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ORIGINAL ARTICLE

Founder vs. non-founder *BRCA1/2* pathogenic alleles: the analysis of Belarusian breast and ovarian cancer patients and review of other studies on ethnically homogenous populations

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Abstract

The spectrum of *BRCA1/2* mutations demonstrates significant interethnic variations. We analyzed for the first time the entire *BRCA1/2* coding region in 340 Belarusian cancer patients with clinical signs of *BRCA1/2*-related disease, including 168 women with bilateral and/or early-onset breast cancer (BC), 104 patients with ovarian cancer and 68 subjects with multiple primary malignancies involving BC and/or OC. *BRCA1/2* pathogenic alleles were detected in 98 (29%) women, with 67 (68%) of these being represented by founder alleles. Systematic comparison with other relevant studies revealed that the founder effect observed in Belarus is among the highest estimates observed worldwide. These findings are surprising, given that the population of Belarus did not experience geographic or cultural isolation throughout history.

Keywords Belarus · *BRCA1/2* · Breast cancer · Founder mutations · Ovarian cancer

Introduction

BRCA1/2 germline mutations make a significant contribution to breast and ovarian cancer morbidity. The spectrum of *BRCA1/2* pathogenic variants is characterized by a high level of diversity; therefore, *BRCA1/2* testing involves a thorough analysis of nucleotide sequences of these genes. Some countries and ethnic groups demonstrate a so-called founder effect, which is attributed to geographic and/or cultural isolation. Countries with predominantly Slavic population, such as Poland, Belarus, Ukraine, and Russia, have surprisingly pronounced genetic homogeneity. For example, recurrent mutations in *BRCA1/2* genes constitute at least half of *BRCA1/2* pathogenic alleles detected in the breast or ovarian cancer patients [1–6].

Recent NGS-based studies provided a more systematic overview with regard to the *BRCA1/2* mutation spectrum in Poland and Russia. It has been convincingly demonstrated that earlier investigations overestimated the ratio between founder and non-founder pathogenic alleles in these countries and provided grounds for full-length *BRCA1/2* clinical testing in at-risk groups. Belarus is a country with a Slavic population, which is located between Poland and Russia, has over 9 million inhabitants, and is characterized by the predominance of ethnic Belarusians coupled with a relatively low presence of non-Slavic people. The analysis of several founder mutations in Belarusian consecutive ovarian cancer patients revealed pathogenic alleles in 25% of analyzed women suggesting that PCR-based *BRCA1/2* testing is highly efficient in this ethnic group [7, 8]. This study aimed to provide a comprehensive overview of the distribution of *BRCA1/2* pathogenic alleles in patients from Belarus.

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Materials and methods

This study included 340 consecutive patients who had clinical signs of *BRCA1/2*-related cancer disease and were referred to Grodno University Clinic within the years 2019–2021. The inclusion criteria were the diagnosis of ovarian cancer (OC; n = 104), bilateral or early-onset (aged < 50 years) breast cancer (BC; n = 168), or multiple primary malignancies involving BC and/or OC (n = 68). In addition, we considered 97 OCs from the study [8] that were negative for 13 Central European / Slavic founder alleles (*BRCA1*: c.68_69delAG [p.Glu23fs], c.181T > G [p.Cys61Gly], c.676delT [p.Cys226fs], c.1687C > T [p.Gln563Ter], c.3756_3759delGTCT [p.Ser1253fs], c.3700_3704delGTAAA [p.Val1234fs], c.4035delA [p.Glu1346fs], c.5251C > T [p.Arg1751Ter], c.5266dupC [p.Gln1756fs]; *BRCA2*: c.658_659delGT [p.Val220fs], c.3847_3848delGT [p.Val1283fs], c.5946delT [p.Ser1982fs], c.7913_7917delTTCCT [p.Ala2637_Phe2638insTer]). Clinical characteristics of BC and OC cases and the flowchart summarizing the patient recruitment are presented in Supplementary Fig. S1 and Table 1.

DNA from blood lymphocytes was extracted either by conventional protocol [9] or with ReliaPrep Blood gDNA Miniprep System (Promega). 400 ng of genomic DNA were subjected to the library preparation with Kapa HyperPlus Kit (Roche) according to the manufacturer's instructions. Dual-index libraries were used to pool up to 96 samples into one

Table 1 Patient cohorts and *BRCA1/2* mutation frequencies

Clinical features	*BRCA1* pathogenic variants frequency	*BRCA2* pathogenic variants frequency	Total	Notes
Ovarian cancer				
Age				
</= 50	11/40 (27.5%)	1/40 (2.5%)	12/40 (30%)	*BRCA1: p = 0.21*
> 50	10/64 (15.6%)	5/64 (7.8%)	15/64 (23.4%)	*BRCA2: p = 0.4*
Family history of BC or OC in first-degree relatives				
Yes	7/17 (41.2%)	1/17 (5.9%)	8/17 (47%)	*BRCA1:*
No	14/87 (16.1%)	5/87 (5.7%)	19/87 (21.8%)	***p = 0.03*** *BRCA2: p = 1*
Total	21/104 (20.2%)	6/104 (5.8%)	27/104 (26%)	
Breast cancer				
Bilaterality				
Yes	12/29 (41.4%)	5/29 (17.2%)	17/29 (58.6%)	*BRCA1:*
No	29/139 (20.9%)	2/139 (1.4%)	31/139 (22.3%)	***p = 0.03*** *BRCA2:* ***p = 0.002***
Family history of BC or OC in first-degree relatives				
Yes	18/41 (43.9%)	5/41 (12.2%)	23/41 (56.1%)	*BRCA1:*
No	23/127 (18.1%)	2/127 (1.6%)	25/127 (19.7%)	***p = 0.0015*** *BRCA2:* ***p = 0.01***
Total	41/168 (24.4%)	7/168 (4.2%)	48/168 (28.6%)	
Multiple primaries				
First cancer before age 50				
Yes	13/30 (43.3%)	2/30 (6.7%)	15/30 (50%)	*BRCA1:*
No	4/38 (10.5%)	4/38 (10.5%)	8/38 (21%)	***p = 0.004*** *BRCA2:* ***p = 0.6901***
OC + BC	13/23 (56.5%)	4/23 (17.4%)	17/23 (74%)	
OC and other malignancy*	3/17 (17.6%)	0/17 (0)	3/17 (17.6%)	
BC and other malignancy**	1/28 (3.6%)	2/28 (7.1%)	3/28 (10.7%)	
All cases	79/340 (23.2%)	19/340 (5.6%)	98/340 (28.8%)	

*OC and endometrial cancer (n = 9); OC and colorectal cancer (n = 3), OC and renal cancer (n = 2), OC and lung cancer (n = 2), OC and gastric cancer (n = 1)

**BC and endometrial cancer (n = 13), BC and thyroid cancer (n = 3), BC and cervical cancer (n = 2), BC and colorectal cancer (n = 1), BC and renal cancer (n = 1), BC and vaginal cancer (n = 1), BC and melanoma (n = 1), BC and gastric cancer (n = 1), BC, and gastric cancer, and granulosa cell tumor (n = 1), BC, and renal cancer, and endometrial cancer (n = 1), BC, and colorectal cancer, and esophageal cancer (n = 1), BC, and endometrial cancer, and colorectal cancer, and bladder cancer (n = 1), BC, and renal cancer, and vulvar cancer (n = 1)

enrichment reaction. 1000 ng of pooled DNA libraries were enriched with a custom panel of biotinylated probes covering coding sequences as well as exon-intron boundaries and 5'- and 3'-untranslated regions of *BRCA1* and *BRCA2*. Due to the small size of the panel, two-round overnight hybridization was performed. Enriched libraries were sequenced on the Illumina NextSeq 500 platform with the Mid Output Kit v2.5 reagents in a paired-end mode for 150 cycles in both orientations. Mean depth-of-coverage reached x1500 with 99.9% of bases read at least 100 times. The bioinformatic pipeline included standard steps, i.e., FASTQ files generation, quality assessment, and mapping of the obtained sequences to the hg19 genome using the BWA tool. Aligned reads were subjected to SNVs and indels calling with the HaplotypeCaller [GATK4]. DNA sequence annotation was made with the SnpEff software instrument.

Results

The analysis of 340 genetically enriched BC and OC patients revealed 98 (29%) carriers of *BRCA1/2* pathogenic alleles (Table 1). Interestingly, DNA testing of consecutive women with OC diagnosis, either alone or as part of multiple primary malignancies, identified *BRCA1/2* germline mutations in 47/144 (33%) cases, which is among the highest estimates reported worldwide [10–12].

We compared the spectrum of identified mutations towards 13 Central European / Slavic founder alleles described in [8]. Two *BRCA1* mutations, c.5266dupC and c.4035delA, were observed in more than a half of 98 *BRCA1/2* heterozygotes (41 (42%) and 13 (13%), respectively). In addition to these two variants, only four of previously considered 13 alleles were detected in Belarusian patients; each of these mutations occurred more than once (*BRCA1* c.68_69delAG: n = 2; c.181T > G: n = 3; c.3756_3759delGTCT: n = 3; *BRCA2* c.658_659delGT: n = 3). In addition, *BRCA1* c.4689C > G pathogenic substitution was revealed in 4 patients. The analysis of 97 founder mutation-negative OC patients described in [8] identified only 8 *BRCA1/2* mutation carriers (*BRCA1* c.1612C > T: n = 1; c.1961dupA: n = 1; c.3477_3480delAAAG: n = 1; c.3770_3771delAG: n = 1; c.5095C > T: n = 1; *BRCA2* c.1813dupA: n = 1; c.4652_4664del13: n = 1; c.9097dupA: n = 1), with none of the pathogenic variants occurring more than once in this series. Three of these eight alleles (*BRCA1* c.1961dupA, *BRCA1* c.3770_3771delAG, *BRCA2* c.9097dupA) were observed once each in both analyzed groups, i.e., in 340 newly collected genetically enriched BC and OC patients and patients taken from the study of Savanevich et al. [8].

We attempted to evaluate the ratio between founder and non-founder mutations among 98 *BRCA1/2* heterozygotes. If we consider 3 instances of the same allele as the threshold, recurrent mutations constituted 67/98 (68%) of pathogenic genetic variants (*BRCA1* c.5266dupC: n = 41; c.4035delA: n = 13; c.4689C > G: n = 4; c.181T > G: n = 3; c.3756_3759delGTCT: n = 3; *BRCA2* c.658_659delGT: n = 3). It is questionable whether it is appropriate to add to this list *BRCA1* c.68_69delAG allele (n = 2), and, particularly, *BRCA1* c.1961dupA, *BRCA1* c.3770_3771delAG, and *BRCA2* c.9097dupA alleles, each observed twice in the combined set of patients, but if we do so, the contribution of recurrent pathogenic variants would be 72/98 (73%). While considering the frequency of founder and non-founder alleles in the entire group of 340 genetically enriched patients, the contribution of the former approached 20–21%, while the frequency of the latter was below 10% (Supplementary Table S2).

Discussion

The contribution of *BRCA1/2* mutations to BC and OC incidence varies across different ethnic groups. This is the first study involving full-length *BRCA1/2* analysis in Belarusian cancer patients. It demonstrates that the share of *BRCA1/2* alleles among BC and OC patients is on the upper limit of interethnic variations [10–12] and, therefore, suggests a high population frequency of *BRCA1/2* heterozygotes. It is reasonable to undertake a large-scale study of healthy Belarusians to evaluate the feasibility of population screening for recurrent *BRCA1/2* mutations.

A systematic description of *BRCA1/2* founder alleles is presented in Table 2. Most of the founder alleles were observed in populations characterized by pronounced geographical or cultural isolation. For example, Ashkenazi Jews did not mix with other nations in Europe due to religious barriers, which explains the dominant role of recurrent alleles in this population [15, 18]. Belgian inhabitants, although residing in the middle of Western Europe and being involved in international trade, apparently experienced complicated relationships with neighboring communities over the course of history, which may explain an unexpectedly high contribution of founder alleles [2, 28]. There are examples of founder alleles observed in islandic populations, e.g., in Iceland or Greenland [4, 39]. None of the above situations is applicable to Belarus; therefore, the presence of a highly pronounced founder effect is surprising.

The obtained findings are beneficial for the health care system in Belarus and for other ethnic communities with similar genetic architecture. Non-expensive PCR testing for a few recurrent mutations is a method of choice for the

Table 2 *BRCA1/2* allelic composition in selected founder populations

Population/Country	Gene	Variant (HGVS and BIC nomenclature, ClinVar accession)	Relative prevalence among all pathogenic alleles in the corresponding gene	Comments (variants)	Comments (population)
Afrikaner population of South Africa [1]	*BRCA1*	HGVS: **c.1374delC** (p.Asp458Glufs) BIC: 1493delC VCV000054224.8	9/45 (20%)	This is a minor Afrikaner founder allele. Haplotyping and genealogical studies revealed a founding European family in which this mutation has emerged [13].	Afrikaner population, currently accounting to 2.5–3.5 million people, has originated from less than 150 individuals of Dutch ancestry in the first half of XVII century. It experienced influx of immigrants from Netherlands, Germany and France. Three founder alleles in *BRCA1/2* are responsible for approximately 88% of hereditary BC and OC [1].
	BRCA1	HGVS: **c.2641G > T** (p.Glu881Ter) BIC: 2760G > T VCV000054625.9	25/45 (56%)	This mutation is an Afrikaner founder allele apparently brought by a French family [14].	
	BRCA2	HGVS: **c.7934delG** (p.Arg2645Asnfs) BIC: 8162delG VCV000052440.26	135/146 (92%)	This is the most frequent Afrikaner founder allele. A founding European family was identified through haplotyping and genealogical studies [13].	
Ashkenazi Jewish [15]	*BRCA1*	HGVS: **c.68_69delAG** (p.Glu23fs) BIC: 185delAG VCV000017662	42/70 (60%)	This is a "pan-Jewish" mutation. Jewish carriers of the mutation share the same haplotype. It is located within a hotspot: there are at least two examples of independent emergence of this mutation in non-Jewish populations, both having different haplotypes [16].	Ashkenazi Jews is perhaps the most classical example of a human founder population, which remained isolated over its history due to cultural and religious barriers. Ashkenazi Jewish community, which currently includes 10–14 million people, has been originated from ~ 15,000–20,000 people living around 1500 AD [18]. Three founder mutations constitute around 90% of *BRCA1/2* pathogenic variants in Ashkenazi Jewish BC and OC patients. Population prevalence of these alleles is within 1.2–2.5% [15, 19–23].
	BRCA1	HGVS: **c.5266dupC** (p.Gln1756fs) BIC: 5382insC VCV000017677	25/70 (36%)	This is the most common *BRCA1* mutation worldwide. It was initially described as a Jewish mutation, although later studies revealed that the majority of carriers belong to Western and Eastern Slavic populations.	
	BRCA2	HGVS: **c.5946delT** (p.Ser1982fs) BIC: 6174delT VCV000009325	37/41 (90%)	This is an Ashkenazi Jewish founder mutation [17].	
Bahamas [24]	*BRCA1*	HGVS: **c.4357 + 1G > A** BIC: IVS13 + 1G > A VCV000037584.16	24/43 (56%)	This mutation is a minor founder allele in African Americans.	Bahamas have less than 400,000 inhabitants, mostly people of African descent. Consecutive BC patients demonstrate the highest frequency of *BRCA1/2* mutations worldwide (~ 24%). Population frequency of *BRCA1/2* mutations is above 1%. Three founder mutations constitute around two thirds of *BRCA1/2* pathogenic alleles [24, 26, 27].
	BRCA1	HGVS: **c.5324T > G** (p.Met1775Arg) BIC: 5443T > G VCV000017694.16	5/43 (12%)	This mutation is located within a hotspot, being occasionally reported in other ethnic groups [25].	
	BRCA2	HGVS: **c.7900delA** (p.Met2634fs) BIC: 8128delA VCV000627790.4	4/6 (66%)	This mutation is exceptionally rare outside Bahamas.	

Table 2 (continued)

Population/Country	Gene	Variant (HGVS and BIC nomenclature, ClinVar accession)	Relative prevalence among all pathogenic alleles in the corresponding gene	Comments (variants)	Comments (population)
Belgium [28]	*BRCA1*	HGVS: **c.212 + 3 A > G** BIC: IVS5 + 3 A > G VCV000054467.13	12/49 (25%)	Belgian carriers share the same haplotype. This mutation is occasionally reported in Dutch, French and German patients.	Belgium, a country with 11.5 million inhabitants located in the center of Western Europe, was heavily involved in trade routes through the course of history and therefore cannot be regarded as an isolated community. Still, there is an unexpectedly strong founder effect for *BRCA1/2* protein-inactivating variants, with 6 recurrent mutations representing approximately 57% of all pathogenic alleles in these genes. This is in line with population genetic studies, which demonstrated the distinct genetic background of the Belgian population as compared to neighboring European countries [2].
	BRCA1	HGVS: **c.2359dupG** (p.Glu787fs) BIC: 2478–2479insG VCV000054549.8	11/49 (22%)	Belgian carriers share the same haplotype. This mutation is rarely reported outside Belgium.	
	BRCA1	HGVS: **c.3661G > T** (p.Glu1221Ter) BIC: 3780G > T VCV000054957.15	5/49 (10%)	This mutation is occasionally reported in Dutch, French, German and Far Eastern patients.	
	BRCA2	HGVS: **c.516 + 1G > A** BIC: IVS6 + 1G > A VCV000051786.7	7/26 (27%)	Belgian carriers share the same haplotype. This mutation is rarely reported outside Belgium.	
	BRCA2	HGVS: **c.6275_6276delTT** (p.Leu2092fs) BIC: 6503-6504delTT VCV000009318.36	4/26 (15%)	This allele represents a mutational hotspot, being reported in multiple populations across the world. It is also common in the Southern part of Netherlands.	
	BRCA2	HGVS: **c.8904delC** (p.Val2969fs) BIC: 9132delC VCV000038192.28	4/26 (15%)	This mutation is occasionally observed in other European populations.	
Chile [29]	*BRCA2*	HGVS: **c.4740_4742dupTG** (p.Glu1581Valfs*37) BIC: 4970insTG VCV000220160.7	10/39 (26%)	Chilean carriers share the same haplotype. This mutation is also observed in Argentina and Brazil.	The population of Chile (~ 17.5 million people) originates from Spanish conquistadors and a relatively small number of Indians. The mountainous geography of this country complicates admixture; consequently, there are multiple founder alleles showing geographical clustering. Five founder mutations constitute around 55% of *BRCA1/2* pathogenic alleles [29].
	BRCA1	HGVS: **c.3331_3334delCAAG** (p.Gln1111Asnfs*5) BIC: 3450del4 VCV000037523.21	9/32 (28%)	Chilean carriers share the same haplotype. This mutation is also frequent in Brazil, Columbia, and Spain.	
	BRCA2	HGVS: **c.5146_5149delTATG** (p.Tyr1716Lysfs*8) BIC: 5373delGTAT VCV000051779.12	9/39 (23%)	Chilean carriers share the same haplotype. This mutation is recurrent in Spain.	
	BRCA1	HGVS: **c.3759dupT** (p.Lys1254Ter) BIC: 3878insT VCV000054992.15	7/32 (22%)	Chilean carriers share the same haplotype. This mutation was occasionally reported in other (mainly European) populations.	
	BRCA2	HGVS: **c.8987T > A** (p.Leu2996Ter) BIC: N/A VCV000219665.7	6/39 (15%)	Chilean carriers share the same haplotype. This mutation is extremely rare outside Chile.	

Table 2 (continued)

Population/Country	Gene	Variant (HGVS and BIC nomenclature, ClinVar accession)	Relative prevalence among all pathogenic alleles in the corresponding gene	Comments (variants)	Comments (population)
Finland [30–32]	*BRCA1* and *BRCA2*	Multiple rare recurrent mutations	"Negative" founder effect	N/A	Finns (~5.5 million individuals) originated from several thousand ancestors and experienced serial bottlenecks throughout history coupled with relative isolation from neighboring countries. Geographical, linguistic, and religious differences with neighboring regions contributed to the relative isolation of Finland. There are 36 genetic conditions, which are relatively specific for Finns. However, some of the disorders are unusually rare in Finland, due to the absence of corresponding mutations in ancestors of the nation [33]. There are several rare recurrent *BRCA1/2* pathogenic variants, however, the overall contribution of *BRCA1/2* mutations in BC and OC incidence is lower than in other countries [30–32].
Greece [3]	*BRCA1*	HGVS: **c.5266dupC** (p.Gln1756fs) BIC: 5382insC VCV000017677	26/135 (36%)	This is the most common *BRCA1* mutation worldwide. The majority of carriers belong to Western and Eastern Slavic populations. It is also common in Ashkenazi Jews and Hungarians [34]. The origin of this allele in Greeks is obscure.	Greeks (~10 million individuals; >95% population of Greece) are usually not considered as a founder population, except some genetic isolates living in mountains or islands [35]. However, there is a founder effect with respect to *BRCA1/2* pathogenic variants, with approximately a half of alleles represented by recurrent mutations [3].
	BRCA1	HGVS: **c.5406 + 664_*8273del** BIC: g.80280_91331del11052)	22/135 (16%)	This is a Greek founder mutation. Its carriers share the same haplotype [36].	
	BRCA1	HGVS: **c.5212G > A** (p.Gly1738Arg) BIC: 5331G > A VCV000055461.16	17/135 (13%)	This is a Greek founder mutation. Its carriers share the same haplotype. This mutation is also occasionally reported in apparent non-Greeks [37].	
	BRCA1	HGVS: **c.5468 − 285_5592 + 4019del4429_insCACAG** BIC: g.82651_87079del4429_ins5	13/135 (10%)	This is a Greek founder mutation. Its carriers share the same haplotype [36].	
Greenland Inuit [38–40]	*BRCA1*	HGVS: **c.115T > G** (p.Cys39Gly) BIC: 234T > G VCV000054153.4	18/19 (95%)	This is a Greenland Inuit founder mutation, which is also recurrent in Denmark and Norway. Inuit and Danish carriers share the same haplotype.	Greenland has a population of approximately 55,000 inhabitants (~89% Greenland Inuits and ~11% people of Northern European ancestry). *BRCA1* c.115T > G founder mutation constitutes the majority of *BRCA1/2* pathogenic alleles. The population occurrence of this mutation is 1.6% [38, 39]. This allele is likely to have a Northern European origin. Its frequency is 9.7% in the town of Ammassalik (Tasiilaq), which was founded by Danes in the late XIX century [38].

Table 2 (continued)

Population/Country	Gene	Variant (HGVS and BIC nomenclature, ClinVar accession)	Relative prevalence among all pathogenic alleles in the corresponding gene	Comments (variants)	Comments (population)
Hungary [41]	*BRCA1*	HGVS: **c.181T > G** (p.Cys61Gly) BIC: 300T > G VCV000017661.54	13/28 (46%) (the full *BRCA1/2* sequence was not evaluated)	This allele is the second most common in Germany, and frequently occurs throughout Europe, especially in its Central and Eastern regions. Its carriers share the same haplotype [42].	Hungarian population (~ 10 million people) is characteristic of its unique Finno-Uralic language. There are examples of unique patterns of founder alleles in Hungarians, differing from those in neighboring German and Slavic countries [43]. There are no extensive studies, which evaluate the proportion between the founder and non-founder alleles in Hungarian *BRCA1/2*-related cancers. However, the very high prevalence of the Central European *BRCA1* 300T > G founder allele deserves to be acknowledged [41].
	BRCA1	HGVS: **c.5266dupC** (p.Gln1756fs) BIC: 5382insC VCV000017677	8/28 (28%)	This is the most common *BRCA1* mutation worldwide. The majority of carriers belong to Western and Eastern Slavic populations. It is also particularly common in Ashkenazi Jewish, Baltic States, and Greece [34].	
Iceland [44]	*BRCA2*	HGVS: **c.771_775delTCAAA** (p.Asn257fs) BIC: 999del5 VCV000009326.20	10/10 (100%)	This is a major founder mutation in Icelanders. It is rarely reported outside this population.	Icelanders are a classical example of a geographically isolated founder population. Iceland was initially colonized by several thousand settlers from Scandinavia and the British/Irish Islands. Iceland currently has slightly more than 300,000 inhabitants [45]. Several rare recurrent mutations other than the *BRCA2* 999del5 founder allele have been identified in Iceland, e.g., *BRCA1* G5193A. Large-scale exome studies revealed that *BRCA1/2* mutations are observed in 1.6% of people, with 90% of carriers being represented by the *BRCA2* 999del5 variant [4].
Lithuania [5]	*BRCA1*	HGVS: **c.4035delA** (p.Glu1346Lysfs*2) BIC:4154delA VCV000037560.32	96/219 (44%)	This is a Baltic founder mutation originating from Lithuania. Its carriers share the same haplotype. It is also common in neighboring countries with predominantly Slavic population (Poland, Belarus, Russia) [46].	The majority of the population of Lithuania (roughly 3 million inhabitants) and Latvia (roughly 2 million people) have originated mostly from Baltic tribes as well as from Slavic, Finno-Ugric, and German ethnic groups, in varying proportions. Balts culturally and linguistically separated from Slavs approximately 4000 years ago but remained in close contact with Slavic tribes and Slavic states thereafter. There is a number of founder alleles shared by Baltic and Slavic people [46, 47]. Two founder alleles account for approximately 69% of *BRCA1/2*-driven cancers in Lithuania [5].
	BRCA1	HGVS: **c.5266dupC** (p.Gln1756fs) BIC: 5382insC VCV000017677	56/219 (26%)	This is the most common *BRCA1* mutation worldwide. The majority of carriers belong to Western and Eastern Slavic populations. It is also common in Ashkenazi Jews, Hungary, and Greece [34].	
North African/ Maghreb (Tunisia, Algeria, Morocco) [48]	*BRCA1*	HGVS: **c.798_799delTT** (p.Ser267fs) BIC: 917delTT VCV000037698.22	18/129 (14%)	Maghrebian carriers of this allele share the same haplotype. This mutation is also occasionally detected in Western Mediterranean countries (Spain, Italy).	The North African Mediterranean populations (> 90 million people) represent a mixture of several ancestries and are characterized by high heterogeneity. Maghrebian ethnic groups are clearly distinct from all neighboring ones and demonstrate a strong founder effect for a number of genetic diseases [49]. Four *BRCA1* and 1 *BRCA2* recurrent mutations account for 46% of *BRCA1/2*-related cancers [48].

Table 2 (continued)

Population/Country	Gene	Variant (HGVS and BIC nomenclature, ClinVar accession)	Relative prevalence among all pathogenic alleles in the corresponding gene	Comments (variants)	Comments (population)
Norway [50]	*BRCA1*	HGVS: **c.1016dupA** (p.Val340fs) BIC: 1135insA VCV000054102.32	111/669 (17%)	Norwegian carriers of this mutation share identical haplotype. However, this mutation is a hotspot, being occasionally reported in several distant countries [51].	Approximately 5.5 million ethnic Norwegians are descendants of approximately 150,000 survivors of the Bubonic plague pandemic, which heavily affected Medieval Norway. No significant ethnic admixture occurred in Norway until very recently [52]. Initial reports demonstrated a very pronounced founder effect with respect to *BRCA1/2*-related cancers, though recent studies reveal more modest estimates suggesting that approximately 41% of *BRCA1/2* mutations are represented by founder alleles [50].
	BRCA1	HGVS: **c.1556delA** (p.Lys519Argfs*13) BIC: 1675delA VCV000017685.13	95/669 (14%)	Norwegian carriers of this mutation share identical haplotype. This mutation was occasionally reported in other, mainly Northern European, populations.	
	BRCA1	HGVS: **c.3178G > T** (p.Glu1060*) BIC: 3297G > T VCV000054789.12	46/669 (7%)	This mutation was occasionally reported in other, mainly Northern European, populations.	
	BRCA1	HGVS: **c.3228_3229delAG** (p.Gly1077Alafs*8) BIC: 3347_3348delAG VCV000037516.29	45/669 (7%)	Norwegian carriers of this mutation share identical haplotype. This mutation was occasionally reported in other European populations.	
	BRCA1	HGVS: **c.697_698delGT** (p.Val233Asnfs*4) BIC: 816delGT VCV000037695.12	44/669 (7%)	This is Norwegian-only mutation, with all carriers sharing identical haplotype.	
	BRCA2	HGVS: **c.5217_5223delTTTAAGT** p.Thr1738_Tyr1739insTer BIC: 5445del7 VCV000051822.13	61/312 (19%)	Norwegian carriers of this mutation share identical haplotype. This mutation was occasionally reported in other, mainly Northern European, populations.	

Table 2 (continued)

Population/Country	Gene	Variant (HGVS and BIC nomenclature, ClinVar accession)	Relative prevalence among all pathogenic alleles in the corresponding gene	Comments (variants)	Comments (population)
Puerto Rico [53]	*BRCA2*	HGVS: **c.3922G > T** (p.Glu1308Ter) BIC: c.4150G > T VCV000037867.17	8/9 (89%)	Puerto Rican carriers of this mutation share identical haplotype. It was probably brought by Spanish conquistadors and is occasionally observed in some Spanish patients.	More than 3 million modern Puerto Ricans are descendants of Western/Spanish, African, and Indigenous (Taino Indians) ancestors. *BRCA2* c.3922G > T allele was detected in 8/11 (73%) *BRCA1/2* mutation carriers.
Senegal [54]	*BRCA1*	HGVS: **c.815_824dupAGCCATGTGG**, (p.Thr276Alafs) BIC: 943ins10 VCV000055723.11	All evaluated cases	This mutation is a West African founder allele. Its carriers of West African descent (Ivory Coast, Bahamas, Afro-American descendants of African slaves) share the same haplotype [55].	Senegalese population consists of approximately 16 million people and is composed of several major ethnic constituents (Wolof, Fulani/Peul, Mandinka, and others) [56]. In a most comprehensive report, the full *BRCA1/2* sequence was evaluated only in a part of familial BC cases, so the real share of *BRCA1* c.815_824dup10 *BRCA1* variant cannot be estimated precisely [54]. Interestingly, breast cancer in Senegal is noted for an unusually high prevalence of triple-negative cases [57].
Slavic countries	*BRCA1*	HGVS: **c.5266dupC** (p.Gln1756fs) BIC: 5382insC VCV000017677	Poland: 204/370 (55%) [58] Russia: 539/760 (71%) [6] Belarus: 28/52 (54%) [8] Bulgaria: 22/39 (56%) [59] Czech Republic: 329/1021 (32%) [60] Serbia: 11/30 (37%) [61]	This is the most common *BRCA1* mutation worldwide. The majority of carriers belong to Western and Eastern Slavic populations. Haplotyping studies suggest Eastern Slavic or, perhaps, Danish origin of the allele. This allele is also particularly common in Ashkenazi Jewish, Baltic States, Hungary, and Greece [34].	The majority of the Slavic population resides in 13 countries in Eastern Europe. Slavs emerged from a common Balto-Slavic ethnic community approximately 4000 years ago. Southern Slavs emerged as a separate entity in the V-VI century AD, and shortly thereafter the remaining Slavic populations split into Eastern and Western Slavs. Though Slavs are not typically considered a founder population, there is a very significant extent of genetic relatedness between Western Slavs (especially Poles), Eastern Slavs (Belarusians, Russians, and Ukrainians), and, to a lesser extent, Southern Slavs (Bulgarians, Serbians, Bosnians, Macedonians, etc. [47]. A remarkable example of Slavic founder mutation is the *BRCA1* 5382insC allele, which alone accounts for approximately 65% of *BRCA1/2* mutations in Russia and 48% in Poland. The share of this allele is lower in Southern Slavs (except Bulgarians), and in Czechs and Slovaks [6, 58–60].

Note: NM_007294.4 transcript was used for *BRCA1* and NM_000059.3 was utilized for *BRCA2*

time being, which can be applied without cost limitations to all patients with breast and ovarian cancer and is compatible even with low-resource cancer medicine. Comprehensive next-generation sequencing analysis may reveal additional mutations in less than 10% of Belarusian breast or ovarian patients. Therefore, the decision-making process should include personalized consideration of expected medical benefit from the *BRCA1/2* test (e.g., administration of *BRCA1/2*-specific therapy or DNA testing for family members), strength of clinical indicators for the presence of *BRCA1/2* mutation, and available resources.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The study design was approved by the local Ethical Committee. All procedures performed in study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Oosthuizen J, Kotze MJ, Van Der Merwe N, Myburgh EJ, Bester P, van der Merwe NC (2021) Globally Rare *BRCA2* Variants With Founder Haplotypes in the South African Population: Implications for Point-of-Care Testing Based on a Single-Institution *BRCA1/2* Next-Generation Sequencing Study. Front Oncol 10:619469. https://doi.org/10.3389/fonc.2020.619469
2. Van den Eynden J, Descamps T, Delporte E, Roosens NHC, De Keersmaecker SCJ, De Wit V, Vermeesch JR, Goetghebeur E, Tafforeau J, Demarest S, Van den Bulcke M, Van Oyen H (2018) The genetic structure of the Belgian population. Hum Genomics 12:6. https://doi.org/10.1186/s40246-018-0136-8
3. Konstantopoulou I, Tsitlaidou M, Fostira F, Pertesi M, Stavropoulou AV, Triantafyllidou O, Tsotra E, Tsiftsoglou AP, Tsionou C, Droufakou S, Dimitrakakis C, Fountzilas G, Yannoukakos D (2014) High prevalence of BRCA1 founder mutations in Greek breast/ovarian families. Clin Genet 85:36–42. https://doi.org/10.1111/cge.12274
4. Sulem P, Helgason H, Oddson A, Stefansson H, Gudjonsson SA, Zink F, Hjartarson E, Sigurdsson GT, Jonasdottir A, Jonasdottir A, Sigurdsson A, Magnusson OT, Kong A, Helgason A, Holm H, Thorsteinsdottir U, Masson G, Gudbjartsson DF, Stefansson K (2015) Identification of a large set of rare complete human knockouts. Nat Genet 47:448–452. https://doi.org/10.1038/ng.3243
5. Janavičius R, Rudaitis V, Mickys U, Elsakov P, Griškevičius L (2014) Comprehensive BRCA1 and BRCA2 mutational profile in Lithuania. Cancer Genet 207:195–205. https://doi.org/10.1016/j.cancergen.2014.05.002
6. Sokolenko AP, Sokolova TN, Ni VI, Preobrazhenskaya EV, Iyevleva AG, Aleksakhina SN, Romanko AA, Bessonov AA, Gorodnova TV, Anisimova EI, Savonevich EL, Bizin IV, Stepanov IA, Krivorotko PV, Berlev IV, Belyaev AM, Togo AV, Imyanitov EN (2020) Frequency and spectrum of founder and non-founder BRCA1 and BRCA2 mutations in a large series of Russian breast cancer and ovarian cancer patients. Breast Cancer Res Treat 184:229–235. https://doi.org/10.1007/s10549-020-05827-8
7. Savanevich A, Oszurek O, Lubiński J, Cybulski C, Dębniak T, Narod SA, Gronwald J (2014) BRCA1 founder mutations compared to ovarian cancer in Belarus. Fam Cancer 13:445–447. https://doi.org/10.1007/s10689-014-9721-8
8. Savanevich A, Ashuryk O, Cybulski C, Lubiński J, Gronwald J (2021) BRCA1 and BRCA2 mutations in ovarian cancer patients from Belarus: update. Hered Cancer Clin Pract 19:13. https://doi.org/10.1186/s13053-021-00169-y
9. Preobrazhenskaya EV, Shleykina AU, Gorustovich OA, Martianov AS, Bizin IV, Anisimova EI, Sokolova TN, Chuinyshena SA, Kuligina ES, Togo AV, Belyaev AM, Ivantsov AO, Sokolenko AP, Imyanitov EN (2021) Frequency and molecular characteristics of PALB2-associated cancers in Russian patients. Int J Cancer 148:203–210. https://doi.org/10.1002/ijc.33317
10. Bu H, Chen J, Li Q, Hou J, Wei Y, Yang X, Ma Y, He H, Zhang Y, Kong B (2019) BRCA mutation frequency and clinical features of ovarian cancer patients: A report from a Chinese study group. J Obstet Gynaecol Res 45:2267–2274. https://doi.org/10.1111/jog.14090
11. Gupta S, Rajappa S, Advani S, Agarwal A, Aggarwal S, Goswami C, Palanki SD, Arya D, Patil S, Kodagali R (2021) Prevalence of BRCA1 and BRCA2 Mutations Among Patients With Ovarian, Primary Peritoneal, and Fallopian Tube Cancer in India: A Multicenter Cross-Sectional Study. JCO Glob Oncol 7:849–861. https://doi.org/10.1200/GO.21.00051
12. Stegel V, Blatnik A, Škof E, Dragoš V, Krajc M, Gregorič B, Škerl P, Strojnik K, Klančar G, Banjac M, Žgajnar J, Ravnik M, Novaković S (2022) Real-World Data on Detection of Germline and Somatic Pathogenic/Likely Pathogenic Variants in BRCA1/2 and Other Susceptibility Genes in Ovarian Cancer Patients Using Next Generation Sequencing. Cancers (Basel) 14:1434. https://doi.org/10.3390/cancers14061434
13. Van der Merwe NC, van Rensburg EJ (2009) Hereditary breast/ovarian cancer and BRCA mutations: A South African perspective. Abstract, Third International Symposium on Hereditary Breast and Ovarian Cancer. Quebec, Canada 14–16 October 2009. Current Oncology 16:91–110
14. Reeves MD, Yawitch TM, van der Merwe NC, van den Berg HJ, Dreyer G, van Rensburg EJ (2004) BRCA1 mutations in South African breast and/or ovarian cancer families: evidence of a novel founder mutation in Afrikaner families. Int J Cancer 110:677–682. https://doi.org/10.1002/ijc.20186
15. Walsh T, Mandell JB, Norquist BM, Casadei S, Gulsuner S, Lee MK, King MC (2017) Genetic Predisposition to Breast Cancer Due to Mutations Other Than BRCA1 and BRCA2 Founder Alleles Among Ashkenazi Jewish Women. JAMA Oncol 3:1647–1653. https://doi.org/10.1001/jamaoncol.2017.1996
16. Laitman Y, Feng BJ, Zamir IM, Weitzel JN, Duncan P, Port D, Thirthagiri E, Teo SH, Evans G, Latif A, Newman WG, Gershoni-Baruch R, Zidan J, Shimon-Paluch S, Goldgar D, Friedman E (2013) Haplotype analysis of the 185delAG BRCA1 mutation

in ethnically diverse populations. Eur J Hum Genet 21:212–216. https://doi.org/10.1038/ejhg.2012.124
17. Neuhausen SL, Godwin AK, Gershoni-Baruch R, Schubert E, Garber J, Stoppa-Lyonnet D, Olah E, Csokay B, Serova O, Lalloo F, Osorio A, Stratton M, Offit K, Boyd J, Caligo MA, Scott RJ, Schofield A, Teugels E, Schwab M, Cannon-Albright L, Bishop T, Easton D, Benitez J, King MC, Ponder BA, Weber B, Devilee P, Borg A, Narod SA, Goldgar D (1998) Haplotype and phenotype analysis of nine recurrent BRCA2 mutations in 111 families: results of an international study. Am J Hum Genet 62:1381–1388. https://doi.org/10.1086/301885
18. Slatkin M (2004) A population-genetic test of founder effects and implications for Ashkenazi Jewish diseases. Am J Hum Genet 75:282–293. https://doi.org/10.1086/423146
19. Barnes-Kedar I, Bernstein-Molho R, Ginzach N, Hartmajer S, Shapira T, Magal N, Kalis ML, Peretz T, Shohat M, Basel-Salmon L, Friedman E, Bazak L, Goldberg Y (2018) The yield of full BRCA1/2 genotyping in Israeli high-risk breast/ovarian cancer patients who do not carry the predominant mutations. Breast Cancer Res Treat 172:151–157. https://doi.org/10.1007/s10549-018-4887-7
20. Solano AR, Liria NC, Jalil FS, Faggionato DM, Mele PG, Mampel A, Cardoso FC, Podesta EJ (2018) BRCA1 and BRCA2 Mutations Other Than the Founder Alleles Among Ashkenazi Jewish in the Population of Argentina. Front Oncol 8:323. https://doi.org/10.3389/fonc.2018.00323
21. Bernstein-Molho R, Laitman Y, Schayek H, Reish O, Lotan S, Haim S, Zidan J, Friedman E (2017) The yield of targeted genotyping for the recurring mutations in BRCA1/2 in Israel. Breast Cancer Res Treat 167:697–702. https://doi.org/10.1007/s10549-017-4551-7
22. Nielsen SM, De Simone LM, Olopade OI (2018) Cancer Susceptibility Genetic Testing in a High-Risk Cohort of Urban Ashkenazi Jewish Individuals. J Genet Couns 27:1405–1410. https://doi.org/10.1007/s10897-018-0269-x
23. Manchanda R, Lieberman S, Gaba F, Lahad A, Levy-Lahad E (2020) Population Screening for Inherited Predisposition to Breast and Ovarian Cancer. Annu Rev Genomics Hum Genet 21:373–412. https://doi.org/10.1146/annurev-genom-083118-015253
24. Akbari MR, Donenberg T, Lunn J, Curling D, Turnquest T, Krill-Jackson E, Zhang S, Narod SA, Hurley J (2014) The spectrum of *BRCA1* and *BRCA2* mutations in breast cancer patients in the Bahamas. Clin Genet 85:64–67. https://doi.org/10.1111/cge.12132
25. Fackenthal JD, Zhang J, Zhang B, Zheng Y, Hagos F, Burrill DR, Niu Q, Huo D, Sveen WE, Ogundiran T, Adebamowo C, Odetunde A, Falusi AG, Olopade OI (2012) High prevalence of BRCA1 and BRCA2 mutations in unselected Nigerian breast cancer patients. Int J Cancer 131:1114–1123. https://doi.org/10.1002/ijc.27326
26. Trottier M, Lunn J, Butler R, Curling D, Turnquest T, Francis W, Halliday D, Royer R, Zhang S, Li S, Thompson I, Donenberg T, Hurley J, Akbari MR, Narod SA (2016) Prevalence of founder mutations in the BRCA1 and BRCA2 genes among unaffected women from the Bahamas. Clin Genet 89:328–331. https://doi.org/10.1111/cge.12602
27. George SHL, Donenberg T, Alexis C, DeGennaro V Jr, Dyer H, Yin S, Ali J, Butler R, Chin SN, Curling D, Lowe D, Lunn J, Turnquest T, Wharfe G, Cerbon D, Barreto-Coelho P, Schlumbrecht MP, Akbari MR, Narod SA, Hurley JE (2021) Gene Sequencing for Pathogenic Variants Among Adults With Breast and Ovarian Cancer in the Caribbean. JAMA Netw Open 4:e210307. https://doi.org/10.1001/jamanetworkopen.2021.0307
28. Claes K, Poppe B, Coene I, Paepe AD, Messiaen L (2004) BRCA1 and BRCA2 germline mutation spectrum and frequencies in Belgian breast/ovarian cancer families. Br J Cancer 90:1244–1251. https://doi.org/10.1038/sj.bjc.6601656
29. Alvarez C, Tapia T, Perez-Moreno E, Gajardo-Meneses P, Ruiz C, Rios M, Missarelli C, Silva M, Cruz A, Matamala L, Carvajal-Carmona L, Camus M, Carvallo P (2017) *BRCA1* and *BRCA2* founder mutations account for 78% of germline carriers among hereditary breast cancer families in Chile. Oncotarget 8:74233–74243. https://doi.org/10.18632/oncotarget.18815
30. Vehmanen P, Friedman LS, Eerola H, McClure M, Ward B, Sarantaus L, Kainu T, Syrjäkoski K, Pyrhönen S, Kallioniemi OP, Muhonen T, Luce M, Frank TS, Nevanlinna H (1997) Low proportion of BRCA1 and BRCA2 mutations in Finnish breast cancer families: evidence for additional susceptibility genes. Hum Mol Genet 6:2309–2315. https://doi.org/10.1093/hmg/6.13.2309
31. Sarantaus L, Vahteristo P, Bloom E, Tamminen A, Unkila-Kallio L, Butzow R, Nevanlinna H (2001) BRCA1 and BRCA2 mutations among 233 unselected Finnish ovarian carcinoma patients. Eur J Hum Genet 9:424–430. https://doi.org/10.1038/sj.ejhg.5200652
32. Kuusisto KM, Bebel A, Vihinen M, Schleutker J, Sallinen SL (2011) Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2-founder mutation-negative breast and/or ovarian cancer individuals. Breast Cancer Res 13:R20. https://doi.org/10.1186/bcr2832
33. Kääriäinen H, Muilu J, Perola M, Kristiansson K (2017) Genetics in an isolated population like Finland: a different basis for genomic medicine? J Community Genet 8:319–326. https://doi.org/10.1007/s12687-017-0318-4
34. Hamel N, Feng BJ, Foretova L, Stoppa-Lyonnet D, Narod SA, Imyanitov E, Sinilnikova O, Tihomirova L, Lubinski J, Gronwald J, Gorski B, Hansen Tv, Nielsen FC, Thomassen M, Yannoukakos D, Konstantopoulou I, Zajac V, Ciernikova S, Couch FJ, Greenwood CM, Goldgar DE, Foulkes WD (2011) On the origin and diffusion of BRCA1 c.5266dupC (5382insC) in European populations. Eur J Hum Genet 19:300–306. https://doi.org/10.1038/ejhg.2010.203
35. Apostolou P, Fostira F, Kouroussis C, Kalfakakou D, Delimitsou A, Agelaki S, Androulakis N, Christodoulou C, Kalbakis K, Kalykaki A, Sanidas E, Papadimitriou C, Vamvakas L, Georgoulias V, Mavroudis D, Yannoukakos D, Konstantopoulou I, Saloustros E (2020) *BRCA1* and *BRCA2* germline testing in Cretan isolates reveals novel and strong founder effects. Int J Cancer 147:1334–1342. https://doi.org/10.1002/ijc.32903
36. Pertesi M, Konstantopoulou I, Yannoukakos D (2011) Haplotype analysis of two recurrent genomic rearrangements in the BRCA1 gene suggests they are founder mutations for the Greek population. Clin Genet 80:375–382. https://doi.org/10.1111/j.1399-0004.2010.01532.x
37. Anagnostopoulos T, Pertesi M, Konstantopoulou I, Armaou S, Kamakari S, Nasioulas G, Athanasiou A, Dobrovic A, Young MA, Goldgar D, Fountzilas G, Yannoukakos D (2008) G1738R is a BRCA1 founder mutation in Greek breast/ovarian cancer patients: evaluation of its pathogenicity and inferences on its genealogical history. Breast Cancer Res Treat 110:377–385. https://doi.org/10.1007/s10549-007-9729-y
38. Hansen TV, Ejlertsen B, Albrechtsen A, Bergsten E, Bjerregaard P, Hansen T, Myrhøj T, Nielsen PB, Timmermans-Wielenga V, Andersen MK, Jønson L, Nielsen FC (2009) A common Greenlandic Inuit BRCA1 RING domain founder mutation. Breast Cancer Res Treat 115:69–76. https://doi.org/10.1007/s10549-008-0060-z
39. Harboe TL, Eiberg H, Kern P, Ejlertsen B, Nedergaard L, Timmermans-Wielenga V, Nielsen IM, Bisgaard ML (2009) A high frequent BRCA1 founder mutation identified in the Greenlandic population. Fam Cancer 8:413–419. https://doi.org/10.1007/s10689-009-9257-5
40. Hansen TV, Jønson L, Albrechtsen A, Steffensen AY, Bergsten E, Myrhøj T, Ejlertsen B, Nielsen FC (2010) Identification of a novel BRCA1 nucleotide 4803delCC/c.4684delCC mutation and

a nucleotide 249T > A/c.130T > A (p.Cys44Ser) mutation in two Greenlandic Inuit families: implications for genetic screening of Greenlandic Inuit families with high risk for breast and/or ovarian cancer. Breast Cancer Res Treat 124:259–264. https://doi.org/10.1007/s10549-010-0909-9

41. Van Der Looij M, Szabo C, Besznyak I, Liszka G, Csokay B, Pulay T, Toth J, Devilee P, King MC, Olah E (2000) Prevalence of founder BRCA1 and BRCA2 mutations among breast and ovarian cancer patients in Hungary. Int J Cancer 86:737–740. https://doi.org/10.1002/(sici)1097-0215(20000601)86:53.0.co;2-1
42. Kaufman B, Laitman Y, Gronwald J, Lubinski J, Friedman E (2009) Haplotype of the C61G BRCA1 mutation in Polish and Jewish individuals. Genet Test Mol Biomarkers 13:465–469. https://doi.org/10.1089/gtmb.2009.0001
43. Papp J, Kovacs ME, Matrai Z, Orosz E, Kásler M, Børresen-Dale AL, Olah E (2016) Contribution of APC and MUTYH mutations to familial adenomatous polyposis susceptibility in Hungary. Fam Cancer 15:85–97. https://doi.org/10.1007/s10689-015-9845-5
44. Rafnar T, Benediktsdottir KR, Eldon BJ, Gestsson T, Saemundsson H, Olafsson K, Salvarsdottir A, Steingrimsson E, Thorlacius S (2004) BRCA2, but not BRCA1, mutations account for familial ovarian cancer in Iceland: a population-based study. Eur J Cancer 40:2788–2793. https://doi.org/ 10.1016/j.ejca.2004.09.008
45. Ebenesersdóttir SS, Sandoval-Velasco M, Gunnarsdóttir ED, Jagadeesan A, Guðmundsdóttir VB, Thordardóttir EL, Einarsdóttir MS, Moore KHS, Sigurðsson Á, Magnúsdóttir DN, Jónsson H, Snorradóttir S, Hovig E, Møller P, Kockum I, Olsson T, Alfredsson L, Hansen TF, Werge T, Cavalleri GL, Gilbert E, Lalueza-Fox C, Walser JW 3rd, Kristjánsdóttir S, Gopalakrishnan S, Árnadóttir L, Magnússon ÓÞ, Gilbert MTP, Stefánsson K, Helgason A (2018) Ancient genomes from Iceland reveal the making of a human population. Science 360:1028–1032. https://doi.org/10.1126/science.aar2625
46. Janavičius R, Rudaitis V, Feng BJ, Ozolina S, Griškevičius L, Goldgar D, Tihomirova L (2013) Haplotype analysis and ancient origin of the BRCA1 c.4035delA Baltic founder mutation. Eur J Med Genet 56:125–130. https://doi.org/10.1016/j.ejmg.2012.12.007
47. Kushniarevich A, Utevska O, Chuhryaeva M, Agdzhoyan A, Dibirova K, Uktveryte I, Möls M, Mulahasanovic L, Pshenichnov A, Frolova S, Shanko A, Metspalu E, Reidla M, Tambets K, Tamm E, Koshel S, Zaporozhchenko V, Atramentova L, Kučinskas V, Davydenko O, Goncharova O, Evseeva I, Churnosov M, Pocheshchova E, Yunusbayev B, Khusnutdinova E, Marjanović D, Rudan P, Rootsi S, Yankovsky N, Endicott P, Kassian A, Dybo A, Genographic Consortium, Tyler-Smith C, Balanovska E, Metspalu M, Kivisild T, Villems R, Balanovsky O (2015) Genetic Heritage of the Balto-Slavic Speaking Populations: A Synthesis of Autosomal, Mitochondrial and Y-Chromosomal Data. PLoS ONE 10:e0135820. https://doi.org/10.1371/journal.pone.0135820
48. ElBiad O, Laraqui A, El Boukhrissi F, Mounjid C, Lamsisi M, Bajjou T, Elannaz H, Lahlou AI, Kouach J, Benchekroune K, Oukabli M, Chahdi H, Ennaji MM, Tanz R, Sbitti Y, Ichou M, Ennibi K, Badaoui B, Sekhsokh Y (2022) Prevalence of specific and recurrent/founder pathogenic variants in BRCA genes in breast and ovarian cancer in North Africa. BMC Cancer 22:208. https://doi.org/10.1186/s12885-022-09181-4
49. Charoute H, Bakhchane A, Benrahma H, Romdhane L, Gabi K, Rouba H, Fakiri M, Abdelhak S, Lenaers G, Barakat A (2015) Mediterranean Founder Mutation Database (MFMD): Taking Advantage from Founder Mutations in Genetics Diagnosis, Genetic Diversity and Migration History of the Mediterranean Population. Hum Mutat 36:E2441–E2453. https://doi.org/10.1002/humu.22835
50. Heramb C, Wangensteen T, Grindedal EM, Ariansen SL, Lothe S, Heimdal KR, Mæhle L (2018) BRCA1 and BRCA2 mutation spectrum – an update on mutation distribution in a large cancer genetics clinic in Norway. Hered Cancer Clin Pract 16:3. https://doi.org/10.1186/s13053-017-0085-6
51. Rudkin TM, Hamel N, Galvez M, Hogervorst F, Gille JJ, Møller P, Apold J, Foulkes WD (2006) The frequent BRCA1 mutation 1135insA has multiple origins: a haplotype study in different populations. BMC Med Genet 7:15. https://doi.org/10.1186/1471-2350-7-15
52. Møller P, Hagen AI, Apold J, Maehle L, Clark N, Fiane B, Løvslett K, Hovig E, Vabø A (2007) Genetic epidemiology of BRCA mutations–family history detects less than 50% of the mutation carriers. Eur J Cancer 43:1713–1717. https://doi.org/10.1016/j.ejca.2007.04.023
53. Diaz-Zabala HJ, Ortiz AP, Garland L, Jones K, Perez CM, Mora E, Arroyo N, Oleksyk TK, Echenique M, Matta JL, Dean M, Dutil J (2018) A Recurrent BRCA2 Mutation Explains the Majority of Hereditary Breast and Ovarian Cancer Syndrome Cases in Puerto Rico. Cancers (Basel) 10:419. https://doi.org/10.3390/cancers10110419
54. Ndiaye R, Diop JPD, Bourdon-Huguenin V, Dem A, Diouf D, Dieng MM, Diop PS, Kane Gueye SM, Ba SA, Dia Y, Ka S, Mbengue B, Thiam A, Sylla Niang M, Gueye PM, Faye O, Lopez Sall P, Cisse A, Diop PA, Sobol H, Dieye A (2020) Evidence for an ancient BRCA1 pathogenic variant in inherited breast cancer patients from Senegal. NPJ Genom Med 5:8. https://doi.org/10.1038/s41525-020-0114-7
55. Mefford HC, Baumbach L, Panguluri RC, Whitfield-Broome C, Szabo C, Smith S, King MC, Dunston G, Stoppa-Lyonnet D, Arena F (1999) Evidence for a BRCA1 founder mutation in families of West African ancestry. Am J Hum Genet 65:575–578. https://doi.org/10.1086/302511
56. Blanc M, Sanchez-Mazas A, Van Blyenburgh NH, Sevin A, Pison G, Langaney A (1990) Interethnic genetic differentiation: GM polymorphism in eastern Senegal. Am J Hum Genet 46:383–392
57. Fitzpatrick MB, Rendi MH, Kiviat NB, Toure P, Dem A, Sow PS, Hawes SE, Feng Q, Allison KH (2019) Pathology of Senegalese breast cancers. Pan Afr Med J 34:67. https://doi.org/10.11604/pamj.2019.34.67.17993
58. Cybulski C, Kluźniak W, Huzarski T, Wokołorczyk D, Kashyap A, Rusak B, Stempa K, Gronwald J, Szymiczek A, Bagherzadeh M, Jakubowska A, Dębniak T, Lener M, Rudnicka H, Szwiec M, Jarkiewicz-Tretyn J, Stawicka M, Domagała P, Narod SA, Lubiński J, Akbari MR, Polish Hereditary Breast Cancer Consortium (2019) The spectrum of mutations predisposing to familial breast cancer in Poland. Int J Cancer 145:3311–3320. https://doi.org/10.1002/ijc.32492
59. Dodova RI, Mitkova AV, Dacheva DR, Hadjo LB, Vlahova AI, Hadjieva MST, Valev SS, Caulevska MM, Popova SD, Popov IE, Dikov TI, Sedloev TA, Ionkov AS, Timcheva KV, Christova SL, Kremensky IM, Mitev VI, Kaneva RP (2015) Spectrum and frequencies of BRCA1/2 mutations in Bulgarian high risk breast cancer patients. BMC Cancer 15:523. https://doi.org/10.1186/s12885-015-1516-2
60. Machackova E, Claes K, Mikova M, Házová J, Sťahlová EH, Vasickova P, Trbusek M, Navrátilová M, Svoboda M, Foretová L (2019) Twenty Years of BRCA1 and BRCA2 Molecular Analysis at MMCI - Current Developments for the Classification of Variants. Klin Onkol 32(Supplementum2):51–71. https://doi.org/10.14735/amko2019S51
61. Krivokuca A, Mihajlovic M, Susnjar S, Spasojevic IB, Minic I, Popovic L, Brankovic-Magic M (2021) Mutational profile of hereditary breast and ovarian cancer - Establishing genetic testing guidelines in a developing country. Curr Probl Cancer 10:100767. https://doi.org/10.1016/j.currproblcancer.2021.100767