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The highest frequency of *BRCA1* c.3700_3704del detected among Albanians from Kosovo

Ivana Maleva Kostovska[1], Simona Jakovchevska[1], Milena Jakimovska Özdemir[1], Sanja Kiprijanovska[1], Katerina Kubelka-Sabit[2,3], Dzengis Jasar[2,3], Marina Iljovska[4], Emilija Lazareva[4], Snezhana Smichkoska[4], Dijana Plaseska-Karanfilska[1]

[1]Research Centre for Genetic Engineering and Biotechnology "Geogri D. Efremov", Macedonian Academy of Sciences and Arts, Skopje, R. North Macedonia
[2]Clinical Hospital Acibadem Sistina, Dept. of Histopathology and Cytology, Skopje, R. North Macedonia
[3]University "Goce Delcev", Medical Faculty, Stip, R. North Macedonia
[4]Ss. Cyril and Methodius University, Medical Faculty, University Clinic of Radiotherapy and Oncology, Skopje, R. North Macedonia

ABSTRACT

Background: The spectrum of *BRCA1* and *BRCA2* mutations varies among populations; however, some mutations may be frequent in particular ethnic groups due to the "founder" effect. The c.3700_3704del mutation was previously described as a recurrent *BRCA1* variant in Eastern European countries. This study aimed to investigate the frequency of c.3700_3704del *BRCA1* mutation in Albanian breast and ovarian cancer patients from North Macedonia and Kosovo.

Materials and methods: A total of 327 patients with invasive breast and/or ovarian cancer (111 Albanian women from North Macedonia and 216 from Kosovo) were screened for 13 recurrent *BRCA1/2* mutations. Targeted NGS with a panel of 94 cancer-associated genes including *BRCA1* and *BRCA2* was performed in a selected group of 118 patients.

Results: We have identified 21 *BRCA1*/2 pathogenic variants, 17 (14 *BRCA1* and 3 *BRCA2*) in patients from Kosovo (7.9%) and 4 (1 *BRCA1* and 3 *BRCA2*) in patients from North Macedonia (3.6%). All *BRCA1/2* mutations were found in one patient each, except for c.3700_3704del *BRCA1* mutation which was observed in 14 unrelated families, all except one originating from Kosovo. The c.3700_3704del mutation accounts for 93% of *BRCA1* mutation positive cases and is present with a frequency of 6% among breast cancer patients from Kosovo.

Conclusions: This is the first report of *BRCA1/2* mutations among breast and ovarian cancer patients from Kosovo. The finding that *BRCA1* c.3700_3704del represents a founder mutation in Kosovo with the highest worldwide reported frequency supports the implementation of fast and low-cost screening protocol, regardless of the family history and even a pilot population-based screening in at-risk population.

Key words: BRCA1; c.3700_3704del; founder mutation; breast cancer; Kosovo

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Introduction

Breast cancer is the leading cause of global cancer incidence in 2020, representing 11.7% of all cancer cases worldwide [1]. Mutations in *BRCA1* and *BRCA2* genes account for at least 20% of hereditary breast cancer cases. In general population, about 5–10% of all breast cancer and 10–15% of ovarian cancer cases can be attributed to these well characterized genetic risk factors [2, 3]. The lifetime

Address for correspondence: Dijana Plaseska-Karanfilska, Boulevard Krste Petkov Misirkov 2, 1000 Skopje, R. North Macedonia, tel: +389 2 3235 410; +389 2 3235 400 (Ext 264), fax: +389 2 3115 434; e-mail: dijana@manu.edu.mk

risk for breast and ovarian cancer for *BRCA1* mutation carriers has been estimated between 65–85% and 39–93%, respectively. For *BRCA2* mutation carriers the lifetime risk ranges from 45–85% for breast and 11–27% for ovarian cancer [4].

The incidence of pathogenic *BRCA1* and *BRCA2* mutations differs between populations worldwide as well as within Europe. Various populations present a wide spectrum of different mutations, although some mutations may be frequent in particular ethnic groups that are geographically and/or reproductively isolated due to the "founder" effect. The highest frequency of *BRCA1/2* founder mutations is found in Ashkenazi Jews (2–2.5%) where only three mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*) represent 95% of all *BRCA1/2* mutations identified in this population [5]. Founder mutations are present in several European populations, with a strong founder effect observed in individuals of Slavic descent, including the Czech Republic, Poland, Russia and Belarus [6]. There is limited knowledge about the *BRCA1/2* mutational profile in breast and ovarian cancer patients in West Balkan countries. In our previous study we reported the presence of c.3700_3704del mutation in *BRCA1* only among our cohort of Albanian breast cancer patients [7, 8]. The mutation was previously described as a recurrent *BRCA1* variant in Eastern European countries in multiple individuals affected with hereditary breast and ovarian cancer [9–15]. This study aimed to investigate the frequency of c.3700_3704del mutation in larger Albanian breast and ovarian cancer cohort from the Republic of North Macedonia and Republic of Kosovo. The findings of this study may help to optimize the genetic testing strategy for breast and ovarian cancer among individuals with Albanian ethnic origin in the region.

Materials and methods

A total of 327 Albanian patients diagnosed with invasive breast and/or ovarian cancer during the years 2010–2021 were included in this study (111 Albanian women from N. Macedonia and 216 from Kosovo). The patients were recruited from the Histopathology Laboratory of the Clinical Hospital Acibadem Sistina, Skopje, and University Clinic of Radiotherapy and Oncology, Medical Faculty, Skopje. Written informed consent was obtained from each participant. The study was approved by the Ethics Committee of the Macedonian Academy of Sciences and Arts, Skopje, Republic of North Macedonia. Personal data (origin, age at diagnosis and familiar history of the disease), histopathological classification, stage, receptor status (estrogen, progesterone and HER2) are given in Table 1. Median age at diagnosis was 50 years (range 22–81 years) and 19% of patients reported first-degree relative(s) with breast or/and ovarian cancer. Genomic DNA was isolated from peripheral white blood cells using standard phenol-chloroform extraction.

All patients were screened for 13 recurrent *BRCA1/2* mutations detected among Macedonian population (c.181T>G, c.1102G>T, c.3700_3704del, c.4035del, c.4065_4068del, c.5266dup, c.68_69del in *BRCA1* and c.5722_5723del, c.5946del, c.7879A>T, c.8317_8330del, c.8168A>G, c.9098dup in *BRCA2*) by a single nucleotide primer extension assay utilizing the ABI PRISM™ SNaPshot Multiplex Kit (Life Technologies, Carlsbad, CA, USA) following the manufacturer's instructions [16]. The analysis of the amplified fragments was performed on the ABI PRISM® 3130 Genetic Analyzer (Thermo Fisher Scientific, Waltham, MA, USA). Additionally, for 118 patients we performed targeted next generation sequencing (NGS) using TruSight Cancer sequencing panel to analyze 94 cancer-associated genes including *BRCA1* and *BRCA2* (Illumina, San Diego, CA, USA). The sequencing was done on the NGS MiSeq Illumina Personal Sequencer. The patients for NGS were selected according to their family history of cancer, early age of onset, and bilateral and/or triple negative (TN) breast cancer. The identified *BRCA1/2* variants have been evaluated and classified based on the American College of Medical Genetics and Genomics (ACMG) classification guidelines [17].

Results

In our cohort of 327 Albanian women, we identified 21 pathogenic variants in *BRCA1* and *BRCA2* genes with overall mutation detection rate of 6.4% (21/327). The mean age of diagnosis among 21 *BRCA1/2* pathogenic carriers was 39.3 years (range 22-56 years) and 38.1% reported positive family history for breast and/or ovarian cancer. The frequency of *BRCA1* and *BRCA2* pathogenic variants was 4.6% (15/327) and 1.8% (6/327), respectively.

Table 1. Clinical characteristics of 327 breast and/or ovarian cancer patients

Origin	% (n/total)
Albanian patients from North Macedonia	33.9 (111/327)
Albanian patients from Kosovo	66.1 (216/327)
Age of diagnosis	
≤ 50	53.2 (174/327)
> 50	46.8 (153/327)
Family history of cancer	
Breast cancer/Ovarium FH	19.7 (62/315)
Other cancer FH	19.7 (62/315)
No family history	60.6 (191/315)
ND	3.6 (12/327)
Localization	
BC Unilateral	96.9 (310/320)
BC Bilateral/Contralateral	3.1 (10/320)
OC/OC + BC	1.5 (5/324)
ND	0.9 (3/327)
Histopatology data	
Ductal	87.8 (281/320)
Lobular	6.6 (21/320)
Mixed (Ductal & Lobular)	2.2 (7/320)
Medullary	0.9 (3/320)
Papillar	1.2 (4/320)
Mucinous	0.9 (3/320)
Paget disease of the breast	0.3 (1/320)
ND	0.9 (3/323)
Stage	
I	16.3 (52/318)
II	46.2 (147/318)
III	37.1 (118/318)
IV	0.3 (1/318)
ND	2.8 (9/327)
Tumor ER status	
Er+	77.5 (244/315)
Er–	22.5 (71/315)
ND	2.5 (8/323)
Tumor PR status	
Pr+	66.7 (210/315)
Pr–	33.3 (105/315)
ND	2.5 (8/323)
Tumor HER2 status	
Her2+	26.3 (83/316)
Her2–	73.7 (233/316)
ND	2.2 (7/323)
Tumor TN status	
TN	10.4 (33/316)
non-TN	89.6 (283/316)
ND	2.2 (7/323)

FH — Family history; BC — breast cancer; OC — ovarian cancer; ND — no data; ER — estrogen receptor; PR — progesterone receptor; TN — triple negative receptor status

We found only two different deleterious mutations in *BRCA1* and six in *BRCA2* mutation positive cases (Tab. 2). All *BRCA1* and *BRCA2* mutations were found in one patient each, except for 3700_3704del which was identified in 14 patients, representing 93.3% (14/15) of all *BRCA1* observed mutations and general mutation frequency of 4.3% (14/327). Overall mutation frequency for *BRCA1* and *BRCA2* genes in Albanians from Kosovo was 7.9% (17/216), of which 6.5% (14/216) were *BRCA1* and 1.4% (3/216) were *BRCA2* carriers. In Albanians from North Macedonia we observed lower overall mutation frequency compared to Kosovo (3.6%, 4/111) where *BRCA1* was mutated in only one patient (0.9%, 1/111) and *BRCA2* in three patients (2.7%, 3/111). The 3700_3704del mutation was detected in 76% (13/17) of the *BRCA1/2* mutation positive patients and represent 93% (13/14) of *BRCA1* mutation positive patients from Kosovo. In comparison, the 3700_3704del mutation was detected in only one Albanian patient from North Macedonia and was the only mutation detected in the *BRCA1* gene.

Patient and tumour characteristics of the c.3700_3704del carriers are summarized in Table 3. All c.3700_3704del carriers originated from Kosovo, except for one and the mean age of onset was 39.8 years (range 22–56 years). Nine patients (64.3%) reported family history for cancer and seven of them had relatives affected with breast and/or ovarian cancer. Thirteen carriers were diagnosed with invasive ductal carcinoma; one had both breast and ovarian cancer, while another had only ovarian cancer. Triple negative receptor status was found in 71.4% (10/14) of the c.3700_3704del tumours.

Discussion

The spectrum of *BRCA1* and *BRCA2* mutations varies extensively among populations. In some populations, a wide spectrum of different mutations

Table 2. Pathogenic variants in *BRCA1* and *BRCA2* genes identified in 327 Albanian patients from North Macedonia (NMK) and Kosovo (KS).

Exon no.	HGVS nomenclature	AA change	Variant ID	Times observed in patients	Times observed in family members
***BRCA1* (NM_007300.3)**					
11	c.2933dup	p.Tyr978Ter	rs878853292	1 (KS)	0
11	c.3700_3704del	p.Val1234GlnfsTer8	rs80357609	14 (13 KS + 1 NMK)	1 (KS)
***BRCA2* (NM_000059.3)**					
9	c.775A>T	p.Arg259Ter	rs397507937	1 (KS)	0
11	c.5722_5723del	p.Leu1908ArgfsTer2	rs80359530	1 (NMK)	0
11	c.6468_6469del	p.Gln2157IlefsTer18	rs80359596	1 (NMK)	0
17	c.7895del	p.Ala2632GlufsTer16	–	1 (KS)	0
25	c.9304del	p.Ala3102GlnfsTer2	–	1 (NMK)	0
25	c.9352_9353del	p.Met3118ValfsTer31	rs786203318	1 (KS)	0

Table 3. Clinical characteristics of 14 breast and/or ovarian cancer patients with 3700_3704del *BRCA1* mutation

N	Origin	Age at diagnosis (years)	Histopatology data	Stage	ER/PR pos. status	TN pos. status	Family history of cancer
1	N.Macedonia	48	Ductal	IIA	Yes	No	Yes (BC)
2	Kosovo	41	Ductal	IIB	Yes	No	Yes (OC)
3	Kosovo	30	Ductal	IA	No	Yes	Yes (BC)
4	Kosovo	34	Ductal	IIIA	No	Yes	No
5	Kosovo	50	Ductal	IIA	No	Yes	Yes (BC)
6	Kosovo	41	Ductal	IIA	No	Yes	No
7	Kosovo	56	Ductal bc and oc	IIA	No	Yes	No
8	Kosovo	33	Ductal	IA	Yes	No	No
9	Kosovo	50	Oc	IIIC	–	–	Yes (other Ca)
10	Kosovo	39	Ductal with medull. feat.	IIA	No	Yes	Yes (BC)
11	Kosovo	22	Ductal with medull. feat.	IA	No	Yes	Yes (BC)
12	Kosovo	30	Ductal with medull. feat.	IIIC	No	Yes	ND
13	Kosovo	35	Ductal with medull. feat.	IIA	No	Yes	Yes (other Ca)
14	Kosovo	49	Ductal	IIA	No	Yes	No

ER — estrogen receptor; PR — progesterone receptor; TN — triple negative receptor status; pos. — positive; BC — breast cancer; OC — ovarian cancer; ND — no data; Ca — cancer; medull. feat. — medullary features

exists, however, in others only specific *BRCA1*/2 mutations are present with high frequency as a consequence of a founder effect. Founder effects are most prominent in geographically, culturally or religiously isolated populations that undergo rapid expansion from a limited number of ancestors. Identification of founder mutations in certain ethnic groups is a very important step towards the development of screening protocols and improvement of genetic counselling.

We have previously reported that different *BRCA1*/2 mutations were present among breast and ovarian cancer patients from R.N. Macedonia with Macedonian and Albanian ethnic origin. In the current study of 327 breast and ovarian cancer patients with Albanian origin, an overall mutation rate of 6.4% was observed and eight different *BRCA1/2* mutations were identified. All *BRCA1*/2 mutations were found in one patient each, except for c.3700_3704del *BRCA1* mutation that was observed in 14 unrelated families, all except one originating from Kosovo. The c.3700_3704del mutation represents 93.3% of all *BRCA1* observed mutations, thus showing a very

strong founder effect among patients from Kosovo. We have not performed haplotype analysis, but the absence of the common *BRCA1* coding sequence variants in all c.3700_3704del carriers suggests a common chromosomal background and represents an indirect evidence of the mutation founder effect. The c.3700_3704del carriers originated from different regions/cities in Kosovo. The *BRCA1* c.3700_3704del mutation was present in only one of the 111 studied Albanian breast cancer patients from North Macedonia. Furthermore, this mutation was not present among 1023 breast and/or ovarian cancer patients of Macedonian origin screened in our laboratory (unpublished data). Although the majority of Albanians living in North Macedonia and those from Kosovo originate from the same ethnic Albanian sub-group of Ghegs, the frequency of c.3700_3704del mutation was much higher among Albanians from Kosovo. This may suggest the occurrence of the c.3700_3704del mutation after the settlement of the Albanian sub-group of Ghegs in the territory of Kosovo.

The c.3700_3704del *BRCA1* mutation was first reported in 1995, in a small study from Pennsylvania (US) with frequency of 0.09% observed in 115 epithelial ovarian cancer patients [15]. The mutation has been found in several European countries with different frequencies, as well as in Australia and the United States. The highest c.3700_3704del mutation frequency was found in ovarian cancer patients from the Republic of Mordovia (Russia) accounting for 40% of all *BRCA1* mutation positive cases, where haplotype analysis of 4 microsatellite markers confirmed its founder effect [18]. The mutational spectrum in this Russian region was different from *BRCA1* mutation spectrum in St. Petersburg region, where the mutation was observed in 2.3% of the analysed breast cancer patients [19]. In the Czech Republic the mutation was identified in 13–15% *BRCA1*-carriers and has overall mutation frequency between 2.6%-3.2% in breast and ovarian cancer patients [10, 13, 20]. Furthermore, the mutation was reported several times as one of the recurrent mutations in breast and ovarian cancer patients from Poland with a frequency between 1%-3.3%, with the highest frequency observed in Northern Poland [11, 21-24] and a general frequency in Polish population of 0.1% [9]. The c.3700_3704del mutation was reported in Greece with a frequency between 0.3%-1.5% in breast and ovarian cancer cases [12, 25]. Additionally, the mutation was observed in breast and ovarian cancer patients from Turkey, Germany, Denmark, Romania and Slovakia with a frequency between 0.2-0.9% [26-30]. The observation of the *BRCA1* c.3700_3704del mutation in many different populations raise the question of whether it is an ancient mutation with single origin, or whether it has arisen several times in human history. Haplotype analysis of *BRCA1* c.3700_3704del carriers from different populations should be performed (are warranted) to resolve this question.

Conclusions

In conclusion, here we report the spectrum of *BRCA1*/2 mutations in Albanian patients with breast and/or ovarian cancer from Kosovo and North Macedonia. This is the first report of the spectrum of *BRCA1/2* mutations in Kosovo. The finding that *BRCA1* c.3700_3704del represents a founder mutation in Kosovo, with the highest worldwide reported frequency (6.0%, 13/216), supports the implementation of fast and low-cost screening protocol for this mutation in all breast cancer patients, regardless of the family history and even a pilot population-based screening in at-risk population.

Conflict of interest

None declared.

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