A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.

A breast cancer family from Spain with germline mutations in both the BRCA1 and BRCA2 genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura, E Diaz-Rubio


Electron. Lett.
search of DNA variants for all coding exons and intron/exon boundaries of the BRCA1 and BRCA2 genes by PCR-DGGE analysis. The sample exhibited abnormal migration patterns for exon 18 of BRCA1 and exon 11 of BRCA2. Direct sequencing showed BRCA1 A1708E as a missense mutation and BRCA2 6503 del TT as a frameshift mutation that produces a stop codon at position 2098 (fig 1B). Both mutations were confirmed by two independent sequencing PCR reactions and sequenced in both forward and reverse directions. The BRCA1 A1708E mutation has been reported previously in the Breast Cancer Information Core (BIC) database and is one of the very few BRCA1 missense mutations known to have a pathogenic role.

The BRCA2 6503 del TT mutation was a novel mutation not previously reported in the BIC database. The index case has five sibs (four sisters and one brother) and a maternal history of breast cancer (fig 1A). One of the sisters had been diagnosed with breast cancer at the age of 40 years and she died at 42 years. DNA samples were available from her parents. It was therefore possible to determine that both mutations were inherited from her mother. Interestingly, her mother was not diagnosed with breast cancer until then. The knowledge of the mutation status in the proband motivated a number of family members to request testing. Informed consent was signed by each person tested. The maternal side contained two cases of postmenopausal breast cancer (II.11 and II.12) diagnosed at 71 and 66 years of age; she was an obligate carrier of both BRCA1 and BRCA2 mutations because two of her daughters (III.10 and III.12) are carriers of BRCA1 A1708E and another daughter (III.17) is a carrier of BRCA2 6503 del TT. The other postmenopausal breast cancer case, II.12, is a carrier of both BRCA1 and BRCA2 mutations. There was one case of prostate cancer (II.7) diagnosed at the age of 66 years who died at 68 years; he was also an obligate carrier of both mutations because his two daughters are carriers of both BRCA1 A1708E and BRCA2 6503 del TT. There was also one case of early onset breast cancer (III.17) diagnosed at the age of 32 years who is a carrier of only the BRCA2 6503 del TT mutation. Other results of mutation analysis are indicated on the pedigree (fig 1A).

In order to document the involvement of either BRCA1 or BRCA2 in pedigree 121, genetic linkage analysis was performed with markers for BRCA1 (D17S579, D17S1299, D17S855, and D17S1293) and markers for BRCA2 (D13S260, D13S267, and D13S1493). The segregation of BRCA1 and BRCA2 haplotypes is shown in fig 1A. All carriers of BRCA1 and BRCA2 mutations share the same allele at each marker, which is consistent with the presence of a common haplotype.

Given the diversity of phenotype among the double mutation carriers in our family, we decided to study which of the two genes was causing the disease in subjects who carry both mutations. Although not definitive, the best way to address this issue is by examining the tumours in order to characterise the LOH patterns, since the vast majority of BRCA tumours exhibit loss of the wild type allele. The LOH study for both mutations A1708E in BRCA1 and STOP2098 in BRCA2 in the tumour DNA of the index case (fig 2) showed that the wild type allele and the mutant allele were equally retained in
the tumour DNA. The lack of LOH suggests an alternative pathway of causing the disease; this way could include alterations in other genes and/or environmental factors associated with modification of breast cancer risk, which might explain the low incidence of breast cancer in the family.

This case is the first example to date of a double heterozygote for the high penetrance breast cancer susceptibility genes, \textit{BRCA1} and \textit{BRCA2}, in a family from Spain. In this family, in the early onset breast cancer case III.17, the prior probability of being a mutation carrier based on her age at onset and the family history is similar to the early onset breast cancer case III.1, but if we had not studied both the \textit{BRCA1} and \textit{BRCA2} genes in the index case (III.1) we would never have found the \textit{BRCA2} mutation in case III.17. The study shows the importance and benefit of testing for both \textit{BRCA1} and \textit{BRCA2} in order to obtain an accurate result for genetic counselling.

ACKNOWLEDGEMENTS

We thank the members of the family described in this report for their cooperation. This work was supported by grants FIS 01/0024-03, CAM 081/0015/2001, and Aventis.


Authors’ affiliations

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, Servicio de Oncología e Inmunología Molecular, Hospital Universitario San Carlos, Madrid, Spain

M Martin, P Perez-Segura, E Diaz-Rubio, Servicio de Oncología Médica, Hospital Universitario San Carlos, Madrid, Spain

Correspondence to: Dr T Caldes, Servicio de Oncología e Inmunología Molecular, baja sur, Hospital Universitario San Carlos, Martin Lagos s/n, 28040 Madrid, Spain; tcaldes@hsc.es

REFERENCES


12. Randall TC, Bell KA, Rebase BA, Rubin SC, Boyd J. Germline mutations of the \textit{BRCA1} and \textit{BRCA2} genes in a breast and ovarian cancer patient: Gynecol Oncol 1998;70:432-4.


A breast cancer family from Spain with germline mutations in both the \textit{BRCA1} and \textit{BRCA2} genes

T Caldes, M de la Hoya, A Tosar, S Sulleiro, J Godino, D Ibañez, M Martin, P Perez-Segura and E Diaz-Rubio

\textit{J Med Genet} 2002 39: e44
doi: 10.1136/jmg.39.8.e44