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Novel and common BRCA1 mutations in familial breast/ovarian cancer patients from Lithuania

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Background

The germline mutations in the BRCA1 (MIM 113705) and BRCA2 (MIM600185) genes account for the majority of hereditary breast and ovarian cancers cases.

Founder mutations in BRCA1 gene have been recently described in Eastern Baltic Sea region, with variable distribution in Baltic (Latvian [1] and Lithuanian [2]) and Slavic (Polish [3], Belorussian [4], Russian [5]) populations, accounting for 80–90% of all mutations. However, data about its incidence in Lithuania are inconclusive and based on one study where only three mutations were tested in BRCA1 gene [2].

Here we present the complexity of BRCA1 gene mutation profile in familial breast and/or ovarian cancer index cases referred to Vilnius University Hospital Santariskiu Clinics from 1 year period (2006–2007).

Methods

During 1 year period (2006–2007) overall 28 unrelated index cases have attended cancer genetic clinic: 21 female

patients diagnosed with breast cancer, 4 with ovarian cancer and 3 with both breast and ovarian cancer. Comprehensive genetic counselling was performed and after written informed consent genetic material for analysis was obtained from the youngest possible affected individual from each family.

Genomic DNA was extracted from peripheral blood leukocytes with standard ethanol-chloroform method. BRCA1 gene testing was initiated with direct sequencing using ABI Prism 3130XL Genetic Analyzer for already reported common founder mutations: c.4035delA in 11 exon, c.5266dupC in 20 exon and with restriction enzyme digestion (Eco471, MSI Fermentas, Lithuania) for c.181T > G in 5 exon.

After the exclusion of common mutations, gene dosage analysis by multiplex ligation-dependent probe amplification (MLPA P002 kit, MRC Holland) and prescreening by denaturing gradient gel electrophoresis (BRCA1 Ingeny Kit) combined with direct sequencing were performed.

Results

Pathogenic BRCA1 gene mutations were found in 9 of the 28 (32%) unrelated proband patients. Two mutations—c.5266dupC and c.4035delA—accounted for 44 and 33% for all identified mutations respectively. Novel protein truncating mutation c.4516delG was found in breast and ovarian cancer patient. Pathogenic nonsense substitution c.1687C > T was also detected in breast cancer patient (Table 1). Mutations were present in 19, 50 and 100% of breast, ovarian and both breast and ovarian cancer cases, respectively. No c.181T > G mutation and BRCA1 rearrangements were found.

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Table 1 Characteristics of breast/ovarian cancer patients with BRCA1 mutation

Exon	Mutation ^a	Codon	Breast cancer (age)	No. in family (age)	Ovarian cancer (age)	No. in family (age)	Other cancers in family (age at onset)	ER	Her2	TNM (G)	Ethnicity	Family ID
11	c.1687C > T (1806 C > T)	563	27	1 (43)	~60	1	–	NA	NA	NA	Lithuanian	07641
11	c.4035delA (4154delA)	1345	35	1 (44)	–	1 (~30)	–	–	–	pT1N1M0 (G3)	Lithuanian	061450
11	c.4035delA (4154delA)	1345	–	–	45 (bilat.)	2 (50; 45)	–	NA	NA	pT3 (G3), papillary serous adenocarcinoma	Lithuanian	07360
11	c.4035delA (4154delA)	1345	54	–	55	1	–	+	–	pT1CN1AM1(G2)/pT3B(G3)	Lithuanian	071148
15	c.4516delG (4635delG)	1506	44	2 (46)	44	–	–	NA	NA	pT1CN1AM0 (G2)/cT2NxMx	Lithuanian/ Belarusian	05148
20	c.5266dupC (5382insC)	1756	29	1 (40)	–	1 (~40)	–	+	NA	pT1N1M0	Belarusian	0795
20	c.5266dupC (5382insC)	1756	33	1 (41)	–	2 (52; 64)	Cervix (30)	–	NA	NA	Belarusian	061433
20	c.5266dupC (5382insC)	1756	–	1 (35)	45	2 (74; 65)	Lung (70); lymphoma (50)	NA	NA	NA	Lithuanian	061428
20	c.5266dupC (5382insC)	1756	55	–	60 (bilat.)	–	–	NA	NA	NA	Lithuanian	07304

^a Mutation nomenclature is according to GenBank accession number U14680.1 with numbering starting at the A of the first ATG. Between parentheses nomenclature as used in the BIC database (<http://research.nhgri.nih.gov/bic/>); NA, data not available. Novel mutation is written in bold, previously not reported in the region—in italic

Polymorphic variants in BRCA1 gene were found: 2201C/T, 2430T/C, 2731C/T, 3232A/G, 3667A/G, 4427T/C and 4956A/G.

Discussion

The results from our hospital-based analysis bring several important findings. Firstly, they show complexity of BRCA1 gene mutation pattern in Lithuania. We found pathogenic deletion in exon 15 not described elsewhere in the world and nonsense substitution previously was not reported in Eastern Baltic Sea region or neighboring populations. We did not yet found large rearrangements, but they are not so uncommon [6]. Secondly, mutations in BRCA1 gene are influenced by significant founder effect which is similar to that reported from Latvian (Baltic) population [1] and in our study were attributed to 78% of detected mutations. Interestingly, c.4035delA mutation was more frequent in families of Baltic origin (Lithuanians) (3/6), thus supporting Baltic Sea region origin hypothesis of this mutation [1, 2], compared with Slavic (Belarusians) ethnicity, where Slavic/Ashkenazi c.5266dupC mutation was the most prevalent (2/3). This knowledge can be important in clinical decision making for subjecting patients to mutation testing. Thirdly, BRCA1 mutation detection rate for index patients diagnosed with breast cancer ≤ 35 year was 33% (4/12) and mutations were absent in breast cancer patients group diagnosed after 36 years (0/6). Therefore we propose that genetic testing, at least for two common c.5266dupC and c.4035delA mutations in BRCA1 gene, should be strongly considered in all female cancer cases diagnosed with breast cancer under 35 year; breast and ovarian cancer regardless the age; invasive, nonmucinous epithelial ovarian tumor regardless the age.

After the exclusion of common mutations, full BRCA1 gene analysis is further warranted in cases with a significant family history or synchronous/metachronous primary cancers.

This suggested hierarchical, cost-effective BRCA1 mutation screening protocol may have impact on the clinical management of breast-ovarian cancer families on a national healthcare system level.

References

1. Tikhomirova L, Sinicka O, Smite D, Eglitis J, Hodgson SV, Stengrevics A (2005) High prevalence of two BRCA1 mutations, 4154delA and 5382insC, in Latvia. *Fam Cancer* 4(2):77–84. doi: 10.1007/s10689-004-2758-3

2. Gronwald J, Elsakov P, Górski B, Lubiński J (2005) High incidence of 4153delA BRCA1 gene mutations in Lithuanian breast- and breast-ovarian cancer families. *Breast Cancer Res Treat* 94(2):111–113. doi:[10.1007/s10549-005-5150-6](https://doi.org/10.1007/s10549-005-5150-6)
3. Górski B, Byrski T, Huzarski T, Jakubowska A, Menkiszak J, Gronwald J et al (2000) Founder mutations in the BRCA1 gene in Polish families with breast-ovarian cancer. *Am J Hum Genet* 66(6):1963–1968. doi:[10.1086/302922](https://doi.org/10.1086/302922)
4. Oszurek O, Gorski B, Gronwald J, Prosolow Z, Uglanica K, Murinow A et al (2001) Founder mutations in the BRCA1 gene in west Belarusian breast-ovarian cancer families. *Clin Genet* 60(6):470–471. doi:[10.1034/j.1399-0004.2001.600611.x](https://doi.org/10.1034/j.1399-0004.2001.600611.x)
5. Sokolenko AP, Mitiushkina NV, Buslov KG, Bit-Sava EM, Iyevleva AG, Chekmariova EV et al (2006) High frequency of BRCA1 5382insC mutation in Russian breast cancer patients. *Eur J Cancer* 42(10):1380–1384. doi:[10.1016/j.ejca.2006.01.050](https://doi.org/10.1016/j.ejca.2006.01.050)
6. Ratajska M, Brozek I, Senkus-Konefka E, Jassem J, Stepnowska M, Palomba G et al (2008) BRCA1 and BRCA2 point mutations and large rearrangements in breast and ovarian cancer families in Northern Poland. *Oncol Rep* 19(1):263–268