Novel *BRCA1* deleterious mutation (c.1949_1950delTA) in a woman of Senegalese descent with triple-negative early-onset breast cancer

ORLAND DIEZ[1,2], AMADEU PELEGRÍ[3*], NEUS GADEA[4], SARA GUTIÉRREZ-ENRÍQUEZ[2], MIRIAM MASAS[2], ANNA TENÉS[2], NINA BOSCH[4], JUDITH BALMAÑA[4] and BEGOÑA GRAÑA[4]

[1]Oncogenetics Laboratory, University Hospital Vall d'Hebron; [2]Vall d'Hebron Institute of Oncology, Barcelona; [3]Medical Oncology Service, Hospital Sant Pau i Santa Tecla, Tarragona; [4]Medical Oncology Department, University Hospital Vall d'Hebron, Barcelona, Spain

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Abstract. Limited information exists regarding *BRCA1* and *BRCA2* genetic testing and genetic diversity in *BRCA1* and *BRCA2* in sub-Saharan African populations. We report a novel mutation that consists of a deletion of 2 bp (c.1949_1950delTA) in the exon 11 of the *BRCA1* gene. This is a frameshift mutation that causes the disruption of the translational reading frame resulting in a premature stop codon downstream in the BRCA1 protein. The mutation was present in a Senegalese woman with a triple-negative breast tumor and a family history of breast cancer.

Introduction

Breast cancer is the most commonly occurring cancer among women. A family history of breast cancer is one of the main risk factors for developing the disease. It is currently estimated that approximately 5-10% of breast cancers are due to an inherited predisposition, and approximately 20-25% of this risk is explained by two high-penetrance susceptibility genes: *BRCA1* (17q21) (MIM no. 113705) (1) and *BRCA2* (13q12-13) (MIM no. 600185) (2). Both are tumor suppressor genes involved mainly in DNA repair. Mutations in *BRCA1* or *BRCA2* account for a lifetime risk of approximately 40-65% for breast cancer and 11-40% for ovarian cancer (3). Extensive analyses of the *BRCA1* and *BRCA2* genes have resulted in the identification of a large number of different disease-causing germline mutations (4).

Correspondence to: Dr Orland Diez, Oncogenetics Laboratory, University Hospital Vall d'Hebron, Vall d'Hebron Institute of Oncology, Barcelona, Spain
E-mail: Odiez@vhebron.net

*Deceased

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However, limited information exists regarding *BRCA1* and *BRCA2* genetic testing in the majority of non-Caucasian ethnicities and there is a paucity of data regarding the genetic diversity in *BRCA1* and *BRCA2* in populations of African descent. We report a novel mutation that consists of a deletion of 2 bp (c.1949_1950delTA) in the exon 11 of the *BRCA1* gene. This is a frameshift mutation that causes the disruption of the translational reading frame, resulting in a stop codon downstream in the 671 position of the BRCA1 protein. The mutation was present in a Senegalese woman with triple-negative breast cancer and a family history of the disease.

Patient and methods

Patient. As part of genetic studies carried out on breast/ovarian families in the University Hospital Vall d'Hebron (Barcelona, Spain), germ-line *BRCA1* and *BRCA2* mutations were screened in the proband of the family reported in this study.

The proband was a 33 year-old premenopausal Senegalese female of Wolof ethnicity, diagnosed with a triple-negative (ER-, PgR-, HER2-) stage IV breast ductal carcinoma. She had six male and four female siblings. One sister, a maternal cousin and a maternal aunt succumbed to breast cancer at the ages of 47, 50, and approximately 70, respectively (Fig. 1 shows the pedigree of the affected family). The proband underwent genetic counseling and signed informed consent for gene testing of germ-line *BRCA1* and *BRCA2* mutations. The study was approved by the ethics committee of the University Hospital Vall d'Hebron.

Methods. Genomic DNA was extracted from whole blood using a Puregene Genome DNA purification kit (Gentra System, Minneapolis, MN, USA). DNA was amplified by PCR using primers specific for the coding sequence and intron/exon boundaries of the two genes. Analysis of the entire coding and flanking sequences was carried out by sequencing using a BigDye terminator V3.1 cycle sequencing kit on a 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Both forward and reverse strands were sequenced. The variant sequences described in our study were named according to GenBank (*BRCA1* NM_007294; *BRCA2* NM_000059).

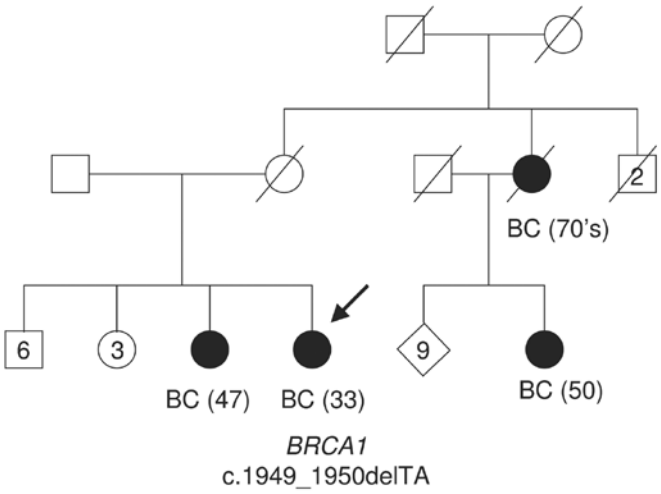

Figure 1. Family pedigree. Numbers in parentheses indicate the age at the time of diagnosis; arrow indicates proband. BC, breast cancer.

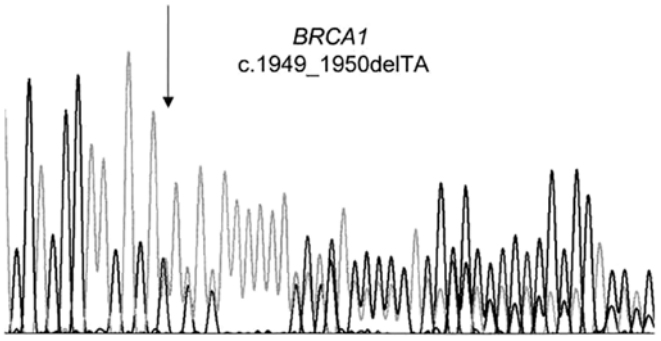

Figure 2. Electropherogram of the forward sequence of the region of the *BRCA1* exon 11, which includes the wild-type and the mutated c.1949_1950delTA allele.

Results

We identified in the exon 11 of the *BRCA1* gene the novel mutation c.1949_1950delTA (p.Ile650LysfsX22) (HGVS nomenclature) or 2068delTA (BIC database nomenclature) (Fig. 2) in the index case of a family with hereditary breast cancer from Senegal.

To the best of our knowledge, this two-base pair deletion is not present in the BIC database and has not previously been published. Furthermore, the index case presented two unclassified variants in *BRCA2*. The first is the novel variant c.296-7dupT in the intron 2 of the gene, which is localized in the poly T(10) of the splicing acceptor site. This variant may cause the same effect as the IVS2-7T>A known variant, which generates an alternative transcript with the in-frame skipping of the exon 3, and is not considered to be completely pathogenic due to its presence in healthy populations (5). An RNA sample from the proband and DNA from other family members to study this variant were not available. The second variant, c.5710C>G in exon 11 (5938C>G, BIC nomenclature), causes the p.L1904V change in the *BRCA2* protein. This variant has been reported eight times in the BIC database. Although it has a weak probability of altering splicing or protein functionality (Alamut Software 1.54, Interactive Biosoftware), this variant remains unclassified.

Discussion

The majority of studies on *BRCA1* and *BRCA2* genes have been performed in Caucasian women of European descent, while little information exists regarding other ethnicities. Nevertheless, several reports have described *BRCA1* and *BRCA2* sequence variants in women of African or African-American descent and have characterized a different spectrum of *BRCA1* and *BRCA2* mutations from that of the North American or European Caucasian population (1,6-18) .

Such studies have revealed ancient mutations originating in the African continent, such as the *BRCA1* recurrent 943ins10 mutation. Haplotype analyses of 943ins10 (c.815_824dup10) carriers indicate that this mutation, which has been identified in African-American and Latin-American/Caribbean families, has an ancient African origin (8,13) in the Ivory Coast in West Africa (7). However, it is unclear whether some of the mutations reported are unique to the African-American population. Of note, the 3036del4 mutation (c.2808_2811delACAA) in *BRCA2,* which was recurrently present in different European populations (19) has also been identified in young African women with breast cancer from Ibadan, Nigeria (14).

As of the end of 2010, the BIC database contains 38 *BRCA1* and 31 *BRCA2* different deleterious mutations and a high number of sequence variants of unknown significance identified in families of African descent. Moreover, other mutations and variants identified in African/African-American families have also been published. These data suggest a significant level of genetic variation in *BRCA1* and *BRCA2* in populations of African descent. The novel c.1949_1950delTA mutation reported in the present study extends the knowledge of genetic susceptibility to breast cancer in sub-Saharan African populations. Furthermore, the finding of this mutation in a Senegalese family can be of interest for other populations originating from western Africa, as is the case for the vast majority of African-Americans.

The incidence and the age of onset of breast cancer vary across geographic regions and ethnic groups. Incidence and average age of onset are lower in African-American women than among Caucasian women (20,21). These differences may be attributed to multiple environmental factors. Breast cancer incidence has increased in the last decades in African populations (22), most likely due to the better reporting and the adoption of a Western lifestyle in urban cities. However, biological and genetic factors may also explain variability between ethnicities. Studies in the United States have documented that breast cancers in young pre-menopausal African-American women were more aggressive, leading to a decrease in the overall survival rates compared to Caucasian women (23-25).

However, little data is currently available concerning the prevalence of *BRCA1/2* mutations among breast cancer patients indigenous to sub-Saharan countries. With the exception of the Ashkenazi population, African-American women

diagnosed with breast cancer under the age of 35 years have been reported to have a higher prevalence of *BRCA1* mutations than any age-matched racial/ethnic group (26). The higher *BRCA1* mutation prevalence correlates with their elevated rates of triple-negative or basal-like breast cancer profile (27). These phenotypic traits are present in the female Senegalese patient carrying the *BRCA1* c.1949_1950delTA mutation described in our report, who was diagnosed at 33 years of age with an ER-, PgR-, Her2- breast tumor.

Bearing in mind that there is a significant racial/ethnic variation in the spectrum of *BRCA1/2* mutations, new data regarding *BRCA1* and *BRCA2* genetic mutation prevalence and penetrance in African women is likely to improve the performance of risk-assessment tools and mutation-prediction models, and affect the clinical genetic testing process and follow-up for individuals of African ancestry (28).

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