

## ELECTRONIC LETTER

Neuronal migration defect in a *BRCA1* gene carrier: possible focal nullisomy?

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A *BRCA1* 5382insC mutation was identified in a family with multiple cases of breast and ovarian cancer and eastern European ancestry. Predictive genetic testing was offered to all family members after standard genetic counselling within the regional clinical genetics service.

## CASE REPORT

An adult male presented to the clinical genetics service for predictive testing. His past medical history was complex. He was the second of twins, born at term (36 weeks) following an uncomplicated pregnancy, and weighed 2300 g. His early development did not cause any concern, but when he achieved independent walking at 18 months, this was slow and awkward. He was noted to have a mild left hemiparesis, the cause of which was not clarified until later. He had no major illnesses as a child and attended normal school with average achievements, although he did less well than his twin sister. At 12 years of age he presented with focal left sided seizures and a CT brain scan showed underdevelopment of the right cerebral hemisphere and hypoplasia of the wing of the sphenoid. He was informed at this stage that a possible diagnosis was neurofibromatosis type 1 and he received anticonvulsant treatment, which was partially effective.

From his position in the pedigree, he had a 50% risk of having inherited the mutated *BRCA1* gene. After appropriate genetic counselling he elected to undergo predictive testing and was found to be a carrier. A short time before predictive testing he had experienced a worsening of his epileptic

## Key points

- The *BRCA1* and *BRCA2* genes are involved in DNA repair, and nullisomy for either gene results in embryonic lethality in mice, with striking neuroepithelial developmental abnormalities.
- We describe a male *BRCA1* gene mutation carrier with the radiological appearances of a gross neuronal migration defect affecting the right cerebral hemisphere.
- We hypothesise that this may represent an additional somatic *BRCA1* mutation in an embryonic stem cell destined to develop into the affected area of brain, rendering this developing tissue functionally nullisomic for *BRCA1* at an early stage in embryogenesis.

control. Investigations included an MRI brain scan, which showed extensive nodular heterotopia of the grey matter of the right cerebral hemisphere; the left cerebral hemisphere was essentially normal (fig 1). The cortex overlying the nodular heterotopia was very thin and abnormal, compatible with a neuronal migration defect.

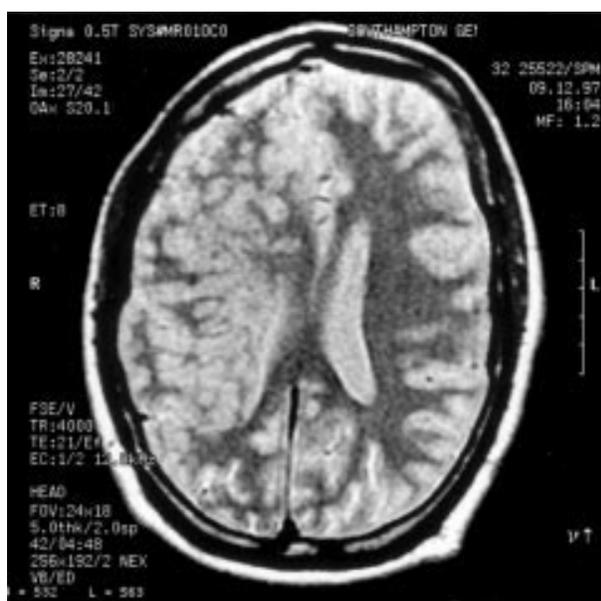
Clinical examination showed an asymmetrical face with a low set orbit on the right, an asymmetrical head shape, normal hair growth, and no evidence of any skin pigmentary abnormalities or neurofibromas either over the right scalp or elsewhere. Slit lamp examination showed no evidence of Lisch nodules.

## DISCUSSION

The diagnostic criteria for neurofibromatosis type 1 are not fulfilled in this case and the sphenoid wing hypoplasia (although a classical feature of NF1) is most likely to be secondary to underdevelopment of the brain. In addition, neuronal migration defects are not a feature of NF1.

The aetiology of neuronal migration defects includes genetic causes and intrauterine infections or hypoperfusion. Infections are unlikely to result in a unilateral cerebral anomaly, or to affect only one of twins, and there was no additional evidence of an intrauterine infection on imaging. Hypoperfusion may be more common in twins<sup>1</sup> and we cannot exclude the possibility that this could have led to the neuronal migration abnormality in this patient. However, we favour an alternative hypothesis. We propose that a possible cause for the neuronal migration defect in our patient, who had already inherited the familial *BRCA1* mutation, is a second somatic mutation in the wild type *BRCA1* gene occurring in an early developing brain cell, which produced progenitors for the developing right cerebral hemisphere. This early somatic event would have led to clonal proliferation of *BRCA1* null neuroepithelium, resulting in abnormal neuronal migration.

The *BRCA1* gene is known to be involved in cellular proliferation and differentiation during embryonic development.<sup>2</sup> *BRCA1* null mice die early during development,



**Figure 1** Axial proton density weighted MRI scan showing nodular heterotopia in the smaller right cerebral hemisphere and a normal left cerebral hemisphere.

and appear structurally disorganised with signs of both rapid proliferation and excessive cell death, particularly in the neuroepithelium.<sup>3</sup> The effect of *BRCA1* nullisomy on humans has yet to be clarified.<sup>4,5</sup>

The only way to verify our hypothesis would be to examine the affected brain tissue for the postulated second (somatic) mutation which is not possible in this case. Clearly if our theory is correct, other examples of similar anomalies may exist. However, these events are likely to be very rare, since the (second) somatic mutation would need to occur in a specific cell at a critical stage in development in a *BRCA1* gene carrier. Other genes involved in neurodevelopment may also be affected by somatic mutations during development with no consequences for the person, unless they had also inherited a mutated copy of the same gene from one or other parent. Focal nullisomy for a variety of genes important in embryogenesis could thus be an unrecognised cause for otherwise unexplained developmental anomalies.

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