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EPIDEMIOLOGY

Ethnicity-specific *BRCA1*, *BRCA2*, *PALB2,* and *ATM* pathogenic alleles in breast and ovarian cancer patients from the North Caucasus

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Abstract

Background Mountain areas of the North Caucasus host several large ethnic communities that have preserved their national identity over the centuries.

Methods This study involved high-grade serous ovarian cancer (HGSOC) and breast cancer (BC) patients from Dagestan (HGSOC: 37; BC: 198), Kabardino-Balkaria (HGSOC: 68; BC: 155), North Ossetia (HGSOC: 51; BC: 104), Chechnya (HGSOC: 68; BC: 79), Ingushetia (HGSOC: 19; BC: 103), Karachay-Cherkessia (HGSOC: 13; BC: 47), and several Armenian settlements (HGSOC: 16; BC: 101). The group of BC patients was enriched by young-onset and/or family history-positive and/or bilateral and/or receptor triple-negative cases. The entire coding region of *BRCA1, BRCA2, PALB2,* and *ATM* genes was analyzed by next-generation sequencing.

Results A significant contribution of *BRCA1/2* pathogenic variants (PVs) to HGSOC and BC development was observed across all North Caucasus regions (HGSOC: 19–39%; BC: 6–13%). Founder alleles were identified in all ethnic groups studied, e.g., *BRCA1* c.3629_3630delAG in Chechens, *BRCA2* c.6341delC in North Ossetians, *BRCA2* c.5351dupA in Ingush, and *BRCA1* c.2907_2910delTAAA in Karachays. Some *BRCA1/2* alleles, particularly *BRCA2* c.9895C > T, were shared by several nationalities. *ATM* PVs were detected in 14 patients, with c.1673delG and c.8876_8879delACTG alleles occurring twice each. *PALB2* heterozygosity was observed in 5 subjects, with one variant seen in 2 unrelated women.

Conclusion This study adds to the evidence for the global-wide contribution of *BRCA1/2* genes to HGSOC and BC morbidity, although the spectrum of their PVs is a subject of ethnicity-specific variations. The data on founder *BRCA1/2* alleles may be considered when adjusting the *BRCA1/2* testing procedure to the ethnic origin of patients.

Keywords *BRCA1* · *BRCA2* · Founder effect · Hereditary cancer · North Caucasus · Pathogenic variants

Abbreviations

BC	Breast cancer
GATK	Genome Analysis Toolkit
HBOC	Hereditary breast and ovarian cancer
HGSOC	High-grade serous ovarian cancer
NGS	Next-generation sequencing
PV	Pathogenic variant

Introduction

Hereditary breast and ovarian cancer syndrome (HBOC) is apparently the most common genetic disease worldwide. Its main causes, i.e., pathogenic variants (PVs) in *BRCA1* and *BRCA2* genes, were identified almost three decades ago [1–3]. Somewhat unexpectedly, the attempts to discover novel HBOC genes ("*BRCA3*") had limited success: indeed, only *RAD51* paralogs have been shown to predispose to both breast cancer (BC) and high-grade serous ovarian cancer (HGSOC), although their overall

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contribution to BC and HGSOC morbidity appears to be small due to low population frequencies of *RAD51B, RAD51C,* and *RAD51D* PVs [4–7]. *PALB2* may be regarded as a third highly penetrant cancer-associated gene after *BRCA1* and *BRCA2*; however, its role is proven only for BC but not for HGSOC predisposition [8, 9]. There is also a spectrum of genes rendering a moderate increase in BC risk, e.g., *ATM*, *CHEK2, BLM, NBS1,* and *RECQL* [10].

BRCA1 and *BRCA2* studies were carried out in several dozen countries and involved a multitude of ethnic groups. These studies indicated that *BRCA1* and *BRCA2* play a key role in HBOC development in virtually all populations studied, although their contribution to BC and HGSOC morbidity is a subject of some variations. For example, *BRCA1* is the leading contributor to BC and HGSOC predisposition in Slavic countries, while the occurrence of *BRCA2* PVs in Poland, Belarus, Russia, and Ukraine is less pronounced [11–13]. Additionally, *BRCA2* is a primary cause of HBOC in several other regions, with Iceland being the most known example [14]. However, some countries are characterized by a "negative founder effect," as a relatively low frequency of *BRCA1/2* PVs in HBOC families [15].

The ethnic composition of the Russian Federation includes unique features, with people of Slavic origin constituting approximately 80% of the population [16]. In addition, there are several large ethnic groups residing on well-defined territories that have managed to maintain their national authenticity over centuries due to religious, cultural, and geographical barriers. The mountains of the North Caucasus host several such communities [17, 18]. Chechnya and Ingushetia are neighboring monoethnic autonomies with carefully preserved Islamic traditions. Dagestan is known for its multiethnic composition, with several dozen folks residing in distinct regions. Ossetia is located close to Georgia and is predominantly Orthodox Christian, whereas most people residing in the North Caucasus practice Islam. Kabardino-Balkaria and Karachay-Cherkessia are each composed of two distinct nations. In addition, there are several Armenian settlements and the Republic of Adygea located in the south of Russia (Table 1).

While the genetics of breast and ovarian cancer in ethnic Slavs, including residents of Russia, is relatively well studied [11–13, 20–22], no systematic investigations have been done for the populations of the North Caucasus. The way of life in these regions, together with the geographical isolation, allows for the expectation of a high contribution of founder alleles, with a unique spectrum of pathogenic variants for each of these groups. Our recent study performed on Chechens provided support for this concept [19]. Here, we describe the distribution of *BRCA1*, *BRCA2*, *PALB2,* and *ATM* PVs in BC and HGSOC patients from the North Caucasus.

Methods

The information on the study was distributed in the year 2020 among practicing oncologists working in the North Caucasus and Southern Russia. The doctors were encouraged to invite patients with BC for DNA analysis, particularly subjects with early-onset and/or family history-positive and/or bilateral and/or receptor triple-negative disease, as well as women with HGSOC. All study participants provided informed consent. The data regarding ethnic origin relied on self-reported information. Patients representing Slavic ethnic groups received identical DNA testing as non-Slavic subjects; however, they were not included in the data analysis. The investigation was approved by the Ethics Committee in the N.N. Petrov Institute of Oncology (ID 20/25; January 23, 2020). The main characteristics of the patients are presented in Table 1.

Next-generation sequencing (NGS) was used to screen *BRCA1*, *BRCA2*, *ATM*, and *PALB2* as described previously [19]. Library preparation was performed using the KAPA HyperPlus Kit (Roche). Dual-index libraries were used to pool up to 96 samples into one enrichment reaction. A custom panel of biotinylated probes covering coding sequences, exon–intron boundaries, and 5′- and 3′-untranslated regions of the mentioned genes was utilized for the enrichment of the DNA libraries. The hybridization step consisted of two rounds and was carried out overnight. Sequencing was performed on the Illumina NextSeq 500 platform with the Mid Output Kit v2.5 in paired-end mode for 150 cycles in both orientations. The bioinformatic pipeline included FASTQ files generation, quality assessment, and mapping of the obtained sequences to the hg19 genome using the BWA tool. The DepthOfCoverage tool [GATK] was utilized for the control of the sequencing quality. DNA specimens with at least 99% of target bases covered at least 15 times were considered for analysis. Aligned reads were subjected to single-nucleotide variants and indels calling with the HaplotypeCaller [GATK]. Annotation was made with the SnpEff software tool. Further selection was made based on variant pathogenicity data from the ClinVar database. Nonsense, frameshift, and essential splice site variants without corresponding records in the ClinVar database were considered as well and checked for presumable pathogenicity with the VarSome tool. Selected PVs were manually checked in the Golden Helix Genome Browser. Discrimination between founder and hotspot recurrent *BRCA1/2* PVs relied on the consideration of neighboring DNA polymorphisms.

Results

The study included 1059 patients, with 787 women affected with BC and 272 diagnosed with HGSOC (Table 2). *BRCA1/2* pathogenic alleles were detected in 77 BC patients,

Table 1 Description of the patients

Region/Ethnic group (no. of patients)	Approximate population in Russia[a]	City/Cancer center	BC patients	HGSOC patients
Chechnya/Chechens ($n=147$)[b]	~1 675 000	Grozny, Chechen Republican Cancer Center	$N=79$ Mean age: 51.2 [range 24–73]	$N=68$ Mean age: 56.9 [range 30–80]
Ingushetia/Ingush ($n=122$)	~517 000	Pliyevo, Republican Cancer Center	$N=103$ Mean age: 47.3 [range: 25–77]	$N=19$ Mean age: 56.7 [range: 29–70]
North Ossetia/Ossetians ($n=155$)	~440 000	Vladikavkaz, Republican Cancer Center	$N=104$ Mean age: 46.7 [range: 30–81]	$N=51$ Mean age: 58.3 [range: 21–85]
Kabardino-Balkaria ($n=223$): Kabardians ($n=184$), Balkars ($n=31$), Kabardin/Balkars or unspecified ($n=8$)	~500 000 Kabardians, ~120 000 Balkars	Nalchik, Cancer Center, City Hospital No.1	$N=155$ Mean age: 48.4 [range: 20–82]	$N=68$ Mean age: 59.8 [range: 19–86]
Dagestan ($n=235$): Avars ($n=67$), Dargins ($n=49$), Kumyks ($n=37$), Lezgins ($n=32$), Laks ($n=16$), Tabasarans ($n=14$), other or unspecified ($n=20$)	~957 000 Avars, ~521 000 Dargins, ~496 000 Kumyks, ~416 000 Lezgins, ~162 000 Laks, ~126 000 Tabasarans	Makhachkala, Republican Cancer Center	$N=198$ Mean age: 49.0 [range: 22–73]	$N=37$ Mean age: 55.6 [range: 27–70]
Karachay-Cherkessia ($n=60$): Karachays ($n=23$), Cherkess ($n=15$), Karachays/Cherkess or unspecified ($n=22$)	~205 000 Karachays, ~59 000 Cherkess	Cherkessk, Cancer Center	$N=47$ Mean age: 53.7 [range: 31–74]	$N=13$ Mean age: 57.2 [range: 45–78]
Armenians ($n=117$)	~947 000	Krasnodar, Clinical Cancer Center; Sochi, Cancer Center	$N=101$ Mean age: 47.2 [range: 27–84]	$N=16$ Mean age: 57.7 [range: 36–72]

[a] According to the population census 2021[16]

[b] Data have been published[19]

with frequencies ranging from 5/79 (6%) in Chechen women to 20/155 (13%) in patients from Kabardino-Balkaria (Table 2). *BRCA1* PVs accounted for 22/787 (2.8%) instances of BCs, with maximal impact observed in Chechens (4/79 (5%)), and no contribution in patients from North Ossetia (0/104 (0%)). *BRCA2* PVs were seen in 55/787 (7%) BCs, being particularly common in Armenians and relatively rare in Chechens (10/101 (10%) and 1/79 (1.3%), respectively) (Table 2). The frequency of *BRCA1/2* pathogenic variants in HGSOCs approached 60/272 (22%), being 32/272 (12%) for *BRCA1* and 28/272 (10%) for *BRCA2*. The contribution of *BRCA1* PVs was the highest in HGSOC patients from Karachay-Cherkessia (4/13 (31%)) and the lowest in Ossetian women with this disease (2/51 (4%)). In comparison, *BRCA2* PVs were particularly characteristic for HGSOC patients of Ingush origin (4/19 (21%)) (Table 2).

The spectrum of *BRCA1/2* pathogenic variants is described in Table 3 and Supplementary Table S1. Several recurrent variants demonstrated strong ethnic specificity (Fig. 1). Some alleles were shared between several North Caucasus folks. For example, *BRCA2* c.9895C > T [p.Gln3299Ter] was detected in Ossetians, Avars, Chechens, and Kumyks, while *BRCA2* c.8437G > T [p.Gly2813Ter] was observed in Kabardians and Armenians. A relatively high contribution of Slavic founder alleles was observed in Kabardians (5 (15%) *BRCA1* c.5266dupC [5382insC] and 4 (12%) *BRCA1* c.1961delA [2080delA] out of 33 *BRCA1/2* PV carriers), while their proportion was small in other nationalities. The ratio between recurrent and unique *BRCA1/2* PVs was exceptionally high in all studied ethnic groups, ranging from 59% in patients from North Ossetia to 82% in Kabardians (Table 4).

Most of the recurrent alleles detected in this study (see Fig. 1) were not frequently observed in other national groups [23], indicating that they are not associated with mutational hotspots, but are most likely to have a single ancestor each. Nevertheless, we considered the status of polymorphic DNA sites located in the vicinity of PVs. Strikingly, virtually all subjects carrying a given PV had identical or very similar haplotypes, thus confirming the founder origin of *BRCA1/2* pathogenic alleles in the North Caucasus (Supplementary Table S2). However, haplotyping revealed variation in carriers of the *BRCA2* c.2808_2811delACAA allele. Interestingly, previous studies have shown that this PV has apparently emerged several times in the human history due to its location within the hotspot [24].

PALB2 mutations were uncommon, being observed only in BC patients (Table 3 and Supplementary Table S1). The overall frequency of *ATM* mutations was 14/1059 (1.3%), with 5/272 (1.8%) in HGSOC patients and 9/787 (1.1%) in women with BC. Interestingly, as many as 8 patients (3.6%) from Kabardino-Balkaria were *ATM* PV carriers, with only one allele (*ATM* c.8874_8877del [rs770704493]) being detected more than once.

Discussion

This study analyzed BC and HGSOC patients of different nationalities residing in the North Caucasus and Southern Russia. All ethnic groups included in the investigation were characterized by the persistence of their own unique founder alleles. These data are consistent with the history and way of life of people living in these mountainous regions. The findings of the study may have an immediate medical impact, as testing for founder alleles is non-expensive and may be applied on a larger scale than comprehensive NGS analysis.

The study has essential limitations. The prospective collection of critical numbers of BC and OC cases is complicated. Furthermore, while *BRCA1* and *BRCA2* have more or less similar penetrance for BC, the role of *BRCA2* in OC development may be somehow less pronounced when compared to *BRCA1* [25, 26]. Furthermore, different regions of *BRCA1* and *BRCA2* have distinct penetrance toward BC and OC [27]. Among the founder mutations, three *BRCA2* alleles recurrent in Kabardino-Balkaria (p.His2623Arg, p.Gly2813Ter, and c.993_994delAA) are located in the BC cluster region. *BRCA1* c.3629_3630delAG (Chechen), *BRCA1* c.2907_2910delTAAA (Karachay), *BRCA1* c.2649_2650insGGCA (Armenian), *BRCA2*

Table 2 Frequency of *BRCA1* and *BRCA2* mutations in different ethnic groups

Ethnic group	BC		HGSOC		Total	
	BRCA1	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*
Ossetians ($n = 155$)	0/104 (0)	7/104 (7%)	2/51 (4%)	8/51 (16%)	2/155 (1%)	15/155 (10%)
Kabardians, Balkars ($n = 223$)	6/155 (4%)	14/155 (9%)	8/68 (12%)	5/68 (7%)	14/223 (6%)	19/223 (9%)
Karachays, Cherkess ($n = 60$)	2/47 (4%)	2/47 (4%)	4/13 (31%)	1/13 (8%)	6/60 (10%)	3/60 (5%)
Dagestan (all) ($n = 235$)	6/198 (3%)	12/198 (6%)	4/37 (11%)	5/37 (14%)	10/235 (4%)	17/235 (7%)
Ingush ($n = 122$)	1/103 (1%)	9/103 (9%)	1/19 (5%)	4/19 (21%)	2/122 (2%)	13/122 (11%)
Armenians ($n = 117$)	3/101 (3%)	10/101 (10%)	3/16 (19%)	0/16 (0)	6/117 (5%)	10/117 (9%)
Chechens ($n = 147$)	4/79 (5%)	1/79 (1%)	10/68 (15%)	5/68 (7%)	14/147 (10%)	6/147 (4%)

Table 3 *BRCA1, BRCA2, PALB2,* and *ATM* PVs observed at least twice in BC or HGSOC patients from the North Caucasus

Gene/Variant	ClinVar Accession	Ethnic group	No. of patients		
			BC	**HGSOC**	**Total**
BRCA2 c.9895C > T [p.Gln3299Ter]	VCV000462540	Ossetians (*n* = 3), Avars (*n* = 3), Chechens (*n* = 3), Kumyks (*n* = 2)	5	6	11
BRCA1 c.3629_3630delAG [p.Glu1210fs]	VCV000054947	Chechens	1	9	10
BRCA1 c.5266dupC [p.Gln1756fs]	VCV000017677	Ossetians (*n* = 1), Kabardians (*n* = 5), Ingush (*n* = 1), Avars (*n* = 1)	4	4	8
BRCA2 c.5351dupA [p.Asn1784fs]	VCV000037960	Ingush (*n* = 6), Chechens (*n* = 1)	4	3	7
BRCA2 c.6341delC [p.Pro2114fs]	–	Ossetians	6	1	7
BRCA2 c.7868A > G [p.His2623Arg]	VCV000038123	Kabardians (*n* = 4), Balkars (*n* = 2)	2	4	6
BRCA1 c.2907_2910delTAAA [p.Lys970fs]	–	Karachays	1	4	5
BRCA2 c.8437G > T [p.Gly2813Ter]	VCV001070329	Kabardians (*n* = 3), Armenians (*n* = 2)	5	0	5
BRCA1 c.1961del [p.Lys654fs]	VCV000037438	Kabardians	1	3	4
BRCA2 c.2808_2811delACAA [p.Ala938Profs]	VCV000009322	Ossetians (*n* = 1), Armenians (*n* = 3)	4	0	4
BRCA2 c.5057 T > G [p.Leu1686Ter]	–	Ingush	3	1	4
BRCA2 c.993_994delAA [p.Lys331fs]	VCV000052922	Kabardians	4	0	4
BRCA1 c.2649_2650insGGCA [p.Thr884Glyfs]	VCV000254417	Armenians	1	2	3
BRCA1 c.66dupA [p.Glu23fs]	VCV000037691	Lezgins	2	1	3
BRCA2 c.429delT [p.Val144fs]	VCV000141697	Kabardians (*n* = 1), Laks (*n* = 2)	3	0	3
BRCA2 c.5621_5624delTTAA [p.Ile1874fs]	VCV000037980	Avars	3	0	3
BRCA2 c.7806-1G > C	VCV000850778	Dargins (*n* = 2), Kumyks	2	1	3
BRCA1 c.115 T > C [p.Cys39Arg]	VCV000054152	Avars, Dargins	1	1	2
BRCA1 c.4065_4068delTCAA [p.Asn1355fs]	VCV000017674	Armenians	1	1	2
BRCA1 c.4205delA [p.His1402fs]	–	Kabardians	1	1	2
BRCA1 c.5296delA [p.Ile1766fs]	–	Chechens	1	1	2
BRCA2 c.6486_6489delACAA [p.Lys2162fs]	VCV000038048	Kabardians	1	1	2
BRCA2 c.6998dupT [p.Pro2334fs]	VCV000219496	Cherkess, Karachays	1	1	2
BRCA2 c.7407_7408delTT [p.Phe2470fs]	VCV000052319	Ingush, Chechens	1	1	2
BRCA2 c.7976G > A [p.Arg2659Lys]	VCV000038131	Avars	1	1	2
BRCA2 c.8009C > A [p.Ser2670Ter]	VCV000052470	Kabardians	2	0	2
BRCA2 c.9027delT [p.His3010fs]	VCV000052731	Armenians	2	0	2
PALB2 c.2218C > T [p.Gln740Ter]	VCV000481035	Ingush	2	0	2
ATM c.1673delG [p.Gly558fs]	–	Ingush	2	0	2
ATM c.8876_8879delACTG [p.Asp2959fs]	VCV000189140	Kabardians	1	1	2

c.5351dupA and p.Leu1686Ter (both Ingush), and *BRCA2* c.5621_5624delTTAA (Avar) have particular associations with OC. *BRCA2* c.6341delC (Ossetian), *BRCA2* c.2808_2811delACAA (Armenian), and *BRCA1* c.66dupA (Lezgyn) cannot be classified in this respect.

The admixture of Slavic founder alleles in the analyzed patient groups is an expected observation, given that Slavic and non-Slavic people have a long history of neighborhood. Still, the degree of this admixture is not proportional to the share of the Slavic population in the studied autonomies. Indeed, the high frequency of *BRCA1* Slavic founder alleles in Kabardians is compatible with data indicating that approximately 20% of residents of Kabardino-Balkaria are ethnic Slavs [16]. However, the presence of Slavic people is the same (19%) or even higher (27%) in North Ossetia or Karachay-Cherkessia, respectively. Nevertheless, the admixture of Slavic alleles was less pronounced in patients from these regions. These trends may be attributed to several historical events or cultural attitudes or simply reflect a sampling bias.

A similarly designed study has been reported for patients residing in the Republic of Armenia [28]. Interestingly, a distinct pattern of *BRCA1/2* mutations has been observed for ethnic Armenians living in the South of Russia. Patients from the capital of the Republic of Armenia (Erevan) most often carried *BRCA1* c.3477_3480delAAAG and *BRCA1* p.Trp1815Ter alleles, which were not seen in Armenian patients from Southern Russia. Armenian founder PVs detected in this study (*BRCA1* c.2649_2650insGGCA and *BRCA2* c.2808_2811delACAA) were previously observed

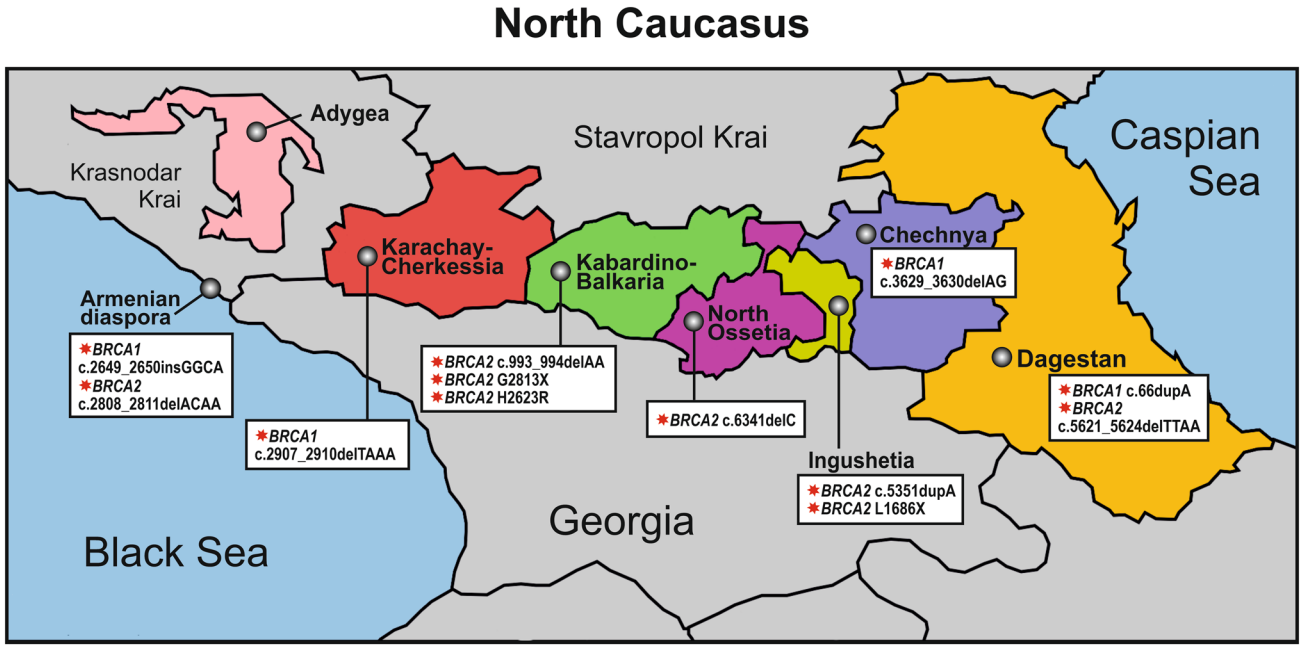

Fig. 1 Most frequent pathogenic *BRCA1* and *BRCA2* alleles in different ethnic groups of the North Caucasus

Table 4 Recurrent vs. unique mutations

	Recurrent	Unique	Total
North Ossetia	10 (59%)	7 (41%)	17
Kabardino-Balkaria	27 (82%)	6 (18%)	33
Karachay-Cherkessia	7 (78%)	2 (22%)	9
Dagestan	20 (74%)	7 (26%)	27
Ingushetia	10 (67%)	5 (33%)	15
Armenians	12 (75%)	4 (25%)	16
Chechnya	15 (75%)	5 (25%)	20

in the study of Moradian et al. [28], although they appeared not to be frequent in Erevan patient series.

A trend toward a relatively high frequency of *ATM* PVs in patients from Kabardino-Balkaria may be of interest. High occurrence of the *ATM* protein-truncating alleles cannot be attributed to a founder effect, given the diversity of the observed variants. There could be some biological selection advantage for *ATM* heterozygotes. However, subjects from neighboring regions, who live in essentially similar conditions, did not demonstrate an increase in the frequency of *ATM* PVs.

Overall, this study adds to the evidence for the global-wide contribution of *BRCA1/2* pathogenic variants to the HBOC incidence. It is of interest that all series of BC and OC cases presented in this study (Tables 1–2) are characterized by a high level of genetic homogeneity, but are distinct from each other. It is likely that some newly described HBOC genes, for example, *RAD* family members, may play a noticeable role in the HBOC incidence at least in some of these ethnic groups. Furthermore, yet unstudied founder populations are particularly promising for the discovery of novel cancer-predisposing genes. While conventional exome sequencing studies have largely failed to identify major contributors to HBOC incidence whose significance is comparable with the role of *BRCA1/2* PVs, their application in monoethnic communities still holds the potential to reveal new genetic determinants of BC and OC risk.

Web Resources

- ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/
- dbSNP, http://www.ncbi.nlm.nih.gov/SNP
- GATK, https://gatk.broadinstitute.org/hc/en-us
- Golden Helix, http://www.goldenhelix.com
- SnpEff, http://pcingola.github.io/SnpEff/
- VarSome, https://varsome.com/

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versions of the manuscript. All authors read and approved the final manuscript.

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Data availability NGS files are not publicly available due to ethical reasons. The enquiries can be directed to the corresponding author.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval The study was approved by the Ethics Committee in the N.N. Petrov Institute of Oncology conducted in accordance with the Declaration of Helsinki protocol. All patients gave informed consent for the collection and use of their data for a scientific purpose.

Consent to participate Written informed consent was obtained from the parents.

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