LETTER TO JMG

Biallelic *BRCA2* mutations are associated with multiple malignancies in childhood including familial Wilms tumour

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J Med Genet 2005;42:147–151. doi: 10.1136/jmg.2004.022673

Wilms tumour (WT) is an embryonal tumour of the kidney that occurs in 1 in 10 000 children. Familial clusters are rare and account for only 1–3% of cases. Mutations in *WT1* account for a minority of WT families and two autosomal dominant familial WT predisposition genes have been mapped to chromosomes 17q21 and 19q13.^{1–3} However, a considerable proportion of familial WT pedigrees are not attributable to any of these loci.⁴

Fanconi anaemia (FA, MIM 227650) is a rare autosomal recessive condition affecting ~1 in 300 000 children. FA is characterised by variable congenital abnormalities, short stature, bone marrow failure, hypersensitivity to DNA cross-linking agents, and a predisposition to haematological malignancies such as acute myeloid leukaemia in childhood.⁵ FA is heterogeneous and consists of at least 11 complementation groups, A, B, C, D1, D2, E, F, G, I, J, and L.^{6–8} Eight FA genes have been cloned and at least six FA proteins, FANCA, FANCC, FANCE, FANCF, FANCG, and FANCL, form a nuclear complex required for monoubiquitination of FANCD2. This modification promotes translocation of FANCD2 to DNA repair foci that also contain BRCA1, BRCA2, and RAD51.⁹

In 2002, Howlett and colleagues reported biallelic *BRCA2* mutations in individuals with Fanconi anaemia D1 (FA-D1). Subsequently, additional FA-D1 and unclassified FA cases were examined and cases with *BRCA2* mutations and WT and/or brain tumours were reported.^{10–13} These data prompted us to investigate *BRCA2* in a familial WT pedigree, WILMS2, which includes siblings with both WT and brain tumours.^{4 14 15}

METHODS

Family report

WILMS2 was ascertained as part of our research on susceptibility to WT, which is approved by the London Multicentre Research Ethics Committee. The family includes two affected brothers with WT. The elder child first came to attention when his cryptorchidism was corrected at 2 years of age. At that time hypo- and hyperpigmented areas and a few café au lait spots were noted and he was below the 3rd centile for weight, height, and head circumference. At 3.5 years of age a stage III WT was surgically removed and the child made an uneventful recovery after radiotherapy and chemotherapy with vincristine and actinomycin D. At 9 years of age he developed seizures and was found to have two intracerebral lesions, which were diagnosed as glioblastoma multiforme on stereotactic biopsy. Due to extensive disease no further surgery was attempted and the child died 13 months later. The second son had an uneventful birth and early infancy with normal height and weight, though he was noted to have three café au lait spots and many small depigmented and hyperpigmented spots. At 7 months a stage 1 WT was

Key points

- We present an unusual pedigree in which two brothers both developed Wilms tumour and brain tumours.
- Two truncating *BRCA2* mutations, 886delGT and S1882X, were present in each child. Biallelic *BRCA2* mutations cause Fanconi anaemia D1 (FA-D1), but neither child had the typical clinical features of Fanconi anaemia.
- Heterozygote *BRCA2* mutation carriers are at risk of breast and other cancers. At presentation there were no cases of cancer in first or second degree relatives. However, after the children died their mother and paternal aunt developed breast cancer.
- Previous reports proposed that biallelic *BRCA2* mutations carriers would likely harbour at least one missense variant or truncation restricted to the carboxy terminus of the protein. However, we show there is no overall bias in mutation position in biallelic cases towards the 3' end of the gene compared with heterozygous *BRCA2* mutation carriers identified from breast cancer pedigrees.
- We also show that *BRCA2* K3326X, which is present in 1% of the population and is not associated with breast cancer predisposition, does not predispose to FA-D1, in contrast to previous suggestions.
- Our data suggest that similar *BRCA2* mutations predispose to breast cancer when monoallelic and Fanconi anaemia when biallelic. Caution in attributing pathogenicity to missense *BRCA2* variants in biallelic cases should be exercised, unless they are known to predispose to breast cancer in monoallelic cases.

diagnosed and surgically removed and he was given actinomycin D without radiotherapy. Then 5 years later, whilst asymptomatic, an MRI brain scan was performed as a screening procedure in view of the family history. A cerebellar lesion was identified and resected. Histology confirmed a grade IV medulloblastoma which was treated with radiotherapy. At 10 years of age he developed pre B cell acute lymphoblastic leukaemia and spontaneous breakages of the chromosomes was noted. He was treated with chemotherapy and suffered a cerebral haemorrhage due to asparaginase. He subsequently died at 12 years of age from diffuse relapse of the medulloblastoma.

Abbreviations: FA, Fanconi anaemia; WT, Wilms tumour

Figure 1 Pedigree and *BRCA2* mutations in WILMS2 and position of all known mutations identified in biallelic *BRCA2* cases. (A) Pedigree structure of WILMS2; closed symbol: affected with cancer, open symbol: unaffected with cancer. The type of cancer and age at presentation are given under the symbol. (B) *BRCA2* mutations identified in WILMS2 and wild type sequence from a control. (C) Position of mutations identified in all reported cases with biallelic *BRCA2* mutations. The exons and positions of functional domains in *BRCA2* are shown. NLS, nuclear localisation signal. The numbers along the top refer to the family numbers in table 1. Boxes around family numbers indicate frameshift or nonsense mutations, while family numbers without a box indicate splice site mutations. Variants of unknown significance and polymorphisms are not shown.

No first or second degree relative had cancer when the family presented. However, after the children had died the mother developed breast cancer at 45 years of age and a paternal aunt developed breast cancer at 48 years of age (fig 1A).

Laboratory analyses

We screened genomic DNA from the two affected brothers through the complete coding sequence of *BRCA2* by a combination of conformation sensitive gel electrophoresis¹⁶ and direct sequencing using the BigDye Terminator Cycle Sequencing Kit and an ABI 3100 automated sequencer. *BRCA2* primer sequences and conditions are available on request.

To evaluate the K3326X and N372H variants we screened 148 *BRCA2* mutation positive cases from 69 families ascertained from the Breast Cancer Susceptibility Collaboration (UK) using the ABI Prism 7900HT Sequence Detection

System (TaqMan; Applied Biosystems, Foster City, CA). TaqMan primers and probes were designed by Applied Biosystems SNP Genotyping Assays-By-Design service (sequences available on request). Assays (12.5 µl) were performed on 10 ng genomic DNA with 1×TaqMan Universal PCR Master Mix and the Assays-By-Demand standard thermal cycler protocol. Plates were read on the ABI Prism 7900HT Sequence Detection System in end point mode using the allelic discrimination Sequence Detection software (Applied Biosystems). Heterozygotes were confirmed by direct sequencing using a fresh template.

RESULTS AND DISCUSSION

Mutational screening of *BRCA2* in the two affected brothers revealed two truncating mutations in each child (fig 1B). The paternally inherited mutation was a deletion in exon 8, 886delTG, which is predicted to truncate the protein at codon 223, before the eight BRC repeats. The maternally inherited

nonsense mutation in exon 11, S1882X, is predicted to truncate the protein such that BRC7 and BRC8 would be absent (fig 1C).

Sixteen other families with biallelic *BRCA2* mutations have been reported, mainly from investigation of unassigned FA cases (table 1, fig 1C).^{10–13} Our findings broaden the spectrum of phenotypes associated with biallelic *BRCA2* mutations to familial WT pedigrees and cases without a pre-existing diagnosis of FA. Although a diagnosis of FA had been made in the other biallelic *BRCA2* families, the clinical features were not always typical and similarities with WILMS2 are apparent. Overall, biallelic *BRCA2* mutations appear to be associated with unusually high spontaneous chromosome aberration rates, less frequent bone marrow suppression, less frequent skeletal abnormalities, and a different spectrum of childhood cancers compared with other FA subtypes.^{10–13} WT (five cases), brain tumours (nine cases including medulloblastoma, glioblastoma multiforme, and astrocytoma), acute myeloid leukaemia (seven cases), and acute lymphoblastic leukaemia (three cases) have been identified in 23 biallelic *BRCA2* mutation carriers. Of these cases, 21 have had childhood cancer and in four cases multiple cancers occurred (table 1). Only one case has reached adulthood without cancer and he is homozygous for an in-frame deletion of four codons and thus may have a milder phenotype.¹⁰ Altogether, although there has been some bias towards screening childhood cancer cases, the available data suggest the cancer risk of children with biallelic *BRCA2* mutations may be very high.

The early identification of the *BRCA2* status of these children is important, as it will likely affect response to cancer therapies. In particular, DNA damaging chemotherapeutic agents may result in severe toxicity at standard doses. The use of radiotherapy will also need careful consideration.

The brothers in WILMS2 both received radiation treatment without obvious toxicity. This is consistent with recent evidence that abrogation of *BRCA2* function has little effect on radiation sensitivity unless the p53 dependent DNA damage checkpoint is also inactivated.¹⁷ However, irradiation of murine cells homozygous for an exon 11 *BRCA2* truncation has been shown to substantially increase the spontaneous somatic mutation rate compared with wild type animals.¹⁸ If this increase in somatic mutation acquisition also occurs in humans, it would suggest that radiotherapy treatment of biallelic *BRCA2* cases might increase the risk of second or third cancers.

The initial report from Howlett and colleagues hypothesised that FA-D1 would occur in cases with at least one *BRCA2* mutation that was less severe, for example, a missense alteration, splicing defect, or truncation in the carboxy terminus of the gene. It is of considerable importance to clarify whether such variants confer a risk of FA, given their prevalence and the implications for genetic counselling. In five reported pedigrees (families 3, 9, 12, 16, and 17; table 1) a missense variant was proposed as one of the FA predisposing mutations. In a further pedigree, family 15, the second mutation was reported as K3326X, which is present in ~1% of the population and a similar proportion of breast cancer cases, and is not associated with high penetrance breast cancer susceptibility.¹⁹ Of these variants, perhaps the most plausible FA predisposing alleles are K3326X, which results in loss of 93 amino acids, and N372H, which is postulated to be a low penetrance breast cancer susceptibility allele as HH homozygotes are reported to have a relative risk of breast cancer of 1.3.²⁰ To evaluate these two variants we screened 148 *BRCA2* mutation positive cases from 69 families ascertained from the Breast Cancer Susceptibility Collaboration (UK).

Table 1 Mutations and cancers in biallelic *BRCA2* mutation cases

Family	Case	Mutation 1			Mutation 2			Other variant	Cancer	Reference
		Nucleotide change	Exon	Effect	Nucleotide change	Exon	Effect			
1	Wilms2-RB Wilms2-CB	886delGT	8	V220fsX233	5873C→A	11	S1882X		Wilms, glioblastoma Wilms, medulloblastoma, B-ALL	This report
2	772/1 772/2	886delGT	8	V220fsX233	8447T→A	18	L2740X		Medulloblastoma Wilms, medulloblastoma	Hirsch <i>et al</i> ¹²
3	Kin2-1 Kin2-2	4876G→T	11	E1550X	–	–	–	L2510P	Wilms, AML T-ALL	Hirsch <i>et al</i> ¹²
4	Kindred 2	886delGT	8	V220fsX233	6174delT	11	S1982fsX2003		Medulloblastoma	Offit <i>et al</i> ¹¹
5	Kindred 3	5301insA	11	K1691fsX1694	–	–	–	I2490T	Medulloblastoma	Offit <i>et al</i> ¹¹
6	Kindred 4	4150G→T	11	E1308X	9424C→T	24	Q3066X		Medulloblastoma	Offit <i>et al</i> ¹¹
7	Kindred 1/1 Kindred 1/2	6174delT	11	S1982fsX2003	9435T→A	24	C3069X		Posterior fossa tumour Astrocytoma	Offit <i>et al</i> ¹¹
8	129/1	IVS7+2T→G	IVS7	del exon 7	IVS7+2T→G	IVS7	del exon 7		AML	Wagner <i>et al</i> ¹³
9	357/1	2041insA	10	I605fsX613	–	–	–	W2626C	AML	Wagner <i>et al</i> ¹³
10	632/1 632/2	IVS7+1G→A	IVS7	del exon 7	5910C→G	11	Y1894X		AML AML	Wagner <i>et al</i> ¹³
11	800/1 800/2	IVS7+2T→G	IVS7	del exon 7	5164del4	11	E1646fsX1668		AML Wilms (occult)	Wagner <i>et al</i> ¹³
12	900/1	2816insA	11	N863fsX880	–	–	–	N372H	T-ALL	Wagner <i>et al</i> ¹³
13	HSC62	IVS19-1G→A	IVS19	del 2830-3	IVS19-1G→A	IVS19	del 2830-3		No cancer at 30 years	Howlett <i>et al</i> ¹⁰
14	EUFA423	7691insAT	15	R2488fsX2512	9900insA	27	I3224fsX3254		Brain tumour	Howlett <i>et al</i> ¹⁰
15	HSC230	3033delAAAC	11	K936fsX958	–	–	–	K3326X	No cancer at 2 years	Howlett <i>et al</i> ¹⁰
16	EUFA579	5837-5838TC→AG	11	F1870X	–	–	–	R2336H	AML	Howlett <i>et al</i> ¹⁰
17	AP37P	8732C→A	20	S2835X	–	–	–	K2729N	AML	Howlett <i>et al</i> ¹⁰

Nine *BRCA2* families carried K3326X. In seven unrelated families K3326X segregated with *BRCA2* 6503delTT, confirming the previous report that this mutation originated on a K3326X haplotype and that the two *BRCA2* sequence alterations are in *cis*.¹⁹ In the remaining two families K3326X did not segregate with the mutations, 3386delTAGA and 6819delTG, indicating that the variant was on separate chromosomes from the mutations. Three individuals from these two families were carriers of a disease causing *BRCA2* mutation and K3326X. None had evidence of FA or childhood cancer although all three developed breast cancer between the ages of 45 and 50, consistent with heterozygosity for the *BRCA2* mutation. For N372H, we identified 13 individuals who carried a *BRCA2* mutation and were homozygous for histidine at codon 372. None had evidence of FA or childhood cancer. These data strongly suggest that neither K3326X nor N372H are FA predisposing alleles and that caution in attributing pathogenicity to unclassified *BRCA2* sequence variants should be exercised. It is likely that a second *BRCA2* mutation is present in families 3, 5, 9, 12, 15, 16, and 17 but has not been identified due to insensitivity of mutation screening, as previously suggested by Offit *et al.*¹¹ The inability to detect an appreciable proportion of *BRCA2* mutations by standard mutation detection techniques has been demonstrated in breast cancer pedigrees with strong linkage to *BRCA2* but no identifiable mutation.²¹

These data also call into question the hypothesis that biallelic *BRCA2* cases are more likely to carry truncations in the carboxy terminus of the protein. To evaluate this we compared the position of truncating (frameshift or nonsense) mutations identified in FA cases with the mutation position in heterozygous *BRCA2* carriers identified from breast cancer pedigrees. Eighteen separate truncating mutations have been identified in 17 independently ascertained FA families (table 1, fig 1C). We used the Breast Cancer Information Core database (<http://research.nhgri.nih.gov/bic/>) to identify truncating mutations detected by full gene sequencing in familial breast cancer pedigrees. A total of 507 different frameshift or nonsense mutations have been reported in breast cancer families. In biallelic *BRCA2* cases, 6/18 (33%) truncating mutations occurred after exon 11. By comparison, in heterozygous *BRCA2* cases, 214/507 (42%) truncating mutations occurred after exon 11. These data do not support a bias in mutation position in biallelic *BRCA2* cases towards the carboxy terminus.

Although the mutations identified in biallelic *BRCA2* cases appear to be similar in type and position to those in heterozygous cases, it is noteworthy that three of 17 families and five of 23 cases carry *BRCA2* 886delGT, and all developed brain tumours. Indeed four of six medulloblastomas identified in biallelic *BRCA2* cases carry the 886delGT mutation. This mutation has been reported in multiple familial breast cancer pedigrees, but there are several *BRCA2* mutations that are known to occur at similar or greater frequency which have not been identified in biallelic *BRCA2* cases. It is difficult to conceive a biological explanation for why a particular truncating mutation should be associated with a specific cancer risk. However, scrutiny of the cancer phenotypes and mutations in additional biallelic cases will be of interest to further evaluate this observation. Interestingly, no case homozygous for *BRCA2* 6174delT has been reported, despite the prevalence of this mutation in ~1% of the Ashkenazim.²² This may be due to chance, but it is also possible that the phenotype associated with biallelic 6174delT mutations is either more or less severe than for other combinations of mutations such that they have thus far not been identified. It is also notable that *BRCA2* heterozygotes do not appear to be at increased risk of childhood cancer. In 173 *BRCA2* families ascertained by the Breast Cancer Linkage Consortium there

were no cases of WT, brain tumours, or childhood leukaemia in confirmed mutation carriers (D Thompson and DF Easton, personal communication on behalf of the Breast Cancer Linkage Consortium).

None of the reported families with biallelic *BRCA2* cases had been investigated for *BRCA2* mutations because of a family history of breast cancer prior to the birth of an affected child. In part this may be because affected children present before their parents, as exemplified by WILMS2, in which the mother and paternal aunt developed breast cancer after the boys had died. Thus, although a family history may be helpful in the identification of some biallelic *BRCA2* families, it will likely need to extend to at least three generations to detect the cancer history, particularly on the paternal side. The lack of clear diagnostic features of FA, an atypical cancer spectrum, and the absence of a strong family history of cancer suggest that a high index of suspicion may be required to identify children with biallelic *BRCA2* mutations.

ACKNOWLEDGEMENTS

We thank the members of WILMS2 for participating in the research and the many members of the Familial Wilms Tumour Collaboration and the Familial Breast Cancer Susceptibility Collaboration (UK) who have provided samples for this research. We thank David Betts for cytogenetic analyses in WILMS2 and Douglas F Easton for helpful discussions.

ELECTRONIC-DATABASE INFORMATION

The URL of the Breast Cancer Information Core database is <http://research.nhgri.nih.gov/bic/>

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This research was funded by the Institute of Cancer Research (UK) and by Cancer Research UK.

Conflict of interest: none declared.

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Received 18 May 2004

Revised version received 8 July 2004

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