Novel BRCA1 and BRCA2 pathogenic mutations in Slovene hereditary breast and ovarian cancer families

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Abstract. The estimated proportion of hereditary breast and ovarian cancers among all breast and ovarian cancer cases is 5-10%. According to the literature, inherited mutations in the BRCA1 and BRCA2 tumour-suppressor genes, account for the majority of hereditary breast and ovarian cancer cases. The aim of this report is to present novel mutations that have not yet been described in the literature and pathogenic BRCA1 and BRCA2 mutations which have been detected in HBOC families for the first time in the last three years. In the period between January 2009 and December 2011, 559 individuals from 379 families affected with breast and/or ovarian cancer were screened for mutations in the BRCA1 and BRCA2 genes. Three novel mutations were detected: one in BRCA1 - c.1193C>A (p.Gln1701*) and two in BRCA2 - c.5101C>T (p.Gln1701*) and c.5433_5436delGGAA (p.Glu1811Aspfs*3). These novel mutations are located in the exons 11 of BRCA1 or BRCA2 and encode truncated proteins. Two of them are nonsense while one is a frameshift mutation. Also, 11 previously known pathogenic mutations were detected for the first time in the HBOC families studied here (three in BRCA1 and eight in BRCA2). All, except one cause premature formation of stop codons leading to truncation of the respective BRCA1 or BRCA2 proteins.

Introduction

Most breast and ovarian cancers are sporadic and only about 5-10% of breast and 10% of ovarian cancers are thought to be hereditary, causing the hereditary breast and ovarian cancer (HBOC) syndrome (1,2). Majority of HBOC cases have underlying cause in germline mutations in the BRCA1 and BRCA2 susceptibility genes (3,4). Carriers of known deleterious mutations in the BRCA genes have a lifetime risk of approximately 60 to 80% for development of breast cancer (BC) and a 15 to 40% lifetime risk for ovarian cancer (OC) and are also at a heightened risk for some other cancer types (4-6). So far, genome-wide association studies have not identified other highly penetrant susceptibility genes linked with HBOC, as reviewed in Mavaddat et al (7). Genetic screening of BRCA1 and BRCA2 therefore remains the only verified strategy for identification of individuals at high risk for hereditary BC and/or OC. To reduce cancer risk, healthy carriers of deleterious BRCA mutations are presented with various preventive options, such as regular intensive screenings, prophylactic mastectomy with breast reconstruction and/or oophorectomy or chemoprevention in the setting of a clinical trial (8,9). Additionally, genetic counseling and BRCA screening can be offered to first degree relatives of the carrier.

The present report continues the previous report of our group from 2011 where pathogenic mutations in the BRCA1 and BRCA2 genes in the Slovene population were described (10). We describe novel pathogenic mutations that have not yet been described in the literature or BRCA mutational databases, such as Breast Cancer Information Core Database (BIC), Human Gene Mutation Database (HGMD-Professional), Universal Mutation Database (UMD) and Leiden Open Variation Database (LOVD). We also report pathogenic mutations for which records already exist but were detected for the first time in the Slovene HBOC families tested between January 2009 and December 2011. The possible effects of novel and pathogenic BRCA1 and BRCA2 mutations which have been detected in Slovene HBOC families for the first time are discussed.

Patients and methods

Tested individuals. In the period from January 2009 to December 2011, 559 new individuals from 379 Slovene HBOC families were submitted through mutational screening of the BRCA1 and/or the BRCA2 genes at the Institute of Oncology Ljubljana, which is the only public institution performing BRCA screenings in Slovenia. Probands were chosen after genetic counseling according to the ASCO guidelines for genetic and genomic testing for cancer susceptibility (11). The family history data were verified in the Slovenian state cancer registry established in 1950. All tested individuals provided
written informed consent and attended genetic counseling sessions before and after testing.

**Mutation screening.** In 362 probands admitted for complete screening of all BRCA1/2 exons, methods for variations searching consisted of multiplex ligation-dependent probe amplification analysis (MLPA; MRC Holland, Amsterdam, Netherlands) for detection of large genomic deletions and insertions and screening for small mutations of all BRCA1 and BRCA2 exons with high-resolution melting (HRM), denaturing gradient gel electrophoresis (DGGE) and direct sequencing methods (10). Probands (197) from cancer-affected families with already confirmed pathogenic BRCA mutation were tested only for the familial pathogenic mutation. The nomenclature of this study follows the Nomenclature for Description of Genetic Variations approved by the Human Genome Variation Society (HGVS).

**Results**

Since the screening for BRCA mutations began in Slovenia in the year 1999, altogether 45 distinct pathogenic BRCA mutations have been detected in the tested Slovene families - 22 in the BRCA1 and 23 in the BRCA2 (Table I). The overall mutation detection rates for the period between January 1999 to December 2008 and from January 2009 to December 2011 were 29.8 and 21.2%, respectively (Table II). The majority of detected pathogenic mutations were nonsense mutations creating premature stop codons or missense mutations and small deletions and/or insertions that cause frameshifting and also lead to premature termination of translation. Of all detected BRCA1 mutations four were large deletions, all of more than one exon. No large deletions or insertions were detected in the BRCA2 gene so far. In the period of the last three years (January 2009 to December 2011) 559 probands were tested either for the known familial mutation or were submitted through the complete screening of all BRCA exons (Table II). Of the tested probands 115 were positive for BRCA1 pathogenic mutation and 41 for BRCA2 pathogenic mutation. In the stated period, three novel mutations were found which have not yet been described, one in the BRCA1 and two in the BRCA2 gene (Table III). The novel BRCA1 pathogenic mutation was detected in a healthy female from a HBOC family (Table III, Fig. 1). All novel BRCA2 mutations were detected in female BC patients (Table III, Fig. 1).

Besides three novel mutations, eleven known pathogenic BRCA mutations were discovered for the first time in the Slovene HBOC families, three BRCA1 and eight BRCA2 (Tables IV and V). All these newly detected pathogenic mutations were detected in female BC and/or OC patients (Tables IV and V). All novel and newly detected pathogenic mutations in Slovenia were small mutations dictating premature stop codon formation and subsequent truncation of BRCA1 or BRCA2 proteins.

**Discussion**

Several recent studies have associated specific BRCA mutations with specific cancer risks and phenotypes (12,13). Many HBOC studies therefore have focused on predicting effects of specific BRCA mutations and reveal possible underlying molecular mechanisms (7). In this context, we discuss here the predicted effects of the individual novel and newly detected Slovene BRCA1 and BRCA2 pathogenic mutations.

**Novel mutations.** All three novel mutations described here - c.1193C>A (p.Ser398*) in the BRCA1 and c.5101C>T (p.Gln1701*) and c.5433_5436delGGAA (p.Glu1811Aspfs*3) in the BRCA2...
Table I. All pathogenic mutations in *BRCA1* and *BRCA2* detected in Slovene HBOC families.

|Mutation* | Amino acid changeb | Type of mutation | No. of positive families |
|-----------|--------------------|------------------|--------------------------|
|**BRCA1**  |                    |                  |                          |
| c.66_67delAG | p.Glu23Valfs’17 | Frameshift       | 1                        |
| c.116G>A     | p.Cys39Tyr        | Missense         | 8                        |
| c.181T>G     | p.Cys61Gly        | Missense         | 31                       |
| c.181T>A     | p.Cys61Ser        | Missense         | 5                        |
| c.191G>A     | p.Cys64Tyr        | Missense         | 3                        |
| c.457_458delAG | p.Ser153Cysfs’5  | Frameshift       | 1                        |
| c.844_850dupTCATTAC | p.Gln284Leufs’5 | Frameshift       | 14                       |
| c.843_846delCTCA | p.Ser282Tyrfs’15 | Frameshift       | 2                        |
| c.1193C>A    | p.Ser398’         | Nonsense         | 1                        |
| c.1687C>T    | p.Gln563’         | Nonsense         | 23                       |
| c.2269_2270delG | p.Val757Phefs’8  | Frameshift       | 1                        |
| c.3018_3021delTTCA | p.His1006Glnfs’17 | Frameshift      | 3                        |
| c.3436_3439delTGTT | p.Cys1146Leufs’8 | Frameshift       | 1                        |
| c.3718C>T    | p.Gln1240’        | Nonsense         | 2                        |
| c.5177_5180delGAAA | p.Arg1726Lysfs’3 | Frameshift       | 2                        |
| c.5251C>T    | p.Arg1751’        | Nonsense         | 2                        |
| c.5266dupC   | p.Gln1756Profs’74 | Frameshift       | 9                        |
| c.5377A>T    | p.Lys1793’        | Nonsense         | 3                        |
| Exon 1-2del  |                   | Large deletion   | 2                        |
| Exon 5-10del |                   | Large deletion   | 4                        |
| Exon 5-8del  |                   | Large deletion   | 1                        |
| Exon 5-7del  |                   | Large deletion   | 3                        |
|**BRCA2**    |                    |                  |                          |
| c.262_263delCT | p.Leu88Alafs’12  | Frameshift       | 1                        |
| c.658_659delGT | p.Val220Ilefs’4  | Frameshift       | 1                        |
| c.775A>T     | p.Arg259’         | Nonsense         | 1                        |
| c.1528G>T    | p.Glu510’         | Nonsense         | 1                        |
| c.1773_1776delTTAT | p.Ile591Metfs’22 | Frameshift       | 1                        |
| c.1813insA   | p.Ile605Asufs’11 | Frameshift       | 1                        |
| c.3265C>T    | p.Gln1089’        | Nonsense         | 2                        |
| c.3975_3978dupTGCT | p.Ser1328Cysfs’3 | Frameshift       | 5                        |
| c.4936_4939delGAAA | p.Glu1646Glnfs’23 | Frameshift      | 1                        |
| c.5101C>T    | p.Gln1701’        | Nonsense         | 2                        |
| c.5213_5216delCTTA | p.Thr1738Ilefs’2 | Frameshift       | 1                        |
| c.5291C>G    | p.Ser1764’        | Nonsense         | 5                        |
| c.5351insA   | p.Asn1784Lysfs’3  | Frameshift       | 1                        |
| c.5433_5436delGGAA | p.Glu1811Asufs’3 | Frameshift       | 1                        |
| c.5609_5610delTCinsAG | p.Phe1870’     | Nonsense         | 2                        |
| c.6491_6494delAGTT | p.Gln2164Argfs’3 | Frameshift       | 1                        |
| c.6641insC   | p.Thr2214Asufs’10 | Frameshift       | 1                        |
| c.6814delA   | p.Arg2272Glufs’8  | Frameshift       | 1                        |
| c.7303C>T    | p.Gln2435’        | Nonsense         | 1                        |
| c.7806-2A>G  | aberrant splicing | Splicing         | 13                       |
| c.8175G>A    | p.Trp2725’        | Nonsense         | 2                        |
| c.9117G>A    | p.Pro3039Pro      | Splicing         | 1                        |
| c.9286C>T    | p.Glu3096’        | Nonsense         | 1                        |

*Description of nucleotide variants is in accordance with HGVS nomenclature (DNA variants are numerated according to NCBI reference NM_007294.2 for *BRCA1* and NM_000059.3 for *BRCA2*; the first nucleotide of the start codon ATG is numerated 1). *Description of amino acid change is in accordance with HGVS nomenclature.
Table II. Screening for mutations in *BRCA* genes in probands from HBOC families in Slovenia.

| Period                  | No. of tested probands | No. of new families | No. of new *BRCA1* positive families | No. of new *BRCA2* positive families |
|-------------------------|------------------------|---------------------|--------------------------------------|--------------------------------------|
| January 1999 - December 2008<sup>a</sup> | 521                   | 322                 | 68                                   | 28                                   |
| January 2009 - December 2011 | 559                   | 349                 | 54                                   | 20                                   |
| Total                   | 1080                  | 671                 | 122                                  | 48                                   |

<sup>a</sup>published in Stegel *et al* (10).

Table III. Novel pathogenic mutations in *BRCA1* and *BRCA2* genes.

| Gene      | HGVS nomenclature<sup>a</sup> | BIC nomenclature<sup>b</sup> | Amino acid change<sup>c</sup> | No. of families | Proband characteristics (age at onset) | Other confirmed carriers in the family | Family history of the BC and/or OC (age at onset) |
|-----------|-------------------------------|-----------------------------|-----------------------------|----------------|--------------------------------------|--------------------------------------|------------------------------------------------|
| *BRCA1*   | c.1193C>A                      | 1312C>A                     | p.Ser398<sup>*</sup>         | 1              | Healthy, age 34                       | /                                    | Mother - BC (53) Maternal aunt - BC (43) OC (54) |
| *BRCA2*   | c.5101C>T                      | 5329C>T                     | p.Gln1701<sup>*</sup>        | 2              | BC (39)                              | Healthy daughter, age 34             | /                                              |
|           |                               |                             |                             |                | OC (49) and BC (51) Healthy daughter, age 34 | /                                    | Mother - OC (73)                              |
|           | c.5433_5436delGGAA             | 5661_5664delGGAA            | p.Glu1811Aspfs<sup>3</sup>  | 1              | BC (53)                              | /                                    | Maternal grandmother - BC (54) Maternal aunt - BC (57) Maternal cousin - bilateral BC (38, 62) |

<sup>a</sup>Description of nucleotide variants is in accordance with HGVS nomenclature (DNA variants are numerated according to NCBI reference NM_007294.2 for *BRCA1* and NM_000059.3 for *BRCA2*; the first nucleotide of the start codon ATG is numerated 1) or <sup>b</sup>BIC nomenclature (DNA variants are numerated according to NCBI reference HSU14680 for mRNA of *BRCA1* and U43746 for mRNA of *BRCA2*).<br><sup>c</sup>Description of amino acid change is in accordance with HGVS nomenclature. BC, breast cancer; OC, ovarian cancer.
gene are located in exon 11 of BRCA1 or BRCA2, which is the largest exon in both genes and also carry the majority of pathogenic mutations described so far. As BRCA mutations causing truncation of the BRCA proteins are regarded as pathogenic, with some exceptions of truncating mutations in the last 27th exon of the BRCA2, we predict that all three novel mutations have deleterious effects (14, 15). More detailed descriptions are given below.

**BRCA1.** Mutation c.1193C>A (p.Ser398*) in exon 11 causes stop codon formation at codon 398. In the BIC database a similar mutation discovered in Asian population, which leads to formation of stop codon 398 (c.1193C>G), is described as a clinically significant variant, but no references are given. Codon 398 lies in one of five conserved regions located at the 5' end of exon 11 (codons 282-554), which include putative interacting sites for several proteins thought to be involved in transcription (16). Codon 398 also forms a part of interacting site (codons 341-748) for DNA repair protein RAD50 which participates in DNA repair by homologous recombination and by non-homologous end joining (16, 17). Accordingly, we predict c.1193C>A mutation to severely impair BRCA1-mediated DNA repair.

**BRCA2.** Mutation c.5101C>T (p.Gln1701*) is a nonsense mutation causing formation of a stop codon at position 1701 which is located in exon 11 in the ovarian cancer cluster region (OCCR) spanning nucleotides 3035 to 6629. Several studies have shown that truncating mutations in the OCCR region confer a higher ratio of ovarian cancer relative to breast cancer (18-20). Also, higher risk of prostate cancer was recently detected in males with mutations in the BRCA2 OCCR region (21). Consistently with these studies, one of the two Slovene BRCA2 c.5101C>T families exhibits a high incidence of OC, besides BC (Table III).

**Known BRCA1 pathogenic mutations that have been detected for the first time in Slovene HBOC families.**

| HGVS nomenclature | BIC nomenclature | Amino acid change | Other cancers in the family | Other confirmed carriers in the family | Family history of BC and OC (age at onset) | Other confirmed carriers in the family (age at onset) | No. of families |
|-------------------|------------------|------------------|-----------------------------|--------------------------------------|------------------------------------------|-------------------------------------------------|---------------|
| c.66_68delAG      | 185_186delAG     | p.Glu23Valfs17   | Healthy daughter, age 31    | Healthy daughter, Sister - OC (53)   | /                                         | /                                               | 1             |
| c.3436_3439delTGTT| 3555_3558delTGTT | p.Cys1146Leufs8  | 1 BC (39), OC (42)          | 1 BC (60)                            | 1 OC (55)                                | /                                               | 2             |
| c.3718C>T         | 3837C>T          | p.Gln1240*       | Sister - bilateral BC (46-49)| Sister - OC (53)                      | Sister - OC (53)                        | Sister - OC (66)                                | 1             |
| c.3718C>T         | 3837C>T          | p.Gln1240*       | OC (38)                     | OC (38)                              | OC (38)                                  | OC (38)                                         | 1             |

Known BRCA pathogenic mutations that have been detected for the first time in Slovene HBOC families

**BRCA1.** From January 2009 to December 2011 three known pathogenic mutations in the BRCA1 and eight in the BRCA2 gene were detected for the first time in the Slovene HBOC families. Except one, all cause premature formation of stop codons leading to truncation of the respective BRCA1 or BRCA2 proteins.
Table V. Known BRCA2 pathogenic mutations that have been detected for the first time in Slovene HBOC families.

| HGVS nomenclature<sup>a</sup> | BIC nomenclature<sup>b</sup> | Amino acid change<sup>c</sup> | No. of families | Proband characteristics (age at onset) | Other confirmed carriers in the family (age at onset) | Family history of BC and OC (age at onset) | Other cancers in the family (age at onset) |
|-------------------------------|-------------------------------|-----------------------------|-----------------|----------------------------------------|-------------------------------------------------|-----------------------------------|---------------------------------|
| c.262_263delCT                | 490_491delCT                  | p.Leu88Alafs<sup>*</sup>12  | 1               | BC (46)                                | /                                               | Sister - BC (55)                  | Mother - EC (44) Brother - BRC (56) |
| c.658_659delGT                | 886_887delGT                  | p. Val220Ilefs<sup>*</sup>4  | 1               | BC (72)                                | /                                               | Sister - OC (59) Sister - OC (64) Sister - OC (78) | / |
| c.1773_1776delTTAT            | 2001_2004delTTAT               | p.Ile591Metfs<sup>*</sup>22 | 1               | BC (54) Daughter - BC (38) Healthy daughter, age 37 | | Mother - BC (68) | / |
| c.5213_5216delCTTA            | 5441_5444delCTTA               | p.Thr1738Ilefs<sup>*</sup>2  | 1               | OC (54) Healthy daughter, age 35       | | Mother - BC (35) | / |
| c.6641insC                    | 6869insC                      | p.Thr2214Asnfs<sup>*</sup>10 | 1               | BC (47)                                | /                                               | Sister - BC (36) Brother - BC (44) | / |
| c.6814delA                    | 7042delA                      | p.Arg2272Glufs<sup>*</sup>8  | 1               | BC (32)                                | /                                               | Mother - bilateral BC (58) Maternal aunt - BC (59) | Maternal grandmother - GC (70) Maternal aunt - BRC (63) |
| c.8175G>A                     | 8403G>A                       | p.Trp2725<sup>*</sup>        | 2               | BC (43) Healthy brother, age 43        | | Mother - BC (46) Paternal grandmother - BC (72) Paternal aunt - BC (31) Paternal aunt - BC (41) | / |
| c.9117G>A                     | 9345G>A                       | p.Pro3039Pro                 | 1               | BC (49) Daughter - OC (24) Healthy daughter, age 24 | | Daughter - OC (24) | Mother - CHC (53) |

<sup>a</sup>Description of nucleotide variants is in accordance with HGVS nomenclature (DNA variants are numerated according to NCBI reference NM_000059.3 for BRCA2; the first nucleotide of the start codon ATG is numerated 1) or BIC nomenclature (DNA variants are numerated according to NCBI reference U43746 for mRNA of BRCA2).  
<sup>b</sup>Description of amino acid change is in accordance with HGVS nomenclature. BC, breast cancer; OC, ovarian cancer; EC, endometrial carcinoma; BRC, brain cancer; GC, gastric cancer; CHC, cholangiocarcinoma.
The mutation c.66_67delAG (p.Glu23Valfs’17) is the most common BRCA1 mutation worldwide which occurs at a frequency of 1.1% in the Ashkenazi Jews (26). Despite being so widespread, this is the first recording of c.66_67delAG in Slovenia, which to note has only very small Jewish population (estimated 500-1,000 people). The c.66_67delAG dictates formation of stop codon in the BRCA1 exon 2 thus forming a truncated BRCA1 protein, BRAt, which lacks all known BRCA1 functional domains (26). Studies have shown that besides being non-functional the truncated BRCA proteins can also impair the function of wild-type BRCA proteins (26,27). It was further suggested that the BRAt mutant protein increases transcription of the protein maspin (mammary serine protease inhibitor), which has been implicated in inhibition of growth, invasion, and metastatic potential of cancer cells (26,28). Jiang et al also demonstrated that maspin sensitizes BRCA deficient breast carcinoma cells to staurosporine-induced apoptosis thus leading to an increased chemosensitivity (29).

The other two newly detected BRCA1 mutations are located in exon 11. Mutation c.3718C>T (p.Gln1240*) is reported few times in the BRCA1 mutational databases but is published only once by Kwong et al, who detected it in an endometrial cancer patient of European origin (30). We detected the c.3718C>T in two Slovene families who are, interestingly, both affected by various cancer types (Table IV). As this mutation was first detected in endometrial cancer, this could imply that the c.3718C>T predisposes to other cancer types besides BC/OC. Further studies are needed to corroborate this observation and uncover possible underlying molecular mechanisms.

Mutation c.3436_3439delTGTT (p.Cys1146Leufs’8) in the 11th exon of BRCA1 was before only found once in the Slovene neighboring country Austria (31). It is predicted to cause termination of protein translation at codon 1153. It can be compared to a similar mutation c.3481_3491del111 (p.Glu1161Phefs’3) that creates stop codon at 1163 (32). The c.3481_3491del111 is a widespread French founder mutation that is frequently detected in hereditary OC (33,34). Comparably, the Slovene c.3436_3493delTGTT family is characterized by higher incidence of OC relative to BC. Future studies are needed to determine whether increased incidence of OC is associated with specific exon 11 truncating BRCA1 mutations.

BCRA2. The eight newly detected BCRA2 mutations are all rather rare with only few existing records or publications. Mutation c.262_263delCT (p.Leu88Alafs’12) is located in exon 3. It was first described in one Polish HBOC family (described as 488_489delCT) and was recently detected in a prostate cancer patient with family history of stomach cancer but no BC or OC (44). No functional characterizations have yet been published for c.1773_1776delITAT, however, the Slovene family having c.1773_1776delITAT is to date affected only by BC (Table V).

Three BCRA2 mutations were detected in the exon 11, c.5213_5216delCTTA, c.6641insC and c.6814delA. Mutation c.5213_5216delCTTA (p.Thr1738Ilefs’2) in exon 11 has been already found in several HBOC families, mainly in the USA, the Netherlands and in Belgium (45-49). It causes formation of termination signal at codon 1739 located between BRC5 and BRC6 in the BRC repeat region, similarly to the novel mutation c.5433_5436delGGAA discussed above. According to the literature no other cancers besides BC and OC are associated with this mutation. This also applies to the Slovene c.5213_5216delCTTA family.

Mutation c.6641insC (p.Thr2214Asnfs’13) in exon 11 is a frameshift mutation reported only once in BIC database. Mutation is predicted to form a stop codon at position 2223 located at the 3’ end of exon 11. The mutation is causing the truncated BCRA2 protein for the subsequent exons 12 to 27. Mutation c.6641insC was identified in Slovene BC patient diagnosed at age 47, with a history of two BC cases in her family, diagnosed at ages 36 and 44. Interestingly, one was male BC (Table V). Similar mutation c.6641dupC (p.Lys2215Tyrfs’10) was detected in nearby Croatia in two unrelated families (50).

Mutation c.6814delA (p.Arg2272Glufs’8) in exon 11 was detected in Slovene BC patient diagnosed at 32 years of age, whose mother had bilateral BC. It is described only once in the UMD database, without references, and is predicted to form stop codon at position 2279 near the 3’ end of exon 11, therefore abrogating exons 12 to 27.

Mutation c.8175G>A (p.Trp2725*) was first reported just recently by Levanat et al (50). Mutation c.8175G>A was identified in two unaffected siblings (with a family history of two BC cases) from Croatia (50). Mutation c.8175G>A lies in the frequently mutated exon 18 of BCRA2 leading to the truncation of the BCRA2 oligonucleotide binding domain (OBI1) in the DNA-binding domain (DBD) (32). The BCRA2 DBD region is needed for binding of single-stranded DNA (ssDNA) that
results from DNA damage or replication errors (51). Through this binding of ssDNA the BRCA2 protein mediates delivery of RAD51 to the sites of exposed single-stranded DNA thus enabling the RAD51 to catalyze homologous pairing and DNA strand exchange (51). Through affecting this recruitment of RAD51 to the ssDNA, mutations in the BRCA2 DBD are predicted to affect the homologous recombination needed for maintaining the integrity of the genome. Besides binding ssDNA, OB1 also binds the 70-amino acid DSS1 which is needed for BRCA2 stability and is also crucial for the BRCA2 functioning in one of the homologous recombination pathways (52,53).

Mutation c.9117G>A (p.Pro3039Pro) is located in exon 23 of BRCA2. This splicing mutation was shown to be truncating (54). By this mutation the OB2 functional domain of BRCA2 protein is affected most probably causing impaired repair of double-strand DNA breaks (51,55). Mutation c.9117G>A was identified in three tested members from one Slovene family. Proband (mother) was diagnosed with BC at the age of 49. Her two daughters were both identified as carriers; one diagnosed with OC at the age 24 and one still unaffected. Mutation c.9117G>A has been already found in several HBOC families of Western/Central/East European origin (56).

The present report describes three novel BRCA pathogenic mutations that have been detected in Slovene HBOC families thereby contributing to the ever-expanding spectrum of the world-wide pathogenic BRCA mutations. Eleven previously known pathogenic mutations that have been discovered for the first time in Slovenia are also presented. For the probands bearing novel or pathogenic BRCA1 and BRCA2 mutations which have been detected in Slovene population for the first time, relevant clinical data and family history are given. Recent literature is reviewed to provide new data, which should help to create specific plans for preventive and/or therapeutic strategies for individual carriers according to their specific mutation.

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