



# *DICER1* syndrome: clarifying the diagnosis, clinical features and management implications of a pleiotropic tumour predisposition syndrome

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## ABSTRACT

**Background** Constitutional *DICER1* mutations were recently reported to cause familial pleuropulmonary blastoma (PPB).

**Aim** To investigate the contribution and phenotypic spectrum of constitutional and somatic *DICER1* mutations to cancer.

**Methods and results** The authors sequenced *DICER1* in constitutional DNA from 823 unrelated patients with a variety of tumours and in 781 cancer cell lines. Constitutional *DICER1* mutations were identified in 19 families including 11/14 with PPB, 2/3 with cystic nephroma, 4/7 with ovarian Sertoli–Leydig-type tumours, 1/243 with Wilms tumour (this patient also had a Sertoli–Leydig tumour), 1/1 with intraocular medulloepithelioma (this patient also had PPB), 1/86 with medulloblastoma/infratentorial primitive neuroectodermal tumour, and 1/172 with germ cell tumour. The inheritance was investigated in 17 families. *DICER1* mutations were identified in 25 relatives: 17 were unaffected, one mother had ovarian Sertoli–Leydig tumour, one half-sibling had cystic nephroma, and six relatives had non-toxic thyroid cysts/goitre. Analysis of eight tumours from *DICER1* mutation-positive patients showed universal retention of the wild-type allele. *DICER1* truncating mutations were identified in 4/781 cancer cell lines; all were in microsatellite unstable lines and therefore unlikely to be driver mutations.

**Conclusion** Constitutional *DICER1* haploinsufficiency predisposes to a broad range of tumours, making a substantial contribution to PPB, cystic nephroma and ovarian Sertoli–Leydig tumours, but a smaller contribution to other tumours. Most mutation carriers are unaffected, indicating that tumour risk is modest. The authors define the clinical contexts in which *DICER1* mutation testing should be considered, the associated tumour risks, and the implications for at-risk individuals. They have termed this condition ‘*DICER1* syndrome’.

**Accession numbers** The cDNA Genbank accession number for the *DICER1* sequence reported in this paper is NM\_030621.2.

## INTRODUCTION

*DICER1* is an RNase endonuclease essential in the production of microRNAs (miRNAs), which are non-protein-coding small RNAs that are estimated to regulate the expression of over 30% of protein-coding genes at the post-transcriptional level.<sup>1,2</sup> miRNAs are transcribed as long precursors, known as pri-miRNAs, which are processed in the nucleus to produce pre-miRNAs.<sup>3</sup> The pre-miRNAs are exported to the cytoplasm, where *DICER1* processing generates a double-strand miRNA duplex.<sup>4</sup> The duplex is unwound to generate the final miRNA, which interacts with mRNA to regulate gene expression, typically through translational repression or mRNA degradation.<sup>2,5,6</sup>

Over 900 human miRNAs are currently recognised.<sup>7,8</sup> These have been implicated in a wide range of biological processes including metabolism, morphogenesis, cell fate determination, cell proliferation and apoptosis.<sup>9,10</sup> There is increasing evidence implicating dysregulation of miRNAs in several human diseases, including cancer.<sup>11,12</sup> Widespread alteration of miRNA levels is seen in cancers, and miRNA profiles characteristic of cancer type and stage are increasingly recognised.<sup>12,13</sup> Furthermore, global downregulation of miRNAs due to abrogation of miRNA processing has been shown to promote tumorigenesis.<sup>14</sup>

Recently, germline-inactivating *DICER1* mutations were shown to cause familial pleuropulmonary blastoma (PPB, OMIM 601200), a rare malignant lung tumour, primarily affecting children before age 6.<sup>15,16</sup> By linkage analysis, Hill *et al* mapped a familial PPB gene to chromosome 14q. They considered *DICER1* to be a promising candidate and identified pathogenic mutations in 11 families.<sup>15</sup> This important finding raises a number of questions. First, what is the contribution of *DICER1* mutations to non-familial, sporadic PPB? Mutations in some cancer-predisposition genes contribute appreciably to both familial and sporadic forms of disease, whereas for others the contribution to non-familial cases is small. Second, do constitutional *DICER1* mutations predispose to tumours other than PPB? The International PPB Registry has collected information from over 200

PPB families, and a variety of different tumours have been reported in PPB cases and/or their relatives<sup>17 18</sup> However, it is unknown which tumour types are genuinely associated with PPB, which are related to *DICER1* mutations, and which reflect ascertainment. Third, do somatic *DICER1* mutations contribute to cancer? This is of particular interest as it has been proposed that somatic 14q loss, which has been reported in many cancers, may be targeted at *DICER1*.<sup>19–21</sup>

To address these questions, we have conducted exhaustive *DICER1* sequencing, in >1600 patient samples, including constitutional DNAs from 823 individuals with a broad range of tumours, but particularly focusing on tumours that have been proposed to be associated with PPB ([http://www.ppbregistry.org/pdf/Doc\\_D.pdf](http://www.ppbregistry.org/pdf/Doc_D.pdf)) (table 1). We also sequenced *DICER1* in DNA from 781 cancer cell lines to assess the impact of somatic *DICER1* mutation on cancer development (online supplementary table 1).

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## METHODS

### Samples

Constitutional DNA was extracted from EDTA venous blood samples and collected through the Factors Associated with Childhood Tumours (FACT) Study, the Royal Marsden Hospital cancer collections, and the Institute of Cancer Research UK-wide testicular germ cell tumour collections, all of which have been approved by an appropriate ethics board. All samples were obtained with full informed consent. The research was undertaken as part of the FACT Study, which was approved by the London Multicentre Research Ethics Committee (05/MRE02/17). The FACT Study aims to identify genetic factors that predispose to the development of childhood tumours (<http://www.icr.ac.uk/fact>). The National Registry of Childhood Tumours was used to identify the total number (indicated in parentheses) of cases nationally for PPB (20, five of whom were deceased), cystic nephroma (15, none deceased) and Sertoli–Leydig cell tumours (seven, none deceased) that had been registered since its inception in 1962. The clinicians were contacted to request that they recruit these patients to the FACT Study. In addition, a small minority of patients referred to our clinical genetics service with these tumours were recruited directly. Tumour DNA from *DICER1* mutation-positive paraffin-embedded tissues was extracted using QIAamp DNA FFPE Tissue kit (Qiagen) according to the manufacturer's instructions. We analysed whole-genome amplified DNA from 781 cancer cell lines as part of the Cancer Genome Project, Cell Line Project (online supplementary table 1).

### *DICER1* sequencing

For analysis of the constitutional DNA, we designed PCR primers to amplify the 26 coding exons and intron–exon boundaries of *DICER1* in a multiplex PCR (online supplementary table 2). Products were sequenced by capillary sequencing using the BigDye Terminator Cycle Sequencing Kit and an ABI3730 Genetic Analyser (Applied Biosystems, Foster City, California, USA). Sequences were analysed using Mutation Surveyor software V.3.20 (SoftGenetics). We only included samples in which at least 90% or more of the coding sequence was successfully screened in subsequent analyses. For the cancer cell lines, PCR primers that amplify 500 bp PCR products encompassing the 26 coding *DICER1* exons and intron–exon boundaries were designed and sequenced as described above. Sequence traces were analysed using AutoCSA software,<sup>22</sup> followed by manual inspection of putative variants. All putative variants were confirmed by bidirectional sequencing of a second independently amplified PCR product. Matched normal cell lines were available for 40 cell lines. The somatic status of variants identified in these 40 cell lines was determined by sequencing DNA from the corresponding normal. In the remaining cell lines, we assumed that cell line variants that were also identified in the constitutional DNA screen were not somatic. We evaluated the likely pathogenicity of sequence variants using Polyphen, SIFT and NNSplice software.

## RESULTS

### Germline *DICER1* mutation analysis

We identified pathogenic mutations in 19/823 index individuals (table 2 and online supplementary figure 1). Seventeen

**Table 1** Tumours in individuals screened for constitutional *DICER1* mutations

Tumour type	No of cases	No with <i>DICER1</i> mutation
Lung tumours		
Pleuropulmonary blastoma	14	11
Congenital lung cyst	1	
Sex cord stromal tumours		
Testicular Sertoli–Leydig/Sertoli/Leydig tumour	11	
Ovarian Sertoli–Leydig tumour	6	3
Ovarian granulosa cell tumour	6	
Gonadal stromal cell tumour unclassified	5	
Mixed stromal cell tumour	1	
Stromal sex cord tumour unclassified	1	1
Renal tumours		
Wilms tumour	243	1*
Cystic nephroma	3	2
Clear cell sarcoma	3	
Central nervous system tumours		
Medulloblastoma/infratentorial PNET	84	1
Eye tumours		
Medulloepithelioma (dictyoma)	1	1†
Germ cell tumours		
Seminoma	71	1
Non-seminoma (testis)	52	
Mixed testicular cancer	14	
Embryonal carcinoma	13	
Testicular cancer unspecified	12	
Teratoma	10	
Dysgerminoma/germinoma	8	
Yolk sac tumour	4	
Gonadoblastoma	1	
Neuroblastoma		
Thyroid carcinoma	73	
Papillary thyroid carcinoma	51	
Follicular thyroid carcinoma	18	
Thyroid cancer unspecified	15	
Anaplastic thyroid carcinoma	4	
Soft tissue and other extraosseous sarcomas		
Rhabdomyosarcoma	19	
Fibrosarcoma	7	
Other soft tissue sarcomas	49	
Malignant bone tumours		
Ewing sarcoma	8	
Osteosarcoma	7	
Chondrosarcoma	4	
Hepatic tumours		
Hepatoblastoma	2	
Hepatocellular carcinoma	2	

\*This patient also had ovarian Sertoli–Leydig cell tumour.

†This patient also had pleuropulmonary blastoma. PNET, primitive neuroectodermal tumour.

**Table 2** Probands and relatives with constitutional *DICER1* mutations

ID	Phenotype	Age at diagnosis (years)	Current age (years)
<b>Family 1 - c.4403_4406delCTCT</b>			
Proband	Pleuropulmonary blastoma	1.5	5
Parent	None		40
Uncle	None		44
Grandparent	None		68
<b>Family 2 - c.1716delT</b>			
Proband	Pleuropulmonary blastoma	0.8	2
Parent	None		36
<b>Family 3 - c.1196_1197dupAG</b>			
Proband	Pleuropulmonary blastoma	4	5
Parent	None		30
Aunt	None		26
Grandparent	None		62
<b>Family 4 - c.3505delT</b>			
Proband	Pleuropulmonary blastoma	3	3
Sibling	None		12
Parent	None		36
<b>Family 5 - c.1966C&gt;T p.R656X</b>			
Proband	Pleuropulmonary blastoma	7	12
Parent	None		52
<b>Family 6 - c.2268_2271delTTTG</b>			
Proband	Pleuropulmonary blastoma	0.9	1
Parent	None		38
<b>Family 7 - c.3665delT</b>			
Proband	Pleuropulmonary blastoma*	4.2	died 5.2
Parent	None		36
<b>Family 8 - c.3583_3584delGA</b>			
Proband	Pleuropulmonary blastoma	1.3	7
	Intraocular medulloepithelioma	6	
parent	None		29
<b>Family 9 - c.2040+1 G&gt;C</b>			
Proband	Pleuropulmonary blastoma	3	13
Parent	Thyroid cysts unclassified	25	38
<b>Family 10 - c.3726C&gt;A p.Y1242X</b>			
Proband	Pleuropulmonary blastoma	4	15
Parent	Thyroid cysts unclassified	30	37
<b>Family 11 - c.5465A&gt;T p.D1822V†</b>			
Proband	Pleuropulmonary blastoma	1.8	9
Parent	Thyroid cysts unclassified	20	40
<b>Family 12 - c.3288_3289insTTTC</b>			
Proband	Cystic nephroma	1.5	11
Half-sibling	Cystic nephroma	0.8	5
Parent	Multinodular colloid goitre	25	39
<b>Family 13 - c.328_338dupGTGTCAGCTGT</b>			
Proband	Cystic nephroma	3	5
Parent	Multinodular colloid goitre	20	35
	Thyroglossal duct cyst	30	
Grandparent	Thyroid cysts unclassified	7	66
Great-aunt	None		59
<b>Family 14 - c.5122_5128delGGAGATG</b>			
Proband	Ovarian Sertoli–Leydig cell tumour L	17	35
	Ovarian Sertoli–Leydig cell tumour R	27	
Parent	Ovarian Sertoli–Leydig cell tumour R	21	71
	Melanoma	50	
	Endometrial cancer	62	
	Breast cancer	68	
<b>Family 15 - c.1966C&gt;T p.R656X</b>			
Proband	Ovarian Sertoli–Leydig cell tumour R	12	17
	Ovarian Sertoli–Leydig cell tumour L	14	
Parent	None		50

Continued

**Table 2** Continued

ID	Phenotype	Age at diagnosis (years)	Current age (years)
<b>Family 16 - c.3793delA</b>			
Proband	Ovarian sex cord stromal tumour R	6	9
Parent	None		29
<b>Family 17 - c.2988-2_2988-1delAGinsCT</b>			
Proband	Wilms tumour	8	15
	Multinodular thyroid goitre unclassified	9	
	Ovarian Sertoli–Leydig cell tumour R	12	
	Ovarian Sertoli–Leydig cell tumour L	12	
Parent	None		40
<b>Family 18 - c.1153delC</b>			
Proband	Medulloblastoma/infratentorial PNET	13	18
<b>Family 19 - c.4740G&gt;T p.Q1580H</b>			
Proband	Seminoma	32	46

\*Individual deceased, no sample available.

†This family includes a sibling with neuroblastoma; no sample available.

mutations led to premature protein truncation as a result of frameshift, nonsense or consensus splice-site mutations. Two mutations are missense alterations, for which there is substantial evidence of pathogenicity. First, they are the only two missense alterations in the 3214 chromosomes screened that are predicted to be pathogenic by SIFT and Polyphen. Second, both target highly conserved residues in the RNase III domain. Third, they are in the vicinity of a missense variant identified by Hill *et al*, which resulted in a similar *DICER1* histochemical profile to truncating mutations.<sup>15</sup> We also identified several non-pathogenic variants including nine missense variants, 23 synonymous variants, and five intronic variants (online supplementary table 3).

### Pleuropulmonary blastoma

We identified *DICER1* mutations in 10 individuals with PPB and in the mother of a child that had died from PPB but from whom no sample was available. One child developed an intraocular medulloepithelioma 4 years after PPB. Three-generational pedigrees were available for most cases, and no relative had PPB. One sibling died from neuroblastoma; her *DICER1* status is not known, but a mutation was present in her mother. There were three children with PPB, in whom we did not identify a *DICER1* mutation.

### Cystic nephroma

The most common reported association of PPB is cystic nephroma,<sup>17</sup> a rare benign renal tumour that typically presents as a multicystic renal mass without solid nodules. It has a bimodal incidence with 50% occurring in children less than 4 years and 30% in the 5th and 6th decades.<sup>23</sup> We had DNA from three unilateral childhood cases, and in two we identified truncating *DICER1* mutations. One of the children had a half-sibling with cystic nephroma who also has the mutation. The child in the second *DICER1* mutation-positive case was recently found to have a small lung cyst, which is being monitored but has not had histological evaluation.

### Ovarian Sertoli–Leydig tumours

We analysed DNA from 30 individuals with sex cord tumours, of which six were ovarian Sertoli–Leydig tumours, which are sex cord tumours that exhibit testicular differentiation.<sup>24</sup> The age range of diagnosis is 2–75 years, but ~75% present in the

second or third decades.<sup>24</sup> We identified truncating *DICER1* mutations in four individuals; three had young-onset bilateral ovarian Sertoli–Leydig tumours, and one had a unilateral ovarian sex cord tumour that could not be further classified because of necrosis. In one of the bilateral cases, Wilms tumour was previously present (see below). The mother of one patient had also developed a Sertoli–Leydig tumour at 21 years and carried the *DICER1* mutation. She has subsequently had melanoma at 50 years, endometrial cancer at 62 years, and breast cancer at 68 years.

#### Wilms tumour

Wilms tumour is an embryonal cancer of the kidney that affects ~1 in 10 000 children, usually before the age of 6 years.<sup>25–26</sup> We analysed DNA from 243 patients with Wilms tumour. We identified one truncating *DICER1* mutation, in a child who developed Wilms tumour of atypical histology at the unusually late age of 8 years. Four years after treatment the child developed bilateral ovarian Sertoli–Leydig cell tumours.

#### Medulloblastoma/infratentorial primitive neuroectodermal tumour (PNET)

Medulloblastoma is a PNET that arises in the posterior fossa.<sup>27</sup> We analysed 84 childhood medulloblastoma/infratentorial PNET cases and identified one truncating mutation in a child of 13 years. No other information or samples were available.

#### Seminoma

We analysed DNA from 185 individuals with germ cell tumour, of which 128 had a family history of testicular cancer. We identified one missense *DICER1* mutation, Q1580H. A maternal first cousin once removed of this proband developed testicular cancer at 27 years, but the proband's mother does not carry the *DICER1* mutation. It is not possible to conclusively establish whether this mutation is pathogenic on the available evidence.

#### Intraocular medulloepithelioma

Intraocular medulloepithelioma, also known as dictyoma, is a very rare embryonal tumour, usually originating in the ciliary body of the eye, which most commonly occurs during childhood.<sup>28</sup> One child with PPB also developed a dictyoma and has a *DICER1* mutation.

#### Thyroid non-toxic goitres/cysts

In the PPB Registry, thyroid cancers and thyroid hyperplasia are reported in both probands and relatives of PPB cases. We analysed DNA from 88 patients with thyroid cancer, but did not identify any mutations. However, one proband and six relatives of *DICER1* mutation-positive individuals developed thyroid cysts/multinodular colloid goitre between the ages of 9 and 30 years. All were non-toxic, associated with normal thyroid function, and non-malignant. Thyroidectomy was required in four patients because of recurrent disease.

#### Other tumours/cysts

We did not identify mutations in any of the other tumour types as detailed in table 1.

#### Family studies in *DICER1* mutation-positive individuals

We had samples from both parents in 17 families in which a *DICER1* mutation had been identified in an index individual. In each, the mutation had been inherited (table 2). We had grandparental samples for five families. In two families, the mutation was absent in the respective grandparents, indicating that the

mutation had arisen de novo in the parent. In the other three families, the mutation was present in a grandparent.

We analysed DNA from 51 relatives, and we identified 25 relatives with *DICER1* mutations. Of these, as described above, one mother had a Sertoli–Leydig tumour, one half-sibling had cystic nephroma, and six relatives had thyroid cysts/goitre. The remaining 17 individuals did not have clinical features or symptoms likely to be related to the *DICER1* mutation, one relative having muscular dystrophy and another Wegener's granulomatosis.

#### Analysis of tumours from *DICER1* mutation-positive individuals

We obtained eight tumours from six *DICER1* mutation-positive individuals. This included three PPB, four Sertoli–Leydig tumours, and one cystic nephroma. We analysed each tumour for the relevant mutation. Each was heterozygous for the mutation—that is, the tumour showed a similar mutational profile to that in the blood and there was no loss of the wild-type allele in any tumour.

#### *DICER1* mutation analysis in cancer cell lines

We screened 781 cancer cell lines (online supplementary table 1) for *DICER1* mutations. These represent an extensive cross-section of cancers, but do not include many of the cancers in which we identified germline *DICER1* mutations. Two hundred and six of the cell lines have previously been shown to have loss of heterozygosity of 14q encompassing *DICER1*.

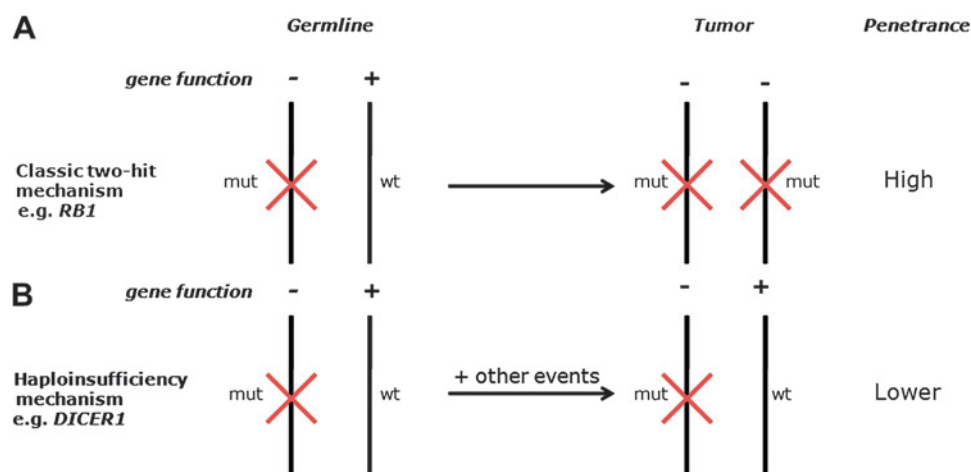
We identified four truncating mutations in the 781 cell lines, and these were in microsatellite unstable lines. We identified 22 non-synonymous variants that were either proven to be somatic or in which normal DNA was not available for evaluation. None were predicted to be deleterious (online supplementary table 4).

#### DISCUSSION

In 2009, germline *DICER1* mutations were identified in familial PPB, adding to the list of rare familial cancer syndromes that have yielded critical evidence linking essential biological processes with cancer causation.<sup>15</sup> In this study, we have expanded knowledge of the link between *DICER1* and cancer. First, we demonstrate that germline *DICER1* mutations are the major cause of PPB. In the UK, 20 cases of PPB have been registered in the National Registry of Childhood Tumours over the last 35 years. We were able to include 14 in this study, none of which had a family history of PPB. We identified *DICER1* mutations in 11 of these cases. This represents one of the largest known contributions of germline mutations of a single gene to a specific tumour type. It is uncertain whether cryptic *DICER1* mutations account for any of the negative cases, whether mutations in another gene can also cause PPB, or whether the remaining cases are not due to germline predisposition genes. However, it is clear that germline *DICER1* mutations are the major cause of both familial and non-familial PPB.

We have also demonstrated that *DICER1* mutations cause a range of phenotypes; not all families include PPB, and a high proportion of mutation carriers are clinically well. In view of this, we suggest that '*DICER1* syndrome' is a preferable term to 'PPB familial tumour syndrome', which has previously sometimes been used. The range of different tumours that can occur in individuals with *DICER1* mutations is broad, and it is likely that more associated tumours will be identified as further mutation testing is undertaken. The contribution of *DICER1* mutations to different tumours is very variable. The major tumours that occur in *DICER1* syndrome appear to be PPB, cystic nephroma and ovarian Sertoli–Leydig tumour.

**Figure 1** Different mechanisms of cancer predisposition resulting from germline mutations in tumour suppressor genes. (A) The classic two-hit mechanism, exemplified by retinoblastoma, involves a germline/constitutional mutation which constitutes the first hit and is present in every cell. A second mutation (hit) targeting the wild-type allele in a retinoblast has to occur for oncogenesis to proceed. (B) Haploinsufficiency mechanism, exemplified by *DICER1* syndrome. A germline/constitutional mutation predisposes to tumours. One or more additional events are required for oncogenesis to proceed, but does not appear to include inactivation of the wild-type *DICER1* allele. mut, mutant; wt, wild-type.



Evidence for this comes from our mutational data, our clinical and mutational investigation of relatives of mutation-positive probands, and from the spectrum of tumours that have been documented in relatives of PPB cases in the PPB Registry.<sup>17 18</sup> The contribution of *DICER1* mutations to different tumours is also very variable. Although germline *DICER1* mutations may contribute significantly to cystic nephroma, ovarian Sertoli–Leydig tumour and intraocular medulloepithelioma, they are unlikely to have a major impact on the incidence of Wilms tumour, medulloblastoma/infratentorial PNET or neuroblastoma.

In addition to tumours, *DICER1* mutations also appear to confer a risk of thyroid cysts. One proband and six *DICER1* mutation-positive relatives developed thyroid cysts in childhood or young adulthood. Although histology results were only available for two cases, both were non-toxic multinodular colloid goitres. This is of particular interest, as the gene for familial non-toxic multinodular thyroid goitre has been previously shown to localise to 14q.<sup>29</sup>

The mutation analyses in cancer cell lines suggest that somatic *DICER1* mutations do not make a substantial contribution to cancer. This is in contrast with recent reports hypothesising that the 14q hemizygoty observed in 206/761 cell lines is targeted at *DICER1*.<sup>19–21</sup> In the great majority of the cell lines, the 14q loss of heterozygosity extends over a very large area and includes many genes. If loss of *DICER1* were the main driver, one would expect that somatic *DICER1* mutations would occur in at least some of the cell lines with normal 14q chromosomes. However, we only identified four truncating mutations, and these were in microsatellite unstable lines and therefore unlikely to be driver mutations. Thus the somatic mutational profile of *DICER1* appears to differ from that of other ubiquitously expressed, critically important genes, such as *TP53* and *RB1*, which also predispose to rare childhood cancers when mutated in the germline.

The mechanism of *DICER1* tumour predisposition also appears to differ from the majority of known cancer-predisposition genes and is likely to operate by a haploinsufficiency mechanism (figure 1). Our analysis of tumours showed no loss of the wild-type allele, and Hill *et al* showed retained *DICER1* expression in tumour cells.<sup>15</sup> Data from mice studies are also consistent with a haploinsufficiency model and indicate that, whereas monoallelic *DICER1* inactivation promotes tumorigenesis, biallelic loss is inhibitory.<sup>20 21</sup> Our data further suggest

that, although inactivation of one *DICER1* allele is the initiating event in *DICER1* syndrome, presumably because it leads to dysregulation of miRNA levels, other events must be required for cancer to occur. It is not known what these additional events are, or how many are required for oncogenesis to proceed. However, the low frequency of tumours in *DICER1* mutation carriers suggests that either more than one additional event is required and/or the likelihood of the event(s) occurring is small.

Our data demonstrate that the risk of tumours in *DICER1* mutation carriers is low, and most mutation carriers do not develop tumours. This modest penetrance and the variable phenotype of *DICER1* syndrome raise significant clinical challenges. We suggest that diagnostic *DICER1* testing should be considered in individuals with possible PPB, cystic nephroma, ovarian Sertoli–Leydig tumour or medulloepithelioma. The prevalence of mutations in these conditions may be considerable, and identification of a *DICER1* mutation can aid diagnosis and management, particularly for PPB, which can show significant clinical overlap with other types of lung cyst.<sup>18 30</sup>

The issue of surveillance in a pleiotropic condition of modest penetrance is also complex. To date, ad hoc, variable screening for PPB has been undertaken in individual families, often using lung CT, which can require an anaesthetic, involves radiation exposure, and is of unproven efficacy.<sup>31</sup> Moreover, the natural history and appropriate management of such screen-detected lesions in a well child is unknown. In view of these considerations and the modest penetrance, we are currently operating an 'open-door' management policy with early investigation of potential

### Web resources

The URLs for data presented herein are as follows:

- ▶ OMIM, <http://www.ncbi.nlm.nih.gov/Omim/>
- ▶ PPB Registry, [http://www.ppbregistry.org/pdf/Doc\\_D.pdf](http://www.ppbregistry.org/pdf/Doc_D.pdf)
- ▶ Cancer Genome Project, Cell Line Project, <http://www.sanger.ac.uk/genetics/CGP/CellLines/>
- ▶ Polyphen, <http://genetics.bwh.harvard.edu/pph/>
- ▶ SIFT, <http://blocks.fhcrc.org/sift/SIFT.html>
- ▶ NNSplice, [http://www.fruitfly.org/seq\\_tools/splice.html](http://www.fruitfly.org/seq_tools/splice.html)
- ▶ Cancer Genome Project, Catalogue of Somatic Mutations in Cancer, <http://www.sanger.ac.uk/perl/genetics/CGP/cosmic>

tumour-related symptoms, but we are not undertaking routine surveillance in healthy mutation-positive individuals. This policy will be under continuous review, particularly over the next few years, when extensive expert discussions about the optimal management of *DICER1* mutation carriers are likely to occur.

In this study, we clarify the phenotypes associated with constitutional *DICER1* mutations and propose that the condition should be called '*DICER1* syndrome'. In the future, additional research will hopefully further clarify the clinical features, tumour risks, and optimal management of this condition and will illuminate the mechanisms by which *DICER1* haploinsufficiency predisposes to human disease.

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