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► **To cite this version:**

Josefa Salgado, José M. Aramendía, Cristina Gutierrez, Carmen Gil, Maitane Robles, et al.. A novel BRCA2 mutation that segregates with breast and prostate cancer in a Spanish family. *Breast Cancer Research and Treatment*, 2009, 121 (1), pp.219-220. 10.1007/s10549-009-0361-x . hal-00486610

**HAL Id: hal-00486610**

**<https://hal.science/hal-00486610>**

Submitted on 26 May 2010

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Running head: **New germline mutation in BRCA2**

Article type: Brief Letter

Title: **A novel BRCA2 mutation that segregates with breast and prostate cancer in a Spanish family.**

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**Key words:** BRCA2, novel mutation, breast cancer, prostatic cancer.

Mutations in BRCA1 and BRCA2 genes have been shown to be disease-associated with inherited susceptibility to breast and/or ovarian cancer [1, 2]. A large number of germ-line mutations in these genes have been reported (Breast Cancer Information Core Database, <http://www.nchgr.nih.gov/bic>). This report concerns a Spanish woman with a family history of breast, ovarian, and prostate cancer, in whom a novel germline mutation was identified. The patient, who is indicated by an arrow in pedigree (Fig.1a), was a 45 years old multiparous, non-Ashkenazi woman. Fifteen years ago, she was diagnosed and treated for a bilateral breast cancer, and mastectomy was performed. The genealogical tree of the patient revealed a history of grade I prostate cancer, grade II breast cancer and grade III ovarian cancer. After giving the informed consent of the patient, genomic DNA was automatically extracted from a peripheral blood sample (MagNapore, Roche). Direct sequencing of BRCA1 and BRCA2 genes was done on an automated sequencer ABI PRISM<sup>®</sup> 377 (Applied Biosystems) and compared to the consensus wild-type sequences (Genebank No U14680, BRCA1 and Genebank NM\_000059, BRCA2). A 5369delATTT frame-shift mutation in exon 11, not yet reported in the BIC database, was detected in BRCA2 (Fig.1b). This mutation, that generates an aberrant stop codon at position 1723, could affect important BRCA2 functions since it causes absence of BRCA2 C-terminal conserved region, necessary for DSS1 and DNA binding process. Moreover, it affects the BRCA2-BRC globular structural motifs that mediate binding to RAD51, involved in directing strand invasion during recombination [3]. The genetic analysis was offered to other family members being II.4, II.9, III.3, III.4, III.6 and IV.1 to IV.4 recruited in this study (Fig. 1a). Four mutation carriers were detected, two of them already diagnosed with disease: the patient's father (II.9, prostatic cancer) and the patient's sister (III.6, breast

cancer). The other two carriers, IV.2 and IV.3, are not affected by the disease at the moment. A twice per year clinical breast examinations and annual mammography has been recommended for the female mutation carrier (IV.3). In addition, the American Cancer Society recently published guidelines recommending that BRCA carriers and first-degree relatives undergo annual breast magnetic resonance imaging screening [4]. For the men (IV.2) an annual clinical breast examination was proposed. The National Comprehensive Cancer Network guidelines recommend that male BRCA mutation carriers should begin prostate screening (digital rectal examination and PSA) beginning at age 50, or earlier, based on the youngest age of diagnosis in the family [5]. Family members II.4, III.3, III.4, IV.1, and IV.4 were not carriers. Frequent truncations found in the Spanish population are 187delAG and 5385insC in BRCA1 and 3036del4, 3492insT, 5374del4, 9254delTCAT and 9538del2 in BRCA2. Geographical variations in the mutations distribution may be due to founder effects [6, 6-9]. We have analyzed the 5369delATTT mutation in 147 families from various Spanish regions with no positive results. Further in low represented Spanish areas will make possible to describe genetic influences and 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.

### **Acknowledgments**

We are grateful to the patients, and their families, for their participation in our research project. We thank clinicians and genetic counselors of the Department of Oncology and the Clinical Genetics Unit for their support and encouragement. Cristina Gutierrez has an ADA fellowship from the University of Navarra, Navarra, Spain.

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