

Short communication

## Association of the *BRCA1* missense variant R1699W with a malignant phyllodes tumor of the breast

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Received 16 January 2007; received in revised form 5 March 2007; accepted 20 March 2007

### Abstract

Familial breast carcinomas that are attributable to *BRCA1* or *BRCA2* mutations have characteristic morphologic and immunohistochemical features. *BRCA1*-associated carcinomas are poorly differentiated infiltrating ductal carcinomas frequently exhibiting morphologic features of typical or atypical medullary carcinomas such as prominent lymphocytic infiltrate and pushing margins. We report on a patient carrying the deleterious *BRCA1* germline mutation R1699W, who presented with a malignant phyllodes tumor of the breast. The re-investigation of archival material by a reference pathologist of the German Consortium for Hereditary Breast and Ovarian Cancer (GCHBOC) revealed *BRCA*-associated pronounced pushing margins. In a total of 618 unrelated index patients who are registered in the GCHBOC database, no other phyllodes tumor has been described, while 10 carriers of the R1699W mutant have been identified. We conclude that the histopathologic appearance of the phyllodes tumor indicates an association with the *BRCA1* mutation R1699W although it is a rare event in *BRCA*-positive families. © 2007 Elsevier Inc. All rights reserved.

### 1. Introduction

*BRCA1* germline mutations predispose carriers to early-onset breast cancer and reveal distinct breast cancer phenotypes, including a high proportion of medullary [1]. Characteristic histologic features of these tumors are pushing margin, stromal lymphocytic response, and syncytial growth pattern. Moreover, *BRCA1*-related tumors are frequently high grade, negative for oestrogen and progesterone receptors and Her2 (triple negative), and rapidly proliferating [2,3]. A genotype–phenotype correlation as for the “ovarian cancer cluster region” in *BRCA2* and the significantly higher ratio of ovarian versus breast cancer cases remains unclear for the majority of *BRCA* mutations. Accordingly, a correlation of the *BRCA1* germline missense mutation 5214C→T with phyllodes tumors as well as the typical *BRCA1*-associated distinct pushing margins in these rare breast tumors are hitherto not described.

### 2. Patient report

A 43-year-old Caucasian woman presented with a palpable, movable mass of about 6 cm in the upper inner quadrant of the right breast. Mammography and ultrasound revealed a 10-cm mass with pleomorphic shape, cystic and nonhomogeneous internal structures, and hypo-echoic echogenicity classified as BIRADS IV according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System Atlas (BI-RADS Atlas). The subsequently conducted core needle biopsy revealed a malignant phyllodes tumor. Additional clinical examinations, including x-ray of the lung, sonography of the liver, bone scintigraphy, and serum level of the tumor marker CA 15-3 were in the normal range. The patient underwent a modified radical mastectomy and dissection of the axillary lymph nodes. Macroscopically, the ablated breast comprised a 110×60×140-mm solid and cystic mass with a central hemorrhagic area. Histopathologic examination confirmed the malignant phyllodes tumor stage pT3 without involvement of axillary lymph nodes (pN0). No additional treatment such as chemotherapy, radiotherapy,

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or antioestrogenic therapy was administered. During the 6-year follow-up, the patient provided no evidence of recurrence, second carcinoma, or distant metastases.

Family history revealed that her mother was affected by an ovarian carcinoma at the age of 49, three maternal aunts suffered from bilateral ductal breast cancer diagnosed at age 55, unilateral ductal breast cancer at age 59, and ovarian carcinoma at 44 years, respectively. The daughter of the latter patient suffered from ductal breast cancer at age 41 and from vulvar cancer at age 43 (Fig. 1).

Genetic testing for *BRCA1* and *BRCA2* mutations was offered to the family. Blood samples were available from four women with breast cancer and from two healthy women. The investigation was approved by the local ethics committee and written consent was obtained from all patients. Genomic DNA was extracted from peripheral leukocytes using a conventional phenol-chloroform protocol. Mutational analysis of the *BRCA* genes was performed by denaturing high pressure liquid chromatography followed by semi-automatic sequencing (model 377; Applied Biosystems, Foster City, CA, USA) as described previously [4].

The heterozygous *BRCA1* missense mutation 5214C→T, R1699W was diagnosed in the patient with the malignant phyllodes tumor and in two other family members, an aunt with bilateral breast cancer, and a healthy 45-year-old sister. Two healthy cousins (39 and 30 years old) tested negative for the *BRCA1* mutation, as did the aunt with breast cancer at the age of 59, indicating that this patient suffered

from sporadic breast cancer, which is further supported by the positive hormone receptor status (Fig. 1).

The single-point mutation (nucleotide C5214T) leads to a nonconservative change from arginine to tryptophan residue at the highly conserved position 1699, which is located in exon 18 at the N-terminal BRCT domain of the gene. This region forms a proteolytically resistant globular domain and is involved in binding to many different proteins that are associated with *BRCA1* and crucial for transcriptional activation. The missense mutant R1699W leads to a BRCT folding defect and thereby reduces the proteolytic stability of the domain [5]. Functional data strongly suggest that the R1699W mutation has a deleterious effect and predisposes carriers to breast and ovarian cancer [5,6]. This is supported by co-segregation with breast and ovarian carcinomas in large kindred [7,8]. Therefore, the sister of the index patient was counseled according to the standard operating procedure of the German Consortium for Hereditary Breast and Ovarian Cancer (GCHBOC). She underwent prophylactic bilateral salpingo-oophorectomy in 2003 and takes part in a structured surveillance program comprising annual magnetic resonance imaging, mammography, and semi-annual breast sonography [9]. Moreover, predictive testing was offered to all healthy individuals in the family.

Archival formalin-embedded material of the malignant phyllodes tumor was obtained and re-analyzed by a reference pathologist (R.B.) of the GCHBOC according to standard procedures and immunohistochemical techniques.

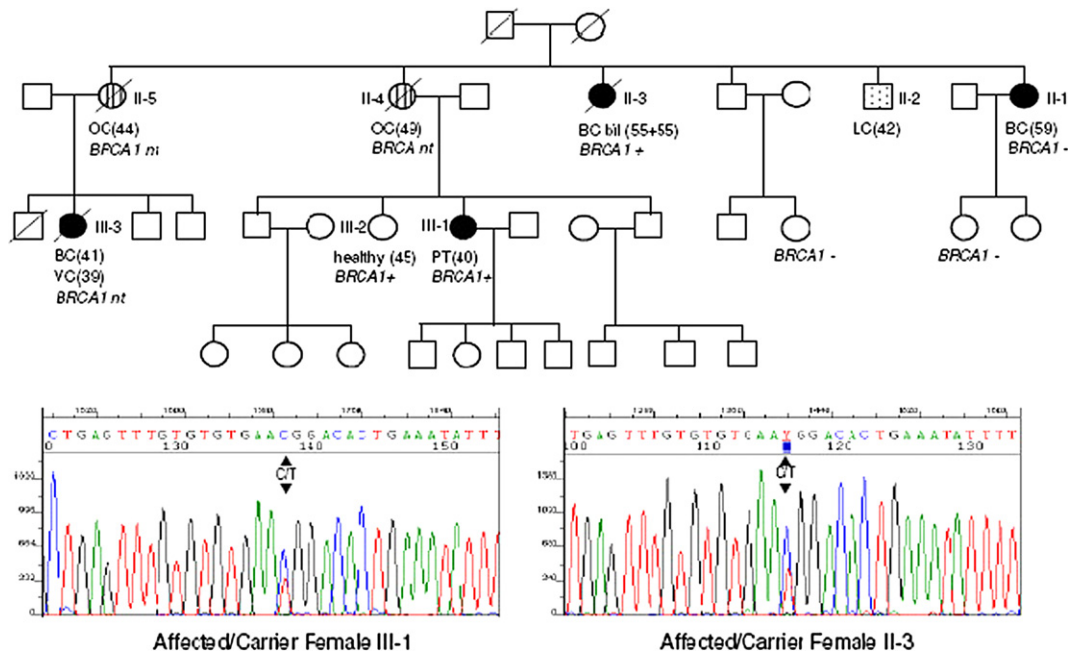


Fig. 1. Identification of the *BRCA1* germline mutant R1699W (5214 C/T) in a patient with a malignant phyllodes tumor (PT) of the breast (III-1) and in a patient with a bilateral ductal breast carcinoma (II-3). In the affected breast cancer patient III-1, the missense mutation was not detected (genomic sequence not shown). BC, breast cancer; bil, bilateral; PT, malignant phyllodes tumor of the breast; OC, ovarian cancer; VC, vulva cancer; LC, lung cancer; BRCA+, R1699W diagnosed; BRCA1<sup>-</sup>, R1699W not diagnosed; BRCA1nt, not tested.

The primary diagnosis of a malignant fibroepithelial tumor fulfilling the typical criteria of phyllodes tumors was confirmed. At the overview, the tumor exhibited a sharp demarcation with only indistinct clefts. In addition, distinct pushing margins typically diagnosed in medullary and *BRCA1*-associated breast cancers prevailed compared to infiltrative margins. In higher magnification, the predominant part of the tumor consisted of a high cellular pleomorphic sarcomatous stromal population with high nuclear atypia and heterochromatic nuclei. Moreover, disseminated multinuclear giant cells, high mitotic activity (more than 10 per 10 high-power field), and distinct nucleoli were detected. Leaf-like clefts lined by monomorphic epithelial components as typical features of malignant phyllodes tumors were diagnosed only in small areas. In contrast, unspecific

high-grade sarcomatous components reflecting the malignant transformation, as well as myxoid change, cystic degeneration, and geographic necrosis were common features of the tumor. A heterologous differentiation such as lipo-, osteo-, chondro-, or rhabdomyosarcoma was not identifiable [10]. The atypical stromal cells demonstrated positive immunoreactivity for vimentin and CD 10, whereas reactions for S-100, actin, and desmin were negative [11]. Negative reactions for keratins and estrogen and progesterone receptors also were recognizable (Fig. 2).

### 3. Discussion

*BRCA1*-associated breast cancers are of epithelial origin and account for 5–10% of all breast cancers. They are mainly of ductal or medullary type with characteristic histologic features such as pushing margins, lymphocytic infiltration, and syncytial growth pattern [2,3]. In contrast, phyllodes tumors are fibroepithelial neoplasms that account for only 0.3–0.5% of all breast tumors [12]. A histopathologic criterium predominantly referring to malignant phyllodes tumors is infiltrative margins, which was not detected in a *BRCA1*-associated phyllodes tumor.

To further elucidate the association between phyllodes tumors and *BRCA* mutations, we performed a search of the GCHBOC comprehensive database, in which *BRCA*-positive families from 12 of the GCHBOC centers are registered. In a total of 618 unrelated index patients, no other phyllodes tumor has been described, while 10 carriers of the R1699W mutation have been identified. Therefore, our data indicate that phyllodes tumors of the breast may represent a phenotypic expression of *BRCA1* mutations, albeit a rare event. Since no data exist on *BRCA1* mutations in a larger set of phyllodes tumors, we recommend that family history be considered when a case of phyllodes tumor is diagnosed.

### Acknowledgments

Technical assistance by Brigitte Kau, Gabi Krebsbach, and Juliane Köhler is gratefully acknowledged.

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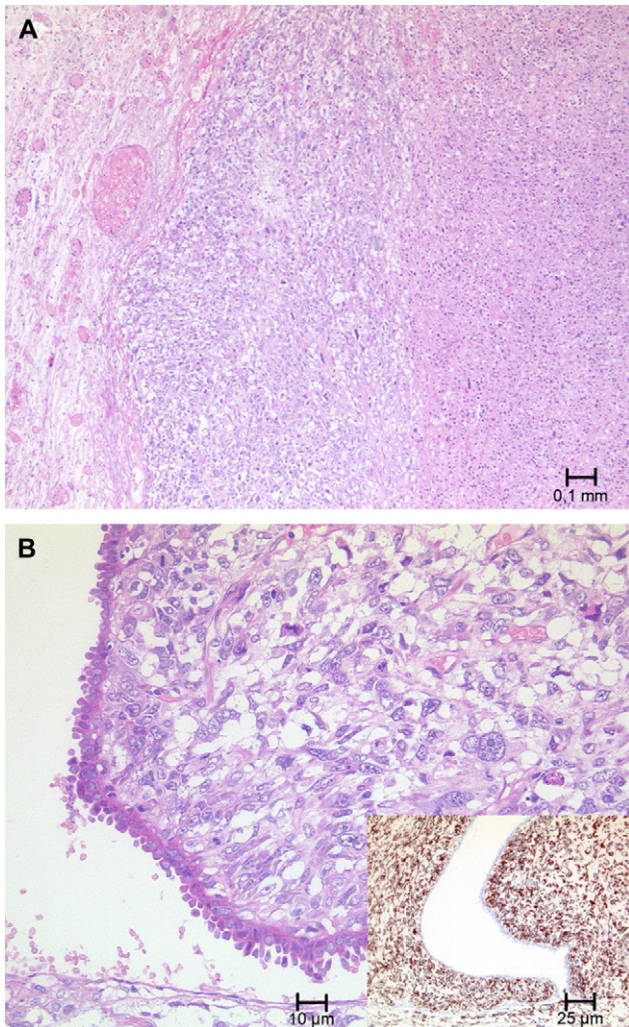


Fig. 2. (A) The top panel shows the distinct pushing margins of the phyllodes tumor (hematoxylin and eosin staining, magnification  $\times 25$ ). (B) The bottom panel shows a small area of a typical leaf-like structure under high magnification ( $\times 400$ ) with sarcomatoid stromal component with mitotic figures. The inset demonstrates the immunoreaction for vimentin.

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