0.17%). 300T >G and 3819del5 mutations were found in respectively 11 out of 13,462 (0.08%) and four out of 3923 (0.10%) samples. 185delAG mutations were not found in any of 12,485 analysed newborn samples. The population frequencies for combined Polish founder 5382insC and 300T >G mutations without the division into provinces was 0.25% (1/400). As using a combination screening methods these two mutations are detected in 70–90% of all *BRCA1*-positive Polish families, we estimated the frequency of *BRCA1* mutations in general population of Poland at about 1/240–1/360.

Figure 2 shows the geographical distribution of analysed mutations with the division of Poland into voivodeships. We observed that the prevalence of recurrent mutations varies according to the geographical origin of the collected samples. For 5382insC mutation, the difference in frequency between three provinces was of statistical significance. This genetic change was the most common in Warmia–Mazury (10/2377, 0.42%) where it was significantly higher than in Pomorze (0/2578, 0.0%) (p=0.001) and Malopolska (2/2231, 0.09%) (p=0.028). For other analysed mutations, the differences in frequency between provinces were not statistically significant.

In the group of unselected breast cancers collected in two provinces, Malopolska and Mazowsze, the most frequent mutation was 5382insC (35/1845, 1.9%) followed by 300T >G (18/1486, 1.2%). Comparing 5382insC mutation frequency in breast cancer cases with the mutation frequency detected in general newborn population of these two provinces (5/4471), we calculate the relative risk of breast cancer for this mutation at OR = 17 (95%CI 6.6–43.4). For 300T >G missense mutation (2 out of 4352 control samples), the relative risk calculated in this way was OR = 26 (95%CI 6.1–113.7).

Discussion

For *BRCA1* and *BRCA2* gene mutations controling large scale series are limited by the relative low prevalence of these mutations in the general population, as well as the complexity and cost of analysis of thousands of control subjects. A crucial factor in this type of studies is the occurrence of population specific, recurrent mutations. Our choice of four *BRCA1* alleles analysed in the present study reflects their high frequency among Polish multiple breast and/or ovarian cancer families (Brozek et al. 2009; Gorski et al. 2000; Grzybowska et al. 2000; Jasinska and Krzyzosiak 2001; Perkowska et al. 2003; Ratajska et al. 2008; Van Der Looij et al. 2000a). As a strong founder effect is noted in Poland, two *BRCA1* mutations, truncating 5382insC and missense 300T >G comprise 70–90% of all *BRCA1* pathogenic alterations. This finding allows for rapid and relatively cheap DNA screening in Polish population.

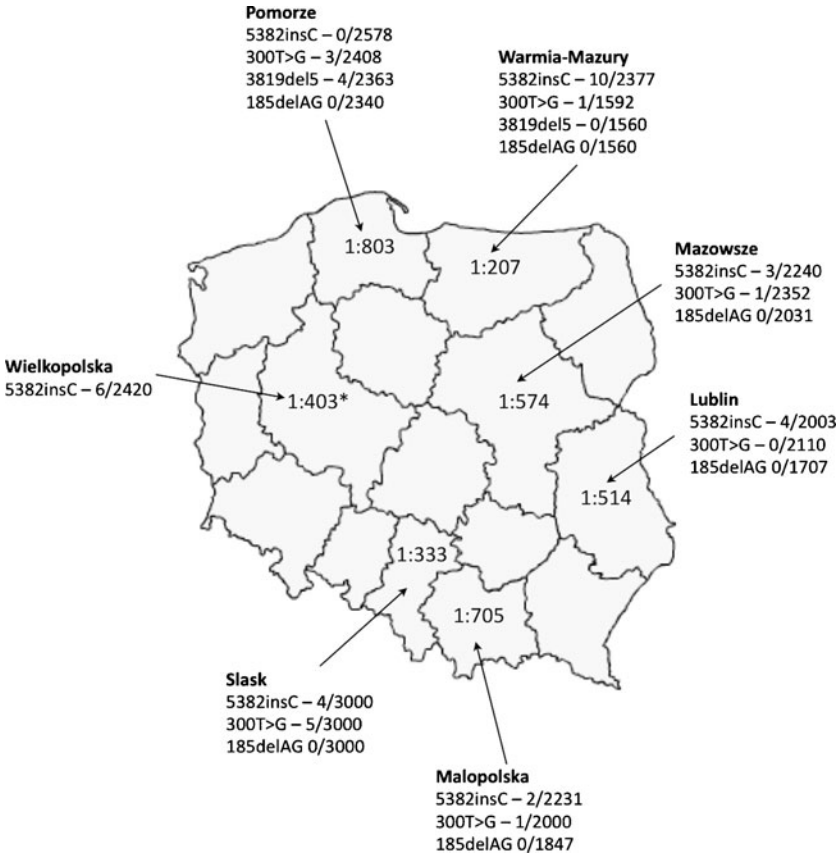

Fig. 2 Map of Poland with division into voivodeships showing geographical distribution and frequencies of *BRCA1* 5382insC, 300T >G, 185delAG, and 3819del5 mutations. * - only 5382insC mutation

In most European and North American countries, *BRCA1/2* mutations occur with the frequency of 0.06–0.24% (Antoniou et al. 2002; Ford et al. 1995; Malone et al. 2006; Whittemore et al. 1997, 2004). Even though Hall et al. (2009) reported that *BRCA1/2* mutation prevalence is remarkably similar among women who undergo genetic testing across diverse ethnicities, in some populations the frequency of mutations can be higher because of strong founder effect. Relatively high prevalence of *BRCA1* (0.32%) and *BRCA2* (0.69%) mutations described in the population of Ontario, Canada, can be caused by the inclusion of subjects from groups that harbour frequent founder mutations (Ashkenazi Jews and French Canadians) (Metcalfe et al. 2010; Risch et al. 2006). In such countries as Israel or Iceland, founder mutations account for the great majority of deleterious *BRCA1/2* mutations. The strongest founder effect was noted in the Ashkenazi Jew population, where two common mutations: 185delAG in *BRCA1* and 6174delT in *BRCA2* occur with cumulative frequency of about 2–2.5% (Ferla et al. 2007; Neuhausen et al. 2009; Struewing et al. 1997). The third relatively common mutation in Ashkenazi Jews is 5382insC, described in this population with the frequency of 0.12–0.32% (Struewing et al. 1997; Fodor et al. 1998). Among the families with multiple breast and ovarian cancers from Western and Central Europe, this mutation is respectively two and four times as common as 185delAG (Hall et al. 2009).

In our study of 16,849 anonymous newborns, 5382insC mutation prevalence was 0.17%, so its frequency is similar to that observed in Ashkenazi Jews, whereas 185delAG mutations were not found in any of 12,485 analysed samples. In population study presented by Gorski et al. (2005) provided on the combined group of 4000 control individuals from north-western Poland 5382insC mutation occurred in 0.35% of analysed subjects. This mutation is also prevalent in many European countries like Russia, where it was detected in 94% of *BRCA1* mutation carriers (Loginova et al. 2003; Sokolenko et al. 2006), Germany (22%) (Meindl et al. 2002), Czech Republic (37–40%) (Foretova et al. 2004; Machackova et al. 2008), and Lithuania (63%) (Csokay et al. 1999).

The second founder mutation for Polish population is 300T >G, detected in 0.082% of the analysed samples. In the study provided by Gorski et al. (2005), this DNA change was detected in 0.05% control subjects. 300T >G mutation is regarded as the founder change in many Central European countries, like Germany, Hungary, Lithuania, Austria and Poland (Csokay et al. 1999; Kroiss et al. 2005; Meindl et al. 2002; Van Der Looij et al. 2000b). We also observed relatively high frequency of 3819del5 *BRCA1*

mutation in Pomorze, previously described in breast and/or ovarian cancer families and in consecutive ovarian cancers in this region (Brozek et al. 2008; Ratajska et al. 2008). This mutation is also frequent in the Czech Republic, where it was detected in 13–15% *BRCA1*-carriers (Foretova et al. 2004; Machackova et al. 2008). Data of DNA analysis collected from Pomorze population will allow us to design a wider panel of recurrent mutations (including 3819del5) useful in providing efficient *BRCA1* screening that may be applicable to Polish breast and/or ovarian cancer families.

On the basis of an analysis of family area of origin before the Second World War (WWII), Gorski et al. did not notice any particular geographical aggregation of specific *BRCA1* mutations in different voivodeships of Poland (Gorski et al. 2005). The present comparison of occurrence of *BRCA1* mutations in seven areas of Poland shows that some mutations differ in their relative frequencies, although the small number of positive samples does not allow us to reach statistical significance. The low frequency of individual mutations means that even large studies often detect only a small number of carriers and, even when we analyse relatively frequent founder changes, the estimates lack precision. Polish population is not ethnically mixed, because of the loss of a considerable number of ethnic groups from Poland's territory and the extensive resettlements and mixing of Poles after WWII (Ploski et al. 2002). In such ethnically homogeneous populations, for a more precise estimation it is more valuable to present mutation frequency for the population at large, without division into voivodeships. Our studies embraced >16,000 samples, which is, to date, the biggest ever published analysis of *BRCA1* mutation frequency and the mutation prevalence estimated in this way seems to be the most precise.

The frequency of *BRCA1/2*-positive breast cancer cases is evaluated at 2–5% (Gorski et al. 2005; John et al. 2007; Kurian 2010; Malone et al. 2006; Sokolenko et al. 2006; Whittemore et al. 2004) and it is in accord with our observations. Comparing population frequency of 5382insC mutation in Mazowsze and Malopolska (5/4471) with the rate of *BRCA1*-carriers among consecutive breast cancer patients (35/1845) in these provinces, we calculate the relative risk of breast cancer for this mutation at OR = 17. For missense 300T >G mutation (present in 18 out of 1486 breast cancer cases and in two out of 4352 control samples) odds ratio calculated in this way is OR = 26. These odds ratios are higher than estimated by Gorski et al. (2005), who calculated the relative risk for 5382insC at OR = 6.2 and for 300T >G at OR = 15. In both studies, ours and those provided by Gorski, the odds ratio for 300T >G *BRCA1* mutation was higher than for 5382insC mutation but since *BRCA1* mutations are relatively rare, estimations calculated in this way lack precision. Knowing the breast cancer risk in the population of Polish women, (0.047 by the age of 70), and the odds ratio for 5382insC mutation, we estimated penetrance for this mutation at 0.8. Our evaluations are slightly higher than those earlier presented for this mutation (Antoniou et al. 2005; Kroiss et al. 2005). A combined analysis of several studies presented by Antoniou et al. has shown that breast cancer lifetime risk for 5382insC mutation in Ashkenazi Jews is 67% and probably does not differ from the risk in non-Ashkenazi Jewish women (Antoniou et al. 2005; Brose et al. 2002).

The advantages of our study include its large sample size and direct mutation scanning in population controls, whereas other large population-based studies extrapolated population carrier prevalence from breast and/or ovarian cancer case studies. We believe that random choice of anonymous newborn samples creates the best control group for estimation *BRCA* mutation prevalence in gthe eneral population, because this type of study eliminates the unwanted family selection present in studies based on volunteers.

Conclusions

Our results, based on large population studies, show high frequencies of founder 5382insC and 300T >G *BRCA1* mutations in Polish general population. The population prevalence for combined Polish founder 5382insC and 300T >G mutations was 0.25% (1/400). Carriage of one of these mutations is connected with a very high relative risk of breast cancer.

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