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BRIEF REPORT

# *PALB2* mutations in German and Russian patients with bilateral breast cancer

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**Abstract** Since germline mutations in the *PALB2* (Partner and Localizer of BRCA2) gene have been identified as breast cancer (BC) susceptibility alleles, the geographical spread and risks associated with *PALB2* mutations are subject of intense investigation. Patients with bilateral breast cancer constitute a valuable group for genetic studies. We have thus scanned the whole coding region of *PALB2* in a total of 203 German or Russian bilateral breast cancer patients using an approach based on high-resolution melting analysis and direct sequencing of genomic DNA samples. Truncating *PALB2* mutations were identified in 4/203 (2%) breast cancer patients with bilateral disease. The two nonsense mutations, p.E545X and p.Q921X, have not been previously described whereas the two other mutations, p.R414X and c.509_510delGA, are recurrent. Our results indicate that *PALB2* germline mutations account for a small, but not negligible, proportion of bilateral breast carcinomas in German and Russian populations.

**Keywords** *PALB2* · Breast cancer · High-resolution melting · Mutation · Review

## Introduction

Breast cancer (BC) has an inherited component, and the high-penetrance breast cancer predisposing genes, *BRCA1* and *BRCA2*, account for up to 10–30% of familial breast cancer clustering [1–3]. Other relevant genes, such as *CHEK2*, *NBS1*, *PALB2*, *BRIP1*, etc., also contribute to hereditary breast cancer, although their impact appears to

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be somewhat more population-specific [4]. The *PALB2* (Partner and Localizer of BRCA2) gene is located on chromosome 16p12.2 and encodes for a protein involved in BRCA2-related pathways [5]. Its biallelic inactivation results in Fanconi anemia, while the presence of a germline mutation in the heterozygous state is associated with increased risk of breast, pancreatic, and possibly some other cancers (Table 1 and references therein). The geographical spread of *PALB2* mutations has not been comprehensively analyzed yet, and several recent studies have failed to identify any *PALB2* mutations in breast cancer series from their population [24–27]. The search for breast cancer predisposing mutations is considered to be particularly effective in patient series with a pronounced family history of the disease. However, the collection of multicase breast cancer families can be complicated in countries with low birth rate and/or recent historical turbulences and/or lack of comprehensive registration of (familial) cancer cases. Others and we have suggested that patients with bilateral occurrence of breast cancer constitute a valuable group for genetic studies [28–31]. It has been calculated that the bilateral occurrence of breast cancer can be considered an equivalent of the presence of two affected first-degree relatives [28].

We have previously employed population-specific series of patients with bilateral breast cancer to study the distribution of germline mutations in *BRCA1*, *BRCA2*, or *CHEK2* [30, 32]. Here we report on the identification of *PALB2* mutations in patients with bilateral breast cancer from Germany and Russia.

## Patients and methods

The German case series consisted of 158 patients from Lower Saxony (Northern Germany) with bilateral breast cancer who had been recruited at the time they received radiotherapy either at Hannover Medical School during the years 1996–2005 ($n = 112$), or at the University Medical Center Göttingen during the years 2007–2009 ($n = 46$). 70 (44%) patients had synchronous bilateral BC (mean age: 59 years; age range 29–83 years) and 88 (56%) patients had metachronous disease (mean age for the first tumor: 51 years; age range 27–72 years; mean age for the second tumor: 60 years; age range 31–82 years). Five (3%) women were diagnosed with her first primary below age 30 years, 16 (10%) between 30 and 39 years, 30 (19%) between 40 and 49 years, and 107 (68%) at the age of 50 years or above. Family history revealed at least one first-degree relative with breast cancer in 29 (18%) of the cases, and a second-degree family history of breast cancer in 14 (9%) additional patients. Two women also had a personal history of ovarian cancer. Pathogenic *BRCA1* or *BRCA2* mutations were known in ten of the German patients (6%); these patients were left within the study.

The Russian bilateral breast cancer patients were represented by 45 *BRCA1/BRCA2* mutation-negative women, who underwent treatment in the N.N. Petrov Institute of Oncology (St.-Petersburg) in the years 1999–2009. 16 (36%) patients had synchronous bilateral BC (mean age: 53 years; age range 30–77 years) and 29 (64%) patients had the metachronous disease (mean age for the first tumor: 47 years; age range 25–77 years; mean age for the second tumor: 58 years; age range: 28–86 years). Age at first BC onset was below 30 years in two (4%) women, between 30 and 39 years in five (11%) cases, between 40 and 49 years in 17 (38%) patients, and 50 years or above in 21 (47%) females. 13 (29%) of the women reported a first-degree family history of the disease, and seven (16%) additional patients had second-degree relatives affected by BC.

PCR amplifications were set up in the presence of the EvaGreen dye (BioBudget, Krefeld, Germany), and high-resolution melting analysis was performed on the Rotor-Gene 6000 real-time PCR machine (Corbett Research, Mortlake, Australia). Primer sequences are described in the Supplementary Table 1. Melting profiles were evaluated using the Melt Curve Analysis tool of the Rotor-Gene 6000 Series Software Version 1.7. All samples with suspicious melting behavior were then subjected to direct sequencing to identify the underlying substitution. The three common *PALB2* polymorphisms, p.Q559R, p.E672Q, and p.G998E, were confirmed by allele-specific TaqMan assays on a 7500FAST Sequence Detection System platform.

The population frequency and the location of missense substitutions were assessed using the SNP database of the NCBI Genbank (http://www.ncbi.nlm.nih.gov/snp) and UniprotKB (http://www.uniprot.org/uniprot/). Bioinformatic analyses of missense substitutions were performed using SIFT (http://sift.jcvi.org/sift-bin/SIFT_BLink_submit.html) or PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/, with Q86YC2 as the protein identifier and in the HumDiv trained mode), which predict pathogenicity on the basis of evolutionary and structural calculations.

The project has been approved by the Ethical Boards of all participating research centers which contributed DNA samples to the study.

## Results and discussion

All portions of the *PALB2* coding region were successfully analyzed by high-resolution melting (Supplementary Fig. 1). Direct sequencing of samples with suspicious melting profiles revealed four truncating and several missense mutations. A list of the identified nucleotide sequence changes is provided in Table 2.

**Table 1** Survey of inactivating *PALB2* mutations in patients with cancer or Fanconi anemia

| Study | Country/ethnicity | Patients | PALB2 mutations | Founder effect |
|---|---|---|---|---|
| Breast cancer | | | | |
| Erkko et al. [6] | Finland | 113 Familial, BRCA1/2 negative | 1592delT (L531fs): 3 | 19/947 (2%) familial BC, 8/1274 (0.6%) sporadic BC, 2/1079 (0.2%) controls [7] |
| Rahman et al. [8] | UK | 923 Familial, BRCA1/2 negative | 2386G>T (G796X): 1; 2982insT (A995fs): 1; 3113G>A (W1038X): 2; 3116delA (N1039fs): 3; 3549C>G (Y1183X): 3 | |
| Tischkowitz et al. [9] | Canada (Ashkenazi Jews, French Canadian, other) | 68 Familial, BRCA1/2 negative | 229delT (C77fs) | |
| Foulkes et al. [10] | Canada (French Canadian) | 50 Young-onset (< 50 years) or familial | 2323C>T (Q775X) | 2/356 (0.6%) young-onset BC |
| Cao et al. [11] | China | 360 Young-onset (< 35 years) or familial | 751C>T (Q251X): 2; 1050_1051delAAinsTCT (Q350fs): 1 | |
| Garcia et al. [12] | Spain | 95 Familial, BRCA1/2 negative | 1056_1057delGA (K353fsX7) | |
| Sluiter et al. [13] | South Africa (whites) | 48 Young-onset (29–45 years) | 697delG (V233fs) | |
| Adank et al. [14] | The Netherlands | 110 Cancer families with BRCA2-like clinical features, BRCA1/2 negative | 509_510delGA (R170fs) | |
| Balia et al. [15] | Italy | 95 Familial, BRCA1/2 negative | 1317delG (G439fs) | |
| Ding YC et al. [16] | USA | 97 Male, BRCA2 negative | 3549C>A (Y1183X) | |
| Papi et al. [17] | Italy | 132 Familial, BRCA1/2 negative | 2257C>T (R753X) | |
| Present study | Germany | 158 Bilateral | 509_510delGA (R170fs), 1633G>T (E545X) | |
| Present study | Russia | 45 Bilateral, BRCA1/2 negative | 1240C>T (R414X), 2761C>T (Q921X) | |
| Pancreatic cancer | | | | |
| Jones et al. [18] | USA | 97 Familial | 172_175delTTGT (S58fs); IVS5-1G>T; 3116delA (N1039fs); 3256C>T (R1086X) | |
| Tischkowitz et al. [19] | Canada | 254 Familial and sporadic | Deletion of the exons 12 and 13 | |
| Slater et al. [20] | Europe | 81 Familial | 1240C>T (R414X), 508_509delAG (R170fs), 3116delA (N1039fs) | |
| Ovarian cancer | | | | |
| Dansonka-Mieszkowska et al. [21] | Poland | 70 | 509_510delGA (R170fs) | 2/339 (0.6%) ovarian cancer cases, 4/648 (0.6%) familial BC, 1/1310 (0.08%) controls |
| | | Fanconi anemia | | |
| Reid et al. [22] | Various | 82, negative for mutations in other known FA genes | Biallelic mutations: 395delT (V132fs)/3113+5G>C (r.2835_3113del279/A946fs); 757_758delCT (L253fs)/3294_3298delGACGA (K1098fs); 2257C>T (R753X)/3549C>A (Y1183X); 2393_2394insCT (T799fs)/3350+4A>G (r.3350insGCAG/F1118fs); 2521delA (T841fs)/3323delA (Y1108fs); 2962C>T (Q988X)/3549C>G (Y1183X); 3116delA (N1039fs)/3549C>G (Y1183X) | |
| Xia et al. [23] | | Case report | Biallelic mutation: Y551X/deletion of the exons 2–6 | |

The analysis of 158 German bilateral breast cancer patients led to the identification of two (1.3%) truncating mutations, both located in exon 4 of the *PALB2* gene. The c.1633G>T allele (p.E545X) has not been described in prior literature, while the c.509_510delGA (p.R170fs) mutation appears to be recurrent in Poland, a neighboring country of both Germany and Russia [21]. The patient with the novel *PALB2* mutation, p.E545X, was diagnosed at the age of 83 years as having bilateral invasive ductal carcinoma (IDC) with estrogen and progesterone receptor negative tumors (T2N1M0 and T2N0M0). She did not have an apparent family history of breast cancer, but reportedly her maternal grandmother suffered from stomach cancer and her sister died at the age of 67 from a cancer of unknown origin. The second German *PALB2* mutation carrier, heterozygous for the c.509_510delGA frameshift mutation, was diagnosed with synchronous bilateral disease at the age of 63 years. She presented with bilateral invasive lobular breast cancer, with an additional invasive ductal component in one tumor; both cancers were of stage 1 (T1N0M0 and T1N0M0) and had positive estrogen and progesterone receptor status. Again, there was no family history of breast cancer, but her father suffered from a stomach cancer. None of the ten patients who carried a mutation in *BRCA1* or *BRCA2* was also a carrier of truncating *PALB2* mutation; if we consider the frequency of *PALB2* heterozygotes in *BRCA1/2*-negative German bilateral breast cancer cases, this estimate will approach to 2/148 (1.4%).

The investigation of 45 (4.4%) Russian patients with bilateral breast cancer revealed another two deleterious mutations. One woman carried the c.1240C >T (p.R414X) allele in exon 4; this mutation has been previously described in a European family with pancreatic cancer [20]. This patient developed first disease at age 66 (IDC, T2N1M0, ER+/PR+) and the contralateral tumor at age 70 (Paget's carcinoma, T1N0M0, ER-/PR+). She reported that her mother was also affected by breast cancer. The second patient had a newly identified mutation, c.2761C >T (p.Q921X). She was diagnosed with synchronous bilateral breast cancer at age 48 (both tumors: IDC, T4N0M0, ER+/PR−); her mother suffered from breast cancer, and her maternal grandfather was diagnosed with stomach cancer.

Six missense substitutions were identified besides the four truncating mutations (Table 2). The variants p.Q559R, p.E672Q, p.V932M, p.L939W and p.G998E are known to be relatively common both in breast cancer patients and in healthy controls [8]. Bioinformatic analysis using SIFT and PolyPhen-2 classified p.Q559R and p.V932M as benign, whereas p.E672Q, p.L939W and p.G998E were predicted as probably damaging by one or both of these software tools [8]. The new missense variant, p.K18R, was observed in two bilateral breast cancer cases from this study. It

**Table 2** *PALB2* coding sequence alterations in 158 German and 45 Russian patients with bilateral breast cancer

| Exon | Nucleotide variation | Amino acid change | Allelic counts in German patients (relative fraction) | Allelic counts in Russian patients (relative fraction) | Reference |
|---|---|---|---|---|---|
| 2 | 53A>G | K18R | 2 (0.01) | – | This study |
| 4 | 509_510delGA | Frameshift mutation (R170X) | 1 (<0.01) | – | Dansonka-Mieszkowska et al. [21] |
| | 807T>C | G269G | 1 (<0.01) | – | This study |
| | 1240C>T | Nonsense mutation (R414X) | – | 1 (0.01) | Slater et al. [20] |
| | 1470C>T | P490P | – | 1 (0.01) | rs45612837 |
| | 1572A>G | S524S | 1 (<0.01) | – | rs45472400 |
| | 1633G>T | Nonsense mutation (E545X) | 1 (<0.01) | – | This study |
| | 1676A>G | Q559R | 18 (0.06) | 6 (0.06) | rs152451 |
| 5 | 2014G>C | E672Q | 11 (0.03) | 1 (0.01) | rs45532440 |
| 8 | 2761C>T | Nonsense mutation (Q921X) | – | 1 (0.01) | This study |
| | 2794G>A | V932 M | 2 (0.01) | 3 (0.03) | rs45624036 |
| | 2816T>G | L939 W | 1 (<0.01) | – | rs45478192 |
| 9 | 2993G>A | G998E | 9 (0.03) | 1 (0.01) | rs45551636 |
| | 3300T>G | T1100T | 7 (0.02) | 1 (0.01) | rs45516100 |
| 13 | 3495G>A | S1165S | 1 (<0.01) | – | rs45439097 |

resides in a putative coiled-coil region of unknown functional importance and is predicted by PolyPhen-2 to be probably damaging. Large-scale case–control comparisons as well as functional studies will be useful to identify any possible disease risks associated with these variants.

While the data indicate that *PALB2* mutations are relatively uncommon in German and Russian populations, it may be noteworthy that the rate of mutation carriers appears somewhat higher in our series of bilateral breast cancer (2%) than in most published series of familial breast cancer from other populations (Table 1). This would be in line with the assumption that patients with bilateral disease constitute a subgroup where the detection of rare at-risk alleles is particularly effective [28–31].

In summary, truncating *PALB2* heterozygous mutations have been identified in 4/203 (2%) breast cancer patients with bilateral disease. We conclude that *PALB2* mutations contribute to a small fraction of bilateral breast cancer in Germany and Russia. The observation that two of the four mutations identified in our study are recurrent [20, 21] may provide a rationale for mutation-specific screening efforts in extended series of Eastern and Central European cancer patients.

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**Conflict of interest** None.

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