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## A novel BRCA1 mutation in a Spanish patient with ovarian cancer

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**Abstract** We report a novel germline 3536delT mutation in BRCA1 gene, detected in a 43-year-old woman with bilateral ovarian adenocarcinoma. The mutation originates a premature stop codon at position 1154 and has not been documented in any published report to the best of our knowledge.

**Keywords** BRCA1 · Direct automatic sequencing · Germline mutation · Ovarian cancer

### Introduction

Breast cancer is the most commonly occurring cancer among women. It accounts for 22% of all female cancers and the estimated annual incidence of breast cancer worldwide is about one million cases. Many risk factors have been identified but a positive family history remains among the most important ones established, with first-degree relatives of the patient having approximately two-fold elevated risk. It is currently estimated that approximately 20–25% of this risk is explained by known breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2). BRCA1 is a tumor suppressor gene which appears to be implicated, among others, in DNA repair, cell proliferation regulation and apoptosis. All these issues have

been discussed in detail in several reviews [1–3]. First-degree relatives of patients, that are BRCA1 mutations carriers, have 50% probability of inheriting mutations. Women will develop breast carcinoma in 50–80% of cases and an ovarian tumor in 20–40%, while in males the risk of develop a breast cancer is less than 6%. Moreover, women who are carriers of a known mutation show a 40–60% risk of developing a second breast tumor, while men with BRCA1 mutations are at higher risk, not only for tumors of the prostate or colon, but also of the pancreas. According to the BIC (Breast Cancer Information Core) database, since the mutations are distributed widely all over the coding regions of the BRCA1 gene, in order to identify its mutations, the whole gene must be sequenced. This report concerns a Spanish woman with a family history of BRCA associated breast cancer, in whom a novel germline mutation was identified.

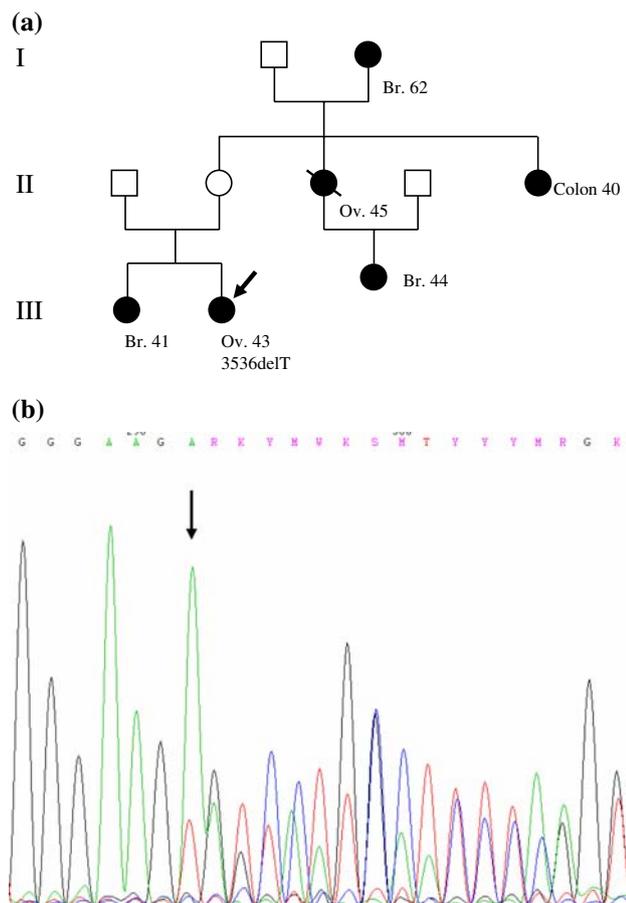
### Case report

The patient, who is indicated by an arrow in pedigree (Fig. 1a), was a multiparous, non-Ashkenazi woman, 43 years old, who, 3 years previously, had been diagnosed and treated for a bilateral ovarian adenocarcinoma in other center. During genetic counseling in our center, the genealogical tree of the patient was reconstructed going back for three generations, and revealed a history of grade I breast cancer, together with several other types of tumors including breast and ovarian cancer in other family members of grade II. The clinical history of this patient leads us to consider that the ovarian adenocarcinoma diagnosed could be BRCA1 and/or BRCA2-associated. Genomic DNA was obtained from a peripheral blood sample and automatically extracted (MagNaPure, Roche). Direct sequencing of the complete

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BRCA1 and BRCA2 genes was done by standard methods on an automated sequencer ABI PRISM<sup>®</sup> 3130XL Genetic Analyzer (Applied Biosystems) and compared to a consensus wild-type sequence constructed for each exon and partial intronic regions of the genes (Genbank No U14680, BRCA1 and Genbank NM\_000059, BRCA2). A 3536delT frameshift mutation in exon 11, not yet reported in the BIC database, was detected in BRCA1 (Fig. 1b). The deletion was confirmed by repeated analysis including reverse-primer sequencing. The analysis of exon 11 of the gene BRCA1 was offered to other members of the family being the patient's sister, diagnosed with breast cancer at the age of 41, participative in this study. The genetic analysis showed exactly the same 3536delT frameshift mutation in the sister. Furthermore, a screening of the 3536delT mutation was done in a group of 134 patients with hereditary and familial ovarian and/or breast cancer in our center. We did not find the mutation in the other families studied.



**Fig. 1** (a) Pedigree with the case reported indicated by an arrow. Black circle indicates women affected by cancer. Diagonal slash indicates deceased. White square and circle indicates man and woman not affected by disease. Br = breast cancer, Ov = ovarian cancer, Colon = colon cancer. (b) Sequence analysis of the exon11 of BRCA1 gene in the case reported. The arrow indicates the T deleted at position 3536

## Discussion

BRCA1 gene encodes an 1863 amino acid protein with two main protein-interaction domains: an N-terminal RING finger and two tandem BRCT domains at the C-terminal end [4]. The Stop codon at position 1154 detected in our patient would, in principle, generate a truncated protein that lack both BRCT domains. We have previously detected novel BRCA1 variants [5], but this is the first case we find a mutation that clearly originates a truncated BRCA1 protein and, moreover, we have the complete pedigree information of the family. In vivo, BRCA1 forms a stable heterodimer with the structurally related protein BARD1. The resulting heterodimer functions as a potent E3 ubiquitin ligase [6, 7]. Different studies have shown that two tandem BRCT motifs, such as those arrayed at the C-termini of BRCA1 and BARD1, can form a structural domain that specifically binds phosphorylated peptide sequences [8, 9]. Therefore, the BRCT motifs of BRCA1 can control distinct cell cycle checkpoints through phosphor-dependent interactions with different cellular proteins. In this way, the transient G2/M checkpoint, induced by ionizing radiation, is dependent on recognition of S327-phosphorylated isoforms of the CtIP protein by the BRCT motifs of BRCA1 [10]. The interaction between these same motifs and the S990-phosphorylated BACH1/BRIP1/FancJ protein is required for activation of the G2 accumulation checkpoint [9]. On the other hand, it is known that BRCA1 is involved in double-strand DNA break (DSB) repair. Recently it has been shown that loss of PTEN is highly associated with basal-like breast cancer subtype, in both human sporadic and BRCA1-associated hereditary breast cancers. Frequent “gross” PTEN mutations (intragenic chromosome breaks, inversions, deletions and micro copy number aberrations) were specifically identified in BRCA1-deficient tumors [11]. BRCA1 hereditary dysfunction is thought to be tumorigenic primarily owing to defective BRCA1-dependent repair, which precipitates and accumulation of secondary mutations in genes as PTEN. Certain BRCA1 mutations are found with greater frequency in specific ethnic groups, where a restricted number of BRCA1 “founder mutations” have been identified [12]. Further extension of the analysis of the mutation we have found to other families in the same geographical area, will make it possible for us to describe the phenotype features associated. At the same time, a study conducted on a population with the same mutation might be of help in determining disease penetrance.

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