Fanconi anaemia, *BRCA2* mutations and childhood cancer: a developmental perspective from clinical and epidemiological observations with implications for genetic counselling

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ABSTRACT

Fanconi anaemia (FA) is an inherited condition characterised by congenital and developmental abnormalities and a strong cancer predisposition. In around 3–5% of cases FA is caused by biallelic mutations in the *BRCA2* gene. Individuals heterozygous for *BRCA2* mutations have an increased risk of inherited breast and ovarian cancer. We reviewed the mutation spectrum in *BRCA2*-associated FA, and the spectrum and frequency of *BRCA2* mutations in distinct populations. The rarity of FA due to biallelic *BRCA2* mutations supports a fundamental role of BRCA2 for prevention of malignant transformation during development. The spectrum of malignancies seen associated with FA support the concept of a tissue selectivity of *BRCA2* mutations for development of FA-associated cancers. This specificity is illustrated by the distinct FA-associated *BRCA2* mutations that appear to predispose to specific brain or haematological malignancies. For some populations, the number of FA-patients with biallelic *BRCA2* disruption is smaller than that expected from the carrier frequency, and this implies that some pregnancies with biallelic *BRCA2* mutations do not go to term. The apparent discrepancy between expected and observed incidence of *BRCA2* mutation-associated FA in high-frequency carrier populations has important implications for the genetic counselling of couples with recurrent miscarriages from high-risk populations.

INTRODUCTION

Fanconi anaemia (FA) is an autosomal recessive and X-linked inherited condition characterised by congenital abnormalities, and an extreme increase in cancer predisposition.[1] FA cells show cross-linker sensitivity and cell-cycle perturbation, in particular in response to DNA damage. FA can be caused by mutations in at least 15 genes encoding for proteins that interact in a DNA damage response pathway active in replication and cross-linker repair.[1–3] These proteins play a fundamental role in the maintenance of DNA integrity with some of the key FA proteins operating downstream of the FA core protein complex, including BRCA2, the gene which is mutated in the 3–5% of FA cases (FA-D1 group).[4 5] Heterozygous mutations in genes of other downstream proteins, such as *FANCN/PALB2* and *FANCJ/BRIP1*, are associated with an increased risk of breast cancer, and mutations in *RAD51C* lead to an increased risk of ovarian cancer.[6–10] This DNA damage repair network links an uncommon, predominantly paediatric, disorder to familial breast and ovarian cancer. FA caused by biallelic mutations in *BRCA2* has been recognised to often have a severe phenotype, with more extensive congenital abnormalities and a particularly strong cancer predisposition where cancers typically develop in the first decade. This pattern is in contrast with the more 'classic' FA phenotype, which can be quite subtle, and does not typically present with cancer in the first decade, but leads to solid tumours, such as squamous cell carcinoma (SSC) from the second and more commonly the third decade onwards.[11 12] In this review, we summarise cancer-related features of biallelic *BRCA2* mutations with biological implications for BRCA2 function. As monoallelic mutations in *BRCA2* cause a high risk of dominantly inherited breast and ovarian cancer (HBOC), the *BRCA2* mutation spectrum and frequency has been determined in many populations.[13] Based on epidemiological data of the spectrum and incidence of *BRCA2* mutations in the general population and the *BRCA2* mutation spectrum associated with FA, we suggest some pragmatic guidelines for counselling couples at risk of a child with FA due to biallelic *BRCA2* mutations in high-frequency carrier populations.

FA-ASSOCIATED *BRCA2* MUTATIONS: IMPLICATIONS FOR BRCA2 FUNCTIONS DURING DEVELOPMENT

We have identified 31 FA patients in 23 pedigrees with confirmed biallelic pathogenic *BRCA2* mutations using PubMed with key words 'Fanconi anemia' and 'BRCA2'.[14–25] We have not included the individual who subsequently was found to have biallelic mutations in *FANCB* underlying the FA phenotype,[26] and individuals in whom identified variants in *BRCA2* subsequently were classified as likely benign. While this series is based on detailed reports of only a small number of cases, most of these individuals have an FA phenotype with multiple congenital abnormalities, which in at least six cases included a combination of features of the VACTERL spectrum (vertebra, anal, cardiac, oesophageal, renal and limb abnormalities).[14 20 21 25] Details of clinical features are listed in the online supplementary table S1. The spectrum of confirmed pathogenic mutations in *BRCA2* in these individuals is illustrated in figure 1. Common mutations in *BRCA2* are IVS7 splice site mutations,

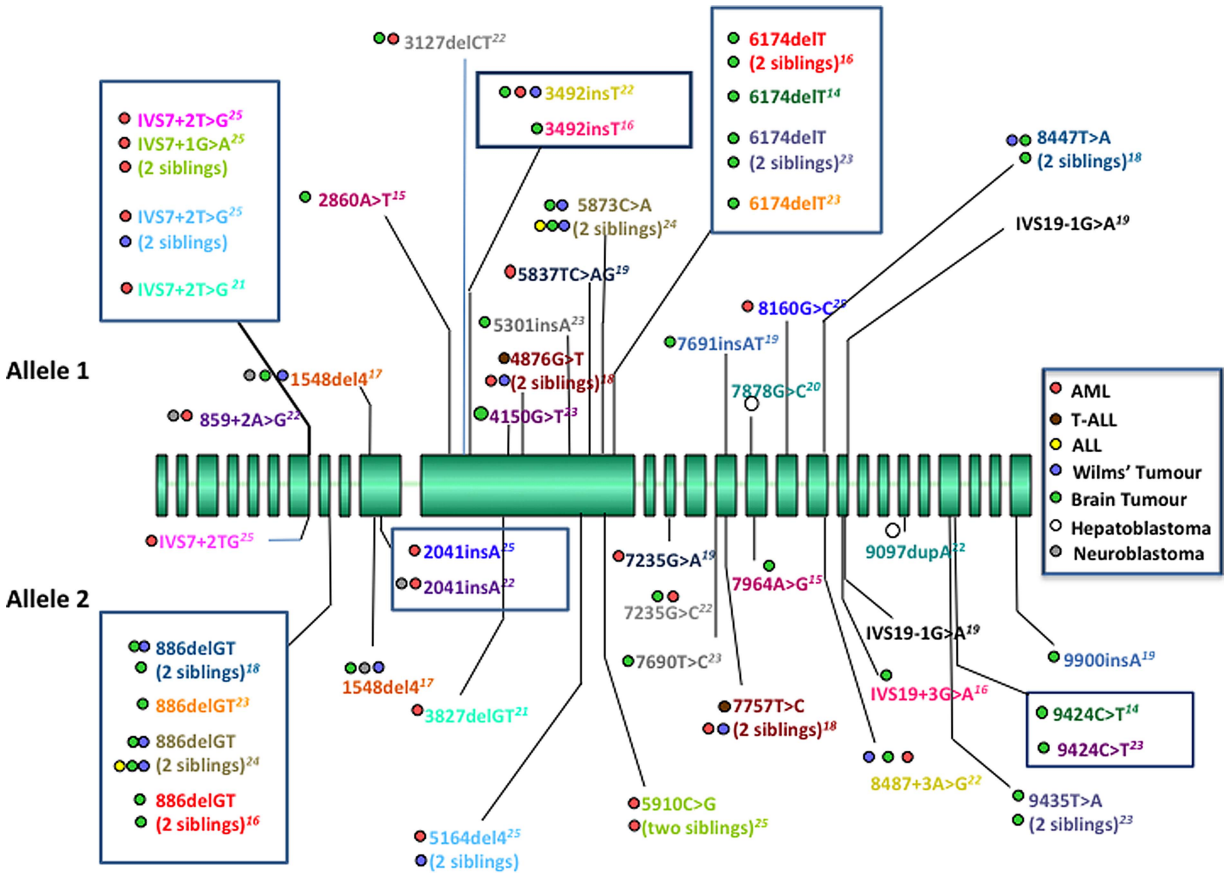

Figure 1 Spectrum of BRCA2 mutations associated with Fanconi anaemia (FA). Spectrum of BRCA2 mutations in FA (Refs.14–25). The individuals are colour coded with the mutation on one allele above the gene cartoon and the other below. Coloured dots indicate malignancies diagnosed in affected individuals. The most frequent mutations and those detected in more than one family are boxed and discussed in the text.

886delGT (c.658_659del) and the Ashkenazi Jewish (AJ) founder mutation 6174delT (c.5946delT). Additionally, the mutations 3492insT (c.3264dupT) and 9424C>T (c.9196C>T) have each been identified in two pedigrees. Only three *BRCA2* mutations have been recorded as homozygous in FA patients, IVS19-1 G>A (c.8487+1G>A),[19] a 1548del4 (c.1320_1323del) deletion in exon 10 in an Algerian child born to a consanguineous couple,[17] and the IVS7+2T>G mutation.[25] From the distribution of mutations across the *BRCA2* sequence, it is difficult to identify a distinct FA-associated cluster. Of these 31 patients, 30 developed cancer in the first 5 years of their lives. Only one patient (HSC63), who was homozygous for the carboxy-terminal mutation IVS19-1G>A[19] [26] has not been reported with cancer at an early age. The majority of malignancies associated with FA caused by biallelic *BRCA2* mutations are acute myeloid leukaemia (AML) and medulloblastoma (MB) and, in contrast with other forms of FA, the spectrum of malignancies in this group is much broader and also includes other embryonic tumours, such as neuroblastoma and hepatoblastoma, as well as one of the rarely reported cases of lymphoid leukaemias associated with FA. The severity of the cancer-predisposition phenotype is reflected in the occurrence of multiple malignancies in the first decade of life in seven individuals with biallelic *BRCA2* mutations. SSCs, which commonly develop in the third and fourth decades of life in other FA patients[11] [12] have not been reported in FA-D1 patients. The absence of reported SSC could be because FA-D1 patients do not survive long enough to develop SCCs. In this context, the distribution of the specific *BRCA2* mutation spectrum in FA-D1 patients has some important implications, in particular from a developmental perspective. The most common mutations in FA-D1 are IVS7 splice site mutations and the 886delGT mutation. IVS7 mutations were detected in four pedigrees, three of them being IVS7+2T>G. These mutations are thus over-represented in FA-D1 and confer fetal viability, probably through expression of splice variants that encode for BRCA2 proteins compatible with fetal viability,[27] but not with normal haematopoiesis after birth and leukaemia prevention as, strikingly, nearly all these patients develop AML. Conversely, none of the reported FA-D1 children with a brain tumour (which in most cases was a MB) has an IVS7 splice site mutation. The 886delGT mutation, which is predicted to result in a truncated protein, was detected in four families, two of whom also carried the 6174delT. The 886delGT mutation appears also to be compatible with fetal viability, but is associated with disruption and malignant transformation, in particular during brain development.

The 6174delT mutation, despite being relatively frequent in the AJ population,[28] has not been detected in the homozygous state and is, therefore, unlikely to confer BRCA2 function compatible with fetal viability in this state. While many common *BRCA2* mutations are located in exon 11, no FA patient homozygous or compound heterozygous for biallelic exon 11 mutations has been reported to date (figure 1). Additional circumstantial evidence supporting the notion of exon 11 mutations being incompatible with fetal viability comes from a study of miscarriages in *BRCA2* mutation carriers which found a frequency of recurrent (three or more) miscarriages among 9/210

Table 1 Suggested guidelines for genetic counselling of *BRCA2* mutation carriers

Scenario		Risk of an affected child with FA due to biallelic *BRCA2* mutations	Suggested management
Partner 1	Partner 2		
AJ *BRCA2* 6174delT+	AJ	Hypothetical risk No recorded cases with biallelic 6174delT mutations. Possibly higher risk of miscarriages.	Consider testing for AJ *BRCA1/BRCA2* founder mutations in the partner, but limited indication for PND if partner also carries 6174delT. Consider offering full *BRCA2* to the partner if their family history is suggestive of HBOC although non-founder mutations are infrequent in the AJ population.[45] Consider screening for the AJ *FANCC* founder mutation.
Non-AJ *BRCA2*+	AJ	Potential risk—1 in 400 or less. Combination may be embryonic lethal if non-AJ mutation in exon 11.	Consider offering testing for AJ *BRCA1/BRCA2* founder mutations to the partner. Offer PGD/PND if the non-AJ partner carries a mutation.
Non-AJ *BRCA2*+	Non-AJ	Potential risk (will depend on whether this is a population with founder mutations). Combination may be embryonic lethal if both mutations in exon 11.	Consider offering *BRCA2* testing to the partner if their family history is suggestive of HBOC. Offer PGD/PND if the partner carries a mutation.

Schematic guidelines for the risk assessment and management with respect to Fanconi anaemia and pregnancy outcome of BRCA2 mutation carriers.
AJ, Ashkenazi Jewish; FA, Fanconi anaemia; HBOC, hereditary breast and ovarian cancer; PGD, preimplantation genetic diagnosis; PND, prenatal diagnosis;

(4.3%) Jewish *BRCA2* carriers compared to 0/110 Jewish non-carrier controls (p=0.03).[29] The finding of an Algerian child homozygous for the 1548del4 mutation in exon 10 implies that this mutation is compatible with fetal viability, but grossly affects normal development.[17] The distinct association of some FA-associated mutations with brain or haematological malignancies suggests the possibility of tissue specificity of *BRCA2* functional disruption in that the presence of specific *BRCA2* mutations might be as important as loss of BRCA2 for developmental disruption and malignant transformation also during early childhood. Tissue specificity has also been discussed in the context of *BRCA2*-associated pancreatic cancer.[30]

SPECTRUM AND INCIDENCE OF *BRCA2* MUTATIONS IN NON-FA POPULATIONS

Data on the spectrum and incidence of *BRCA2* mutations are available for numerous populations and distinct ethnic groups.[28 31–38] In many populations, this corresponds to the reported birth frequency of *BRCA2* mutation carriers of one in 667 that we detected in the Northwest region of England.[37] Common mutations in *BRCA2* encountered in the general population or in cohorts with familial breast cancer of specific populations are not reflected in the spectrum of *BRCA2* mutations detected in FA patients with the exception of the 6174delT mutation, which is found with a high frequency in AJ breast cancer families,[28] while the more frequent FA-associated *BRCA2* mutations 886delGT and IVS7+2T>G are not encountered in high frequency in the general population.[36] Specific *BRCA2* founder mutations have been found in several European populations[31] and other distinct ethnic groups, such as the Afrikaner population in South Africa where c.7934delG is carried by 1 in 200 individuals. In the Icelandic population, 0.5% carry the 999del5 mutation (c.771_775del5),[39 40] and as many as 1.4% of the AJ population carry the 6174delT mutation,[28] which would mean that in AJ populations as many as 1 in 19 600 births would be predicted to have FA as a result of homozygous 6174delT mutations if this combination were viable.

INCIDENCE OF FA IN POPULATIONS WITH DEFINED *BRCA2* MUTATION CARRIER FREQUENCY

In the Northwest region of England we have a reasonably robust estimate of the frequency of BRCA2 mutations from a population-based study of breast cancer of one in 667 and have determined the spectrum and incidence of *BRCA2* mutations.[37 38 41] In the same region during the period from 1990 to 2012, there have been 28 children from 20 families diagnosed with FA (S Meyer, K Chandler and DG Evans, unpublished data). FA cases were from consanguineous Asian in 10 families, and Arabic backgrounds in one family. Only the Arabic family was not of resident origin in the region for more than 20 years. Among the 28 children only two had a severe phenotype with multiple congenital abnormalities and severe bone marrow failure and/or leukaemia or brain tumour in the first 5 years of life, which can be the characteristic phenotype for FA-D1 patients.[42] One of these cases was a boy of consanguineous Asian background with a homozygous *FANCF* mutation (c.496C>T, Q116X) (S Meyer, unpublished data). The second case of severe phenotype FA was a Caucasian British boy who had biallelic *BRCA2* mutations. We have previously reported this case with the *BRCA2* mutations IVS7+2T>G (c.631+2T>G) and 3827delGT (c.3599_3600delGT) who was diagnosed with AML at the age of 2 years.[21] Other FA patients in our region had mutations in *FANCA*, *FANCG* and *FANCD2*.[43] As our centre provides tertiary services for approximately 10% of the UK population, we extrapolate that there have been approximately 250–300 cases with FA in the last 20 years in the UK. In line with the incidence in our region, and from reported frequency of FA-D1 patients, we presume that less than 5% of these carry biallelic *BRCA2* mutations. In Iceland, where the *BRCA2* 999del5 mutation is responsible for a large proportion of familial breast cancer and is carried by 0.5% of people, FA has not been diagnosed in the last 20 years (R Dietrich, ÓG Jónsson, personal communication).

Given the incidence and spectrum of *BRCA2* mutations in FA and the general population, and the relative high incidence of specific mutation in distinct populations, we speculate that biallelic *BRCA2* mutations might be responsible for neonatal deaths in some children with multiple abnormalities before the diagnosis of FA is made, or are simply not compatible with embryonic survival. Another possibility is that an early childhood malignancy is the main feature of FA in cases caused by biallelic *BRCA2* mutations, and the diagnosis of FA is not considered. Childhood cancer as the first manifestation of BRCA2 mutation-associated FA would, in theory, result in a higher incidence of childhood cancer in offspring of BRCA2 carriers. However, no increased incidence of childhood cancer has been reported in a retrospective analysis of *BRCA2* mutation carriers.[44] It would be important to collect data prospectively in order to determine the impact of *BRCA2* mutations on fertility, neonatal death associated with developmental defects, and childhood malignancies.

IMPLICATIONS FOR GENETIC COUNSELLING

The observations described here are relevant for the genetic assessment of couples from populations with a high incidence of *BRCA2* mutations. It is possible that a significant proportion of pregnancies with biallelic *BRCA2* mutations might not go to term, and it might be pertinent to explore the *BRCA2* mutation carrier status in couples with recurrent miscarriages who are from populations with high *BRCA2* mutation carrier frequencies.

It has been 10 years since the first clinical cases of FA due to biallelic *BRCA2* mutations were reported,[23] and we believe there is enough information available to develop and consider pragmatic guidelines to assist with the genetic counselling of *BRCA2* families (table 1). Specifically, the absence of reported cases of FA who are homozygous for the AJ 6174delT *BRCA2* founder mutation is a strong indication that this state is embryonic lethal. In other clinical scenarios, the ever-decreasing cost of *BRCA2* mutation testing by next-generation sequencing means that it is becoming realistic to consider testing in the partner of a *BRCA2* carrier, even if they do not belong to a known founder population. However, this must be undertaken by experienced genetic counsellors and geneticists as there is potential to generate harm and uncertainty, for example, if a variant of unknown significance is identified.

In summary, from epidemiological data, we speculate that many pregnancies with biallelic *BRCA2* mutations do not go to term. This might be relevant for the genetic assessment of couples from populations with a high frequency of *BRCA2* mutations. On the basis of this we have developed some pragmatic guidelines to aid counselling in at-risk families. Additionally, the spectrum of malignancies in FA caused by *BRCA2* disruption implies a pleiotropic role of *BRCA2* for organogenesis, in particular, haematopoiesis and brain development.

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Interactive multiple choice questions

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Code		Mutation 1	Mutation 2	Clinical features	Age and type of Cancer	*Outcome*	*Ref*
HSC62	**M**	**IVS19-1 G>A**	**IVS19-1 G>A**	Abnormal thumb (limited clinical description)	None at 30 years	No details reported	***Howlett et al***
EUFA579	**F**	**7235G _ A (p.R2336H)**	**5837TC _ AG (p.F1807X)**	Pigmented, abnormal thumb (limited clinical description*)	AML, 2 years	No details reported	***Howlett et al***
EUFA423	**F**	**7691/insAT [R2488fs]**	**9900/insA**	Pigmented, abnormal thumb, bone marrow failure (limited clinical description)	Brain, 3 years	No details reported	***Howlett et al***
AP37P	**M**	**8415G RT K2729N**	**8732C RA [S2835X]**	Short, pigmented, cafe´ au lait, abnormal thumb, Sprengel deformity, midfacial hypoplasia	AML, 2 years	Died of AML age 3	***Howlett et al Ikdeda et al***
1A	**M**	**6174delT**	**9435T>A [C3069X]**	Short, cafe´-au-lait, pigmented, abnormal thumbs and radii, microcephaly, imperforate anus, epicanthal folds, micropenis, undescended testes, dislocated hips, hydronephrosis, abnormal hearing (VATER*)	Brain tumour medulloblastoma or astrocytoma, 4.9 years	Died of tumor age 5	***Offit et al***
1B	**M**	**6174delT**	**9435T>A [C3069X]**	Short, abnormal thumbs, microcephaly, imperforate anus with rectovaginal fistula, slanted eyes, anomalous kidneys, small ear, hip dysplasia (VATER*)	Astrocytoma 2 years,	Died of tumour age 2	***Offit et al***
2	**F**	**6174delT**	**886delG**	No detailed clinical features reported	Medulloblastoma, 4.5 years	No details reported	***Offit et al***
3	**F**	**5301insA**	**7690T RC [I2490T**	No detailed clinical features reported	Medulloblastoma 2.5 years	No details reported	***Offit et al***
4	**F**	**4150G>T [E1308X]**	**9424C>T [Q3066X]**	No detailed clinical features reported	Medulloblastoma, 3.5 years	No details reported	***Offit et al***
K1S1	**M**	**886delGT**	**8447T RA [L2740X]**	Cafe´ au lait, microcephaly, Cardiac malformation	Medulloblastoma, 2.3 years	Died of treatment toxicity	***Hirsch et al***

K1S2	**M**	**886delGT**	**8447T RA [L2740X]**	Cafe´ au lait, abnormal facies, epicanthus (limited clinical description)	M Wilms' tumour, 1.3 years Medulloblastoma, 4.3 years	Died of progressive medulloblastoma	***Hirsch et al***
K2S1	**M**	**4876G RT [E1550X]**	**7757T RC [L2510P]**	Short, microcephaly (limited clinical description)	M Wilms' Tumour, 0.5 years, AML, 2 years	Died of refractory AML and toxicity age 2	***Hirsch et al***
K2S2	**F**	**4876G RT [E1550X]**	**7757T RC [L2510P]**	Short, pigmented, bifid thumb, elfin facies, small palpebral fissures	T-ALL, 4.9 years	remission from T-Cell leukaemia age 5, no further outcome reported	***Hirsch et al***
129/1	**Not reported**	**IVS7+2T>G**	**IVS7+2T>G**	Short, IUGR, cafe´ au lait, microcephaly, imperforate anus	AML, 2.2 years	Died of refractory AML	***Wagner et al***
357/1 A	**Not reported**	**8106G RC [W2626C]**	**2041insA**	Short, hypoplastic thumb, imperforate anus	AML, 1.9 years	Died of refractory AML	***Wagner et al***
632/1	**F**	**IVS7+1G>A**	**5910C RG [Y1894X]**	Short, cafe´ au lait, dysplastic hips, pelvic kidney	AML, 3 years	Died of refractory AML	***Wagner et al***
632/2	**F**	**IVS7+1G>A**	**5910C RG [Y1894X]**	Short, imperforate anus, hypoplastic thumb	AML, 21 months	Refractory AML, alive 6 at 6 months follow up. No further outcome reported.	***Wagner et al***
800/1	**M**	**IVS7+2T >G**	**5164del4**	IUGR, microcephaly, FTT, micropenis, cafe´ au lait spots	AML, 0.9 years	Died of refractory AML	***Wagner et al***
800/2	**M**	**IVS7+2T >G**	**5164del4**	IUGR, microcephaly, cafe´ au lait spots, FTT	Wilms' Tumour 0.8 years	Alive 9 months follow up. No further FU reported	***Wagner et al***
RB		**886delTG**	**5873C RA [S1882X]**	Short, pigmented, cafe´ au lait spots, microcephaly, cryptorchidism	Wilms' Tumour 3.5 years, glioblastoma	Died age 10 of brain tumour	***Reid et al***

					multiforme, 9 years		
CB		**886DelTG**	**5873C RA** **[S1882X]**	cafe´ au lait spots (limited clinical description)	Wilms' (0.6), Brain— medulloblastoma (6), B-ALL (10)	Died age 12 of progressive medulloblastoma	***Reid et al***
SB1690CB		**IVS7+2T>G**	**3827delGT**	Hypermobile thumb, microcephaly, imperforate anus, deafness, renal dysplasia, midfacial hypoplasia (VATER*)	AML 2.1 years	Died of progressive AML age 2	***Meyer et al***
NCI 1		**6174delT**	**9424C RT** **[Q3066X]**	Short, cafe´ au lait, microcephaly, facial dysmorphism, abnormal thumbs, anterior anus, cloudy corneas, ectopic kidneys, delayed development, hydrocephaly (VATER*)	Medulloblastoma, 3.1 years	Not reported	***Alter et al***
P5		**c.2860 A>T**	**c.7964 A>G**	Dislocated hips, facial abnormalities, café au lait spots, growth retardation	Medulloblastoma, 3.5 years	Died of progressive medulloblastoma age 5	***Bodd et al***
PT2		**1548del4**	**1548del4**	Short, pigmented, cafe´ au lait,spots, adducted thumbs, microcephaly, sacral hemivertebra, ventricular septal defect, pelvic kidney, oesophageal atresia, micrognathia, CNS gyrations, congenital cataract (VATER*)	Nephroblastoma, Bilat. Neuroblastoma, Posterior fossa tumour before 1.5 years	Died age 16 months	***Faivre et al***
1703		**c.7878G>C (p.W2626C)**	**c.9097dupA p.T3033NfsX10**	vertebral, anal, cardiac, tracheal, renal and limb anomalies with hydrocephalus. VACTERL-H	Hepatoblastoma, 4 years	Died of treatment complications age 4	***Kopic et al***
Pt 1	**11**	**g.3492insT (c.3264dupT)**	**g.8715þ3A>G (c.8487þ3A>G)**	Microcephaly; esotropia; cerebellar hypoplasia; arachnoid cyst; abnormal radii and thumbs; clinodactyly; FTT; cafe´ au lait spots	Bilateral Wilms' Tumour , 1 year myelodysplasia 2 years, , medulloblastoma 2 years	*Died of progressive medulloblastoma age 3*	***Myers et al***
Pt 2	**15**	**g.2041insA (c.1813dupA),**	**g.859þ2A>G (c.631þ2T>G**	Intestinal duplication cysts/mesenteric lymphangioma jejunum; FTT; microcephaly; cafe´ au lait spots; ear anomalies; bilateral clinodactly	Neuroblastoma stage IIb , 17 months, AML 20 months	*Died of refractory AML*	***Myers et al***
Pt 3	**2**	**g.3127delCT**	**g.7235G>C**	Holoprosencephaly; microcephaly; TEF; FTT; ear anomalies;	Differentiating	*Died of refractory*	***Myers et al***

		(c.2899-2900delCT)	**(c.7007G>A)**	sensineural hearing loss; pelvic kidneys; optic anomalies; polydactyly; cafe´ au lait spots; congenital nevus	neuronal neoplasm 21 months , MDS/ AML 24 months	*AML*	
ID12 S1		**6174delT**	**886delGT**	No features reported	Medulloblastoma, 21 months	*Alive 23 moths from diagnosis, no further follow up reported*	***DeWire et al***
ID12 S2		**6174delT**	**886delGT**	No features reported	Medulloblastoma, 15 moths	*Died*	***DeWire et al***
ID 13		**3492insT**	**IVS19+3A>G**	No features reported	Medulloblastoma, 24 months	*Died*	***DeWire et al***