

CORRESPONDENCE

BRCA1 mutation and neuronal migration defect: implications for chemoprevention

Previously we described a BRCA1 carrier with a neuronal migration defect and postulated that the brain abnormality was caused by functional nullisomy for BRCA1.¹ We now describe another family in which a similar type of neuronal migration defect has occurred in one of female identical twins with a BRCA1 gene mutation (MIM 113705). One twin developed unusually early onset multiple primary breast cancers while the second twin remains cancer free over a decade later. The second twin had long standing epilepsy and focal subcortical heterotopia. We hypothesise that the neuronal migration defect is due to focal nullisomy of the BRCA1 and that the modified breast cancer risk is due to the anti-oestrogenic effects of long term anticonvulsant therapy.

Thirty three year old identical twins were referred for genetic counselling. Twin 1 had developed breast cancer aged 29 years and a second primary breast cancer aged 33 years. The early onset of high grade oestrogen receptor negative breast cancer plus the family history (fig 1) suggested an inherited mutation in the BRCA1 gene.

Full mutation analysis on a DNA sample from twin 1 using the protein truncation test and denaturing high performance liquid chromatography failed to reveal any abnormality in BRCA1 or BRCA2. A set of 22 polymorphic markers spread across chromosomes 6, 11, and X were used to compare DNA from twin 1 with DNA from twin 2. All 22 markers were concordant making it highly unlikely that they were not identical. Annual ovarian and breast screening was established for both twins.

Twin 1 developed bilateral multifocal breast carcinoma 10 years after the initial diagnosis. At her most recent screen, age

39 years, breast magnetic resonance imaging as well as conventional breast mammography was normal throughout in twin 2.

Multiplex ligation dependent probe amplification eventually revealed that exons 9–12 of the BRCA1 gene in twin 1 were deleted. Predictive testing confirmed that this multi-exonic deletion was also present in twin 2.

Closer attention to the neurological problems and history of twin 2 revealed that the twins were born at home to non-consanguineous parents after an uneventful pregnancy, although the second twin was undiagnosed prenatally. Both twins were healthy at birth and had an uneventful neonatal period. At 11 months of age twin 2 developed focal right sided seizures usually progressing to grand mal seizures for which she required anti-convulsant treatment. She attended mainstream school with her sister. Twin 1 was right handed whereas twin 2 was left handed. Anti-convulsant treatment initially was with sodium valproate, and phenobarbitone was added at age 5 years and phenytoin at age 21 years, Sodium valproate was stopped 3 years later.

On examination twin 2 had normal tone but mild right sided motor weakness in upper and lower limbs, brisk reflexes, and an extensor plantar reflex on the right hand side with no gross sensory abnormality. The MRI brain scan (fig 2) demonstrates focal subcortical heterotopia and reduced volume in the left cerebral hemisphere.

BRCA1 knockout mice show neuroepithelial developmental anomalies incompatible with development beyond early embryonic life. They exhibit structural disorganisation and in particular the neuroepithelium shows signs of rapid proliferation and excessive cell death.² A second somatic hit affecting the wild type BRCA1 allele in an early neuronal stem cell would result in focal nullisomy for BRCA1 and would mimic focally the situation in a BRCA1 null developing brain. Although compound BRCA1/BRCA2 heterozygotes have been described, there are no reported cases of viable homozygous BRCA1 mutation carriers in any species. Given that the carrier rate for 185delAG BRCA1 mutation in the Ashkenazi Jewish population is around 1% in Israel and parts of North America, homozygote mutation carriers would be expected to occur with a frequency of around 1 in 40 000 if BRCA1 homozygous mutations were compatible with life.^{3–5} BRCA1 has few homologues, but interestingly another gene

involved in brain development, MCPH1 (MIM 251200), in which biallelic mutations led to primary microcephaly, contains three BRCA1 C-terminal repeat domains.⁶ Other possible prenatal insults that could give rise to abnormal development of the brain include infection and an early vascular event leading to hypoperfusion, however the localised nature of the abnormality in this case makes these explanations less likely than the second hit hypothesis postulated here.

BRCA1 gene mutations are highly penetrant with a lifetime cumulative breast cancer risk of 70–80% and a median age at onset of around 43 years. Penetrance is likely to be affected by modifying genes and by environmental factors. In identical twins the effect of modifying genes can be ruled out. Environmental factors presumably therefore explain why twin 2 remains breast cancer free 10 years after her sister developed the first of three unusually early onset primary breast cancers. Twin 1 had a somewhat longer duration of exposure to the oral contraceptive pill from age 15 years for 9 years compared to 4 years for twin 2. There is some evidence suggesting that oral contraceptive pill use increases breast cancer risk in BRCA1 gene carriers.⁷ Twin 1 took 6 months of clomiphene for primary infertility just prior to the diagnosis of her first breast cancer, but this is less likely to be implicated as it is a synthetic anti-oestrogen and was taken probably after the first cancer had started to develop. Her only full term pregnancy occurred after her second breast cancer was diagnosed and is unlikely to have influenced either of the first two cancers. A more compelling modifying factor, however, is the long term anti-convulsant therapy taken by twin 2 since infancy. Many anti-convulsant drugs, including phenytoin and phenobarbitone, act as potent liver inducing enzymes that reduce the bioavailability of both exogenous oestrogen and progesterone. In addition, most categories of anti-convulsant cause an increase in serum sex hormone binding globulin (SHBG).⁸ This increase in SHBG is also seen with synthetic anti-oestrogens including tamoxifen and clomiphene. An increase in SHBG will reduce bioavailability of endogenous sex steroid hormones including oestrogen. Tamoxifen has been shown to reduce the chance of oestrogen receptor positive breast cancer over a 5 year treatment period in older women but

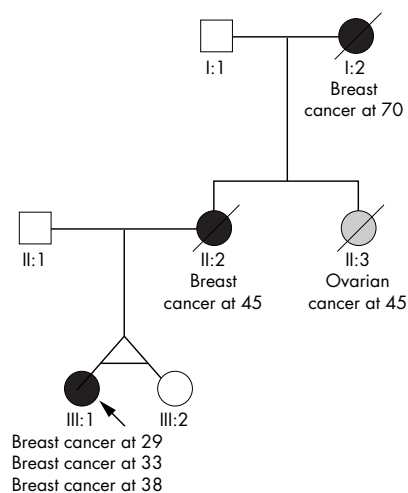


Figure 1 Family history. The early onset, high grade, oestrogen receptor negative breast cancer with multiple new primaries in the index case are typical for BRCA1. The young onset breast and ovarian cancer cases in immediate relatives in the previous generation are also typical.

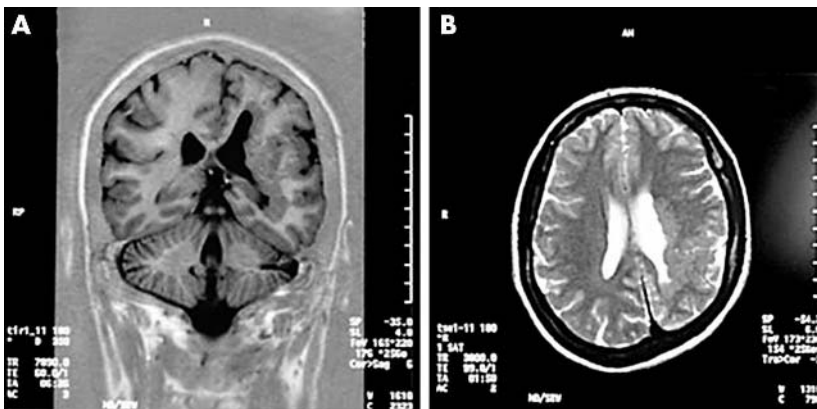


Figure 2 Coronal inversion recovery (A) and axial T2 (B) MRI images show a small left cerebral hemisphere with a nodular mass of grey matter in the left parieto-occipital region extending down to and around the lateral ventricle.

current trials start recruitment only after 35 years of age.⁹ Bilateral oophorectomy leading to an early menopause in BRCA1 gene carriers clearly reduces breast cancer risk so there does appear to be a role for long term reduction in endogenous oestrogen in modifying risk.¹⁰ The earlier the age at which this is instigated, the more potent the inhibitory effects may be.

It is vital that we improve management options for individuals with a genetic predisposition to cancer and a better understanding of environmental factors that may modify cancer risk will help further this goal. Furthermore, since long standing epilepsy without any change in clinical status may not prompt investigation in adults, any localised neurological signs or symptoms in a BRCA1 gene carrier may warrant more detailed investigation including an MRI brain scan although this is likely to be a rare phenomenon.

Acknowledgements

Hilary Bullman, Margaret Connarty, and Julie Sillibourne in the Wessex Regional Genetics NHS Laboratory contributed to the molecular genetic analyses described. We are grateful to the family members for permission to report this case.

D Eccles

Wessex Clinical Genetics Service, Princess Anne Hospital, Coxford Road, Southampton SO16 5YA, UK

D Bunyan

Wessex Regional Genetics Laboratory, Salisbury District Hospital, Odstock, Salisbury, UK

S Barker

Wessex Neurological Centre, Southampton General Hospital, Southampton, UK

B Castle

Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, UK

Correspondence to:

Professor Diana M Eccles, MD, FRCP, Wessex Clinical Genetics Service, Princess Anne Hospital, Coxford Road, Southampton SO16 5YA, UK; de1@soton.ac.uk

Competing interests: none declared

References

- 1 **Eccles DM**, Barker S, Pilz DT, Kennedy C. Neuronal migration defect in a BRCA1 gene carrier: possible focal nullisomy? *J Med Genet* 2003;**40**:e24.
- 2 **Gowen LC**, Johnson BL, Latour AM, Sulik KK, Koller BH. Brca1 deficiency results in early embryonic lethality characterized by neuroepithelial abnormalities. *Nat Genet* 1996;**12**:191–4.
- 3 **Gal I**, Sadetzki S, Gershoni-Baruch R, Oberman B, Carp H, Papa MZ, Diestelman-Menachem T, Eisenberg-Barzilai S, Friedman E. Offspring gender ratio and the rate of recurrent spontaneous miscarriages in Jewish women at high risk for breast/ovarian cancer. *Am J Hum Genet* 2004;**74**:1270–5.
- 4 **Roa BB**, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet* 1996;**14**:185–7.
- 5 **Struewing JP**, Abeliovich D, Peretz T, Avishai N, Kaback MM, Collins FS, Brody LC. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. *Nat Genet* 1995;**11**:198–200.
- 6 **Jackson AP**, Eastwood H, Bell SM, Adu J, Toomes C, Carr IM, Roberts E, Hampshire DJ, Crow YJ, Mighell AJ, Karbani G, Jafri H, Rashid Y, Mueller RF, Markham AF, Woods CG. Identification of microcephalin, a protein implicated in determining the size of the human brain. *Am J Hum Genet* 2002;**71**:136–42.
- 7 **Narod SA**, Dube MP, Klijn J, Lubinski J, Lynch HT, Ghadirian P, Provencher D, Heimdal K, Moller P, Robson M, Offit K, Isaacs C, Weber B, Friedman E, Gershoni-Baruch R, Rennert G, Pasini B, Wagner T, Daly M, Garber JE, Neuhausen SL, Ainsworth P, Olsson H, Evans G, Osborne M, Couch F, Foulkes WD, Warner E, Kim-Sing C, Olopade O, Tung N, Saal HM, Weitzel J, Merajver S, Gauthier-Villars M, Jernstrom H, Sun P, Brunet JS. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 2002;**94**:1773–9.
- 8 **Murialdo G**, Galimberti CA, Gianelli MV, Rollero A, Polleri A, Copello F, Magri F, Ferrari E, Sampaolo P, Manni R, Tartara A. Effects of valproate, phenobarbital, and carbamazepine on sex steroid setup in women with epilepsy. *Clin Neuropharmacol* 1998;**21**:52–8.
- 9 **Cuzick J**, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, Boyle P. Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003;**361**:296–300.
- 10 **Rebbeck TR**, Friebel T, Lynch HT, Neuhausen SL, van't Veer L, Garber JE, Evans GR, Narod SA, Isaacs C, Matloff E, Daly MB, Olopade OI, Weber BL. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2004;**22**:1055–62.