

# Recent Developments in the Molecular Pathology of Paediatric Renal Tumours

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**Abstract:** The renal tumours of childhood include different tumours with distinct clinical presentations and histological features. More than 50 syndromes have been associated with an increased risk of Wilms tumour (WT), but they are present in only ~5% of all children who develop WT. Some children with apparently sporadic WT have a constitutional genetic change that has predisposed them to their tumour. Detailed analysis of histological subtype may aid in their identification, particularly those with tumours showing prominent rhabdomyoblastic changes in association with intralobar nephrogenic rests. Recently, a group of predisposed individuals with constitutional epigenetic mutations affecting imprinting of the *IGF2* locus on chromosome 11p15.5 has been discovered. Rhabdoid tumour of kidney is the only non-Wilms renal tumour of childhood with a recognised genetic predisposition.

Nephrogenic rests are regarded as precursors of WT. Intralobar nephrogenic rests are associated with mutations in the *WT1* gene, whereas perilobar nephrogenic rests are associated with allele loss at 11p15. Loss of heterozygosity (LOH) and loss of imprinting (LOI) are associated with different histological subtypes of Wilms tumour: LOI of *IGF2* is associated with PLNR-like Wilms tumours whereas LOH 11p and/or somatic *WT1* mutation is associated with ILNR-like Wilms tumours, though these associations are not absolute. A recently discovered *WT-X* gene shows no histological subtype correlation.

The currently defined 'high risk' subgroups used for treatment decision making according to therapeutic approach (LOH 1p/16q for immediate nephrectomy cases, 'blastemal type' histology in tumours treated with pre-operative chemotherapy) are insufficiently specific or sensitive to predict the majority of relapses and new molecular insights are needed. Progress in the identification of biomarkers for risk stratification in Wilms tumour is reviewed.

**Keywords:** Renal tumours, heterozygosity, tumours.

## 1. INTRODUCTION

The renal tumours of childhood comprise a diverse set of tumours with distinct clinical presentations and histological features. In early infancy (up to age 3 months), the predominant renal tumour is mesoblastic nephroma [1]. During the remainder of childhood, Wilms tumours account for almost 95% of all primary renal tumours, though this proportion starts to fall above the age of 10 years, where renal cell carcinomas contribute nearly one third of all cases [2]. Clear cell sarcoma of kidney (CCSK) and malignant rhabdoid tumour of kidney (MRTK) each comprise about 2-3% of all childhood renal tumours but they have very different age distributions [2, 3]. The majority of MRTKs are diagnosed in the first year of life whereas CCSK has a similar age distribution to Wilms tumour, with a median age at diagnosis of 3-4 years. These differences in age at presentation undoubtedly reflect the different biological basis of each tumour type, even where the cell of origin remains unclear.

Epidemiology has provided further insights and raised further questions relevant to molecular pathology. For example, the female preponderance of Wilms tumour is in contrast to the majority of childhood cancers, where there is a generally a male predominance. Females are also diagnosed on average 6-12 months later than males with Wilms tumour, a difference that can only be partially ascribed to the underlying biological pathways that are currently known [2, 4]. Anaplastic Wilms tumour shows an even more marked female excess [5], whereas MRTK and CCSK both show a male predominance [3]. Bilateral tumours are nearly always Wilms tumours: among 171 cases of bilateral renal tumours reported to the National Childhood Tumour Registry of Great Britain during the 30 year period 1978-2007, 166 (97%) were Wilms tumours and there was a single case of bilateral MRTK (Charles Stiller, personal communication).

## 2. RECENT ADVANCES IN UNDERSTANDING OF GENETIC PREDISPOSITION

Wilms tumour is the paradigm for the relationship of embryonal tumours to development of the cognate organ. The discovery of the *WT1* gene through its involvement in the Wilms-Aniridia-Genitourinary malformation-mental Retardation (WAGR) syndrome exemplifies how mutations in a critical gene for nephrogenesis can have dominant

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effects on genito-urinary development and yet be recessive, at a cellular level, for tumour development [6]. Furthermore, there is a genotype-phenotype correlation. Children with complete deletion of one *WT1* allele, as in the WAGR syndrome, have less severe genitourinary abnormalities than those with the typical intragenic *WT1* mutations that underlie the triad of WT, nephropathy and genital ambiguity seen in Denys-Drash syndrome [7]. However, following these discoveries, it soon became clear that mutations in the *WT1* gene did not explain the majority of cases of either the rare familial form or the more common sporadic form of the disease, and that several different Wilms tumour predisposition genes must exist [8]. Among the familial Wilms tumour genes, *FWT1* and *FWT2*, mapped to 17q and 19q respectively, still remain to be identified, though they are likely to yield soon to new, high resolution, genome-wide analyses that are in progress.

More than 50 syndromes have been associated with an increased risk of Wilms tumour, though in many their rarity precludes a definitive association [7]. Together, these syndromes are present in only ~ 5% of all children who develop Wilms tumour. However, it is now clear that some children with apparently sporadic Wilms tumour have a constitutional genetic change that has predisposed them to their tumour.

Approximately 2-3% of children without any evidence of genitourinary malformation carry a constitutional *WT1* mutation [9]. Such cases are more likely to develop stromal-predominant Wilms tumours, often with rhabdomyoblastic features, that fail to show any tumour shrinkage with preoperative chemotherapy [10]. Their recognition has important implication for clinical follow up, due to the increased potential for metachronous tumours and the increased risk of longer term renal failure [11, 12].

A second, more recently discovered group of predisposed individuals are those with constitutional epigenetic mutations affecting imprinting of the *IGF2* locus on chromosome 11p15.5 [13]. Abnormalities in this complex region underlie Beckwith-Wiedemann syndrome (BWS) and help define those children at increased tumour risk: only those with abnormalities that result in duplication of the active paternal allele or alterations in the imprinting control region that result in overexpression of the *IGF2* gene, are associated with Wilms tumour [14]. The same spectrum of constitutional 11p15.5 changes is found in 3% of children without evidence of overgrowth and explains a proportion of children with bilateral tumours [13]. Of note, apart from two cases with heritable mutations in the imprinting control region, all other abnormalities were epigenetic and therefore not transmissible to the next generation. This is the first molecular demonstration that not all bilateral tumours are due to heritable abnormalities.

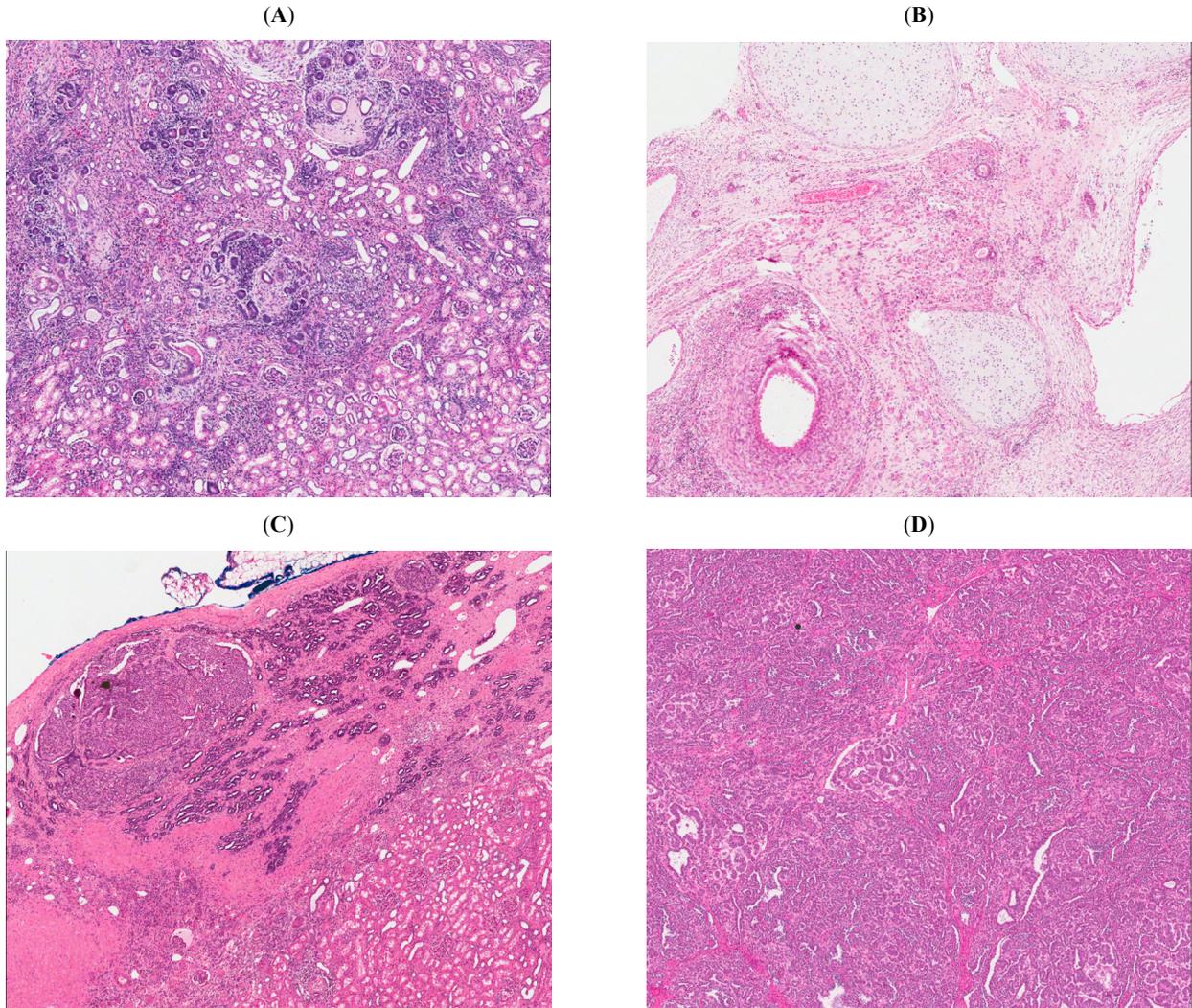
Among the non-Wilms renal tumours of childhood, only malignant rhabdoid tumour has a recognised genetic predisposition. Inactivating mutations of the *SMARCB1/INI1* gene were constitutional in four of 16 renal rhabdoid tumours and in two thirds of cases presenting with

simultaneous brain and renal or other soft tissue tumours [15].

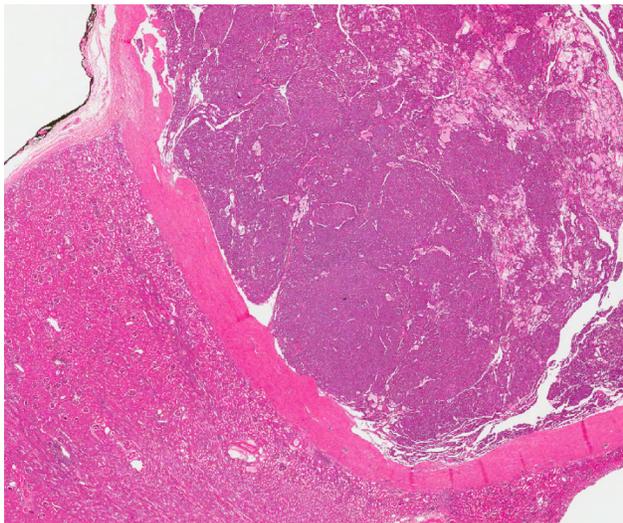
### 3. NEPHROGENIC RESTS AND THE PATHOGENESIS OF WILMS TUMOUR

Wilms tumours are thought to arise from abnormally persistent metanephric blastemal cells that fail to undergo the usual mesenchymal-epithelial transition that occurs in normal nephrogenesis. The generic term 'nephrogenic rests' was first coined for these lesions by Bruce Beckwith, the pathologist for the National Wilms Tumour Study Group. After a careful study of the histology and clinical features of Wilms tumours occurring in association with nephrogenic rests in the adjacent kidney, he proposed a new classification scheme that emphasised their likely different origins [16]. Intralobar nephrogenic rests (ILNRs) (Fig. 1A) are associated with Wilms tumours that can demonstrate the entire spectrum of differentiation of metanephric mesenchyme, including heterologous stromal elements (ILNR-like Wilms tumour) (Fig. 1B). They have an early age of onset (1-2 years old), are very frequent in patients with WAGR or Denys-Drash syndromes and occur in deep-seated locations within the renal lobule, suggesting they result from an early event during development of the metanephric kidney. By contrast, the Wilms tumours occurring in association with perilobar nephrogenic rests (PLNRs) (Fig. 1C), show a much more restricted pattern of differentiation, confined to the expected mesenchymal-epithelial change that accompanies differentiation of the nephron from the metanephric blastema (Fig. 1D). PLNR-like Wilms tumours show the same restricted differentiation pattern, occur in association with BWS/hemihypertrophy and have the typical age of onset of Wilms tumour, around 3-4 years old. These features all suggest that PLNR-associated Wilms tumours arise from a somewhat later insult during embryogenesis and in a more committed metanephric blastemal cell.

Beckwith's classification scheme for nephrogenic rests has largely been borne out with increasing molecular knowledge of their origins and evolution into Wilms tumour. ILNRs are associated with mutations in the *WT1* gene that are already present at the rest stage [17]. PLNRs are associated with allele loss at 11p15 (affecting the BWS locus and *IGF2* expression), again detectable at the 'rest' stage and even in adjacent normal kidney [18, 19]. Variations in the gender and ethnic associations of ILNRs and PLNRs seem to account for the younger age of onset and lack of female predominance seen in Asian children with Wilms tumour compared to their Caucasian counterparts [20]. More recently, it has been shown that epigenetic changes elsewhere in the genome occur during the evolution from rest to tumour [21] as is also the case for allele loss on chromosome 16q [17]. These findings provide useful insights into the biological basis of the evolution of Wilms tumour from a rest. However, they are too infrequent and insufficiently characterised to yet provide a solution to the often thorny clinical question of distinguishing nephrogenic rests from 'true' Wilms tumour at resection margins, particularly in the case of bilateral renal abnormalities pre-treated with chemotherapy (Fig. 2).



**Fig. (1).** Association of Wilms tumour histology with subtype of nephrogenic rest. (A) Intralobar nephrogenic rest; (B) Wilms tumour, showing heterologous stromal elements, is typically associated with ILNR; (C) Perilobar nephrogenic rests; (D) Wilms tumour epithelial type, is typically associated with PLNR.



**Fig. (2).** Challenges in differentiating nephrogenic rests from Wilms tumour. Illustration shows a PLNR with a marked pseudocapsule that formed secondary to preoperative chemotherapy.

#### 4. PATHOLOGICAL CORRELATES OF SOMATIC GENETIC CHANGES

##### 4.1. *WT1*-Mutation and Stromal-Predominant Wilms Tumours

Somatic *WT1* mutations are found in 6-20% of Wilms tumours according to the ethnic origin of the patients [22]. *WT1* mutation is commoner in South East Asian children with Wilms tumour, who also have a younger median age of diagnosis. *WT1* mutation frequently coexists with *CTNNB1* (beta-catenin) mutation [23, 24]. The latter results in constitutive activation of canonical Wnt signaling which is normally switched off during the later stages of nephrogenesis [25].

*WT1* mutant-tumours typically show stromal-predominant histology which may show heterologous differentiation (ectopic mesenchymal elements) [10, 12, 26]. They are also more frequently associated with intralobar nephrogenic rests in the adjacent kidney. All of these factors suggest that these tumours arise from an early insult during nephrogenesis, in a multipotent metanephric blastemal cell.

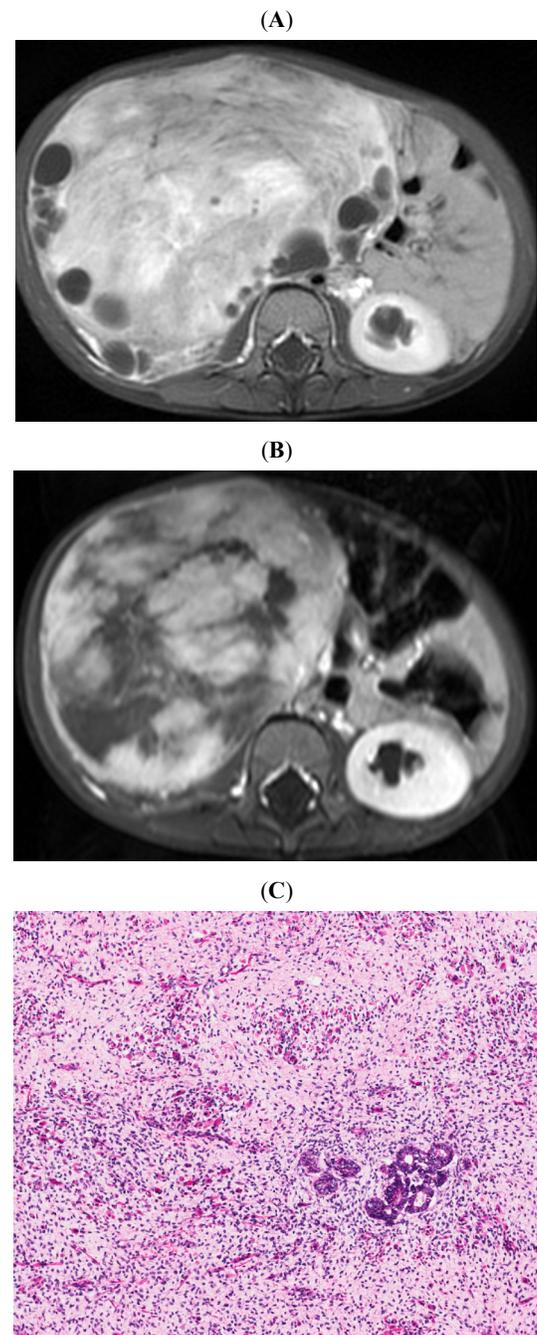
Heterologous rhabdomyoblastic differentiation is associated with reduced expression of WT1 but only ~60% of cases have underlying *WT1* mutation [27]. It is important to recognise that Wilms tumours with stromal-predominant histology often fail to shrink in response to pre-operative chemotherapy, where this is applied. Indeed, if there is marked rhabdomyoblastic change, the tumour can even increase noticeably in size in response to chemotherapy (Figs. 3A-C). However, this does not indicate a poor outcome - stromal-predominant tumours after pre-operative chemo in fact have an excellent prognosis, even better than the other intermediate risk Wilms tumours, providing gross tumour excision can be achieved [28]. Such cases therefore require careful multidisciplinary discussion of the risk-benefit of proceeding to surgery versus increasing chemotherapy, as the latter is unlikely to produce significant tumour shrinkage.

#### 4.2. 11p15 Abnormalities and IGF2-Associated Tumours

Early studies of loss of heterozygosity (LOH) in Wilms tumour highlighted the short arm of chromosome 11 as a frequent site of LOH [29, 30]. LOH 11p, spanning the *WT1* gene at 11p13, occurs in about 30% of tumours, whereas LOH confined to the telomeric 11p15 region is less frequent (~ 8%). 11p15 contains a region with several imprinted genes implicated in embryonal tumours, including the *IGF2* and *H19* genes. Loss of imprinting (LOI) leads to expression of the normally silent maternal *IGF2* allele and silencing of the normally expressed maternal *H19* allele and is found in about 40% of Wilms tumours [31]. Loss of the maternal allele with duplication of the paternal allele (i.e. LOH 11p) results in a similar overexpression of the growth promoting *IGF2* and loss of *H19*, a non-coding RNA with tumour suppressor properties.

Intriguingly, these two different molecular events, LOH or LOI, are associated with different histological subtypes of Wilms tumour, even though they have a similar effect on *IGF2* expression. LOI of *IGF2* is associated with PLNR-like Wilms tumours whereas LOH 11p is associated with ILNR-like Wilms tumours [31]. This raises the question of whether tumour histology is determined by the type of precursor lesion, the timing of the tumourigenic insult or by the molecular drivers.

It has subsequently been found that some tumours with *IGF2* LOI display ILNR-like histology, show activation of the canonical Wnt-signalling pathway and contain *CTNNB1* (beta-catenin) mutations [32]. These latter features are more typically associated with *WT1* mutation, which was excluded in this group. A similar subgroup of stromal histology tumours showing muscle differentiation with *CTNNB1* but no *WT1* mutation was found by another group [33]. These showed activation of the canonical Wnt pathway, had absent *WT1* expression and, where it could be assessed, had increased expression of *IGF2*. This suggests that ILNR-like histology may be determined by specific abnormalities in Wnt-signalling that override the effects of *IGF2* overexpression. While this does not rule out a predominant influence of the type of precursor cell on the ultimate tumour histology, it seems clear that the majority of PLNR-like Wilms tumours and their associated nephrogenic rests have overexpression of *IGF2* [19].



**Fig. (3). Stromal-type Wilms tumours may increase in volume during pre-operative chemotherapy.** (A) At the time of diagnosis a transaxial MRI section (T1-weighted after intravenous gadolinium administration) demonstrates a large right-sided renal tumour with a geographical pattern of viable enhancing (bright) and necrotic non-enhancing (dark) areas. The estimated tumour volume was 707 ml. Note also central cystic lesion in the left kidney. (B) After 4 weeks of pre-operative chemotherapy, a transaxial MRI section (T1-weighted after intravenous gadolinium administration) demonstrates growth of the right-sided renal tumour, which is now overall more homogeneously bright (enhancing) with a whirled appearance, apart from some well-defined peripheral cysts. (C) The estimated volume is 1204 ml, an increase of 70% compared to the time of diagnosis. Wilms tumour from a *WT1* mutant tumour showing marked rhabdomyoblastic differentiation.

### 4.3. WT-X Lacks Histological Subtype Correlation

The *WT-X* gene was discovered as a novel Wilms tumour gene in 2007, through delineation of homozygous deletions on a high resolution screen for DNA copy number alterations [34]. *WT-X* appears to act as a negative regulator of Wnt-signalling through its role in targeting *CTNNB1* for degradation. Initially, it was reported that *WT-X* and *WT1/CTNNB1* mutations (which generally co-exist) are mutually exclusive. However, analyses of larger cohorts have shown that *WT-X* mutation, found in approximately 20-30% of tumours, can sometimes co-exist with *WT1/CTNNB1* mutation [35]. *WT-X* mutation can be heterogeneous within a tumour, shows no clear clinical correlations and appears to occur as a later event in tumorigenesis. Indeed, children with constitutional *WT-X* mutations have an X-linked sclerosing bone dysplasia but are not predisposed to Wilms or any other tumour [36].

### 4.4. Anaplastic Tumours and *p53* Mutation

The definition of anaplasia in a Wilms tumour is by morphological criteria. The observed abnormal nuclear and mitotic appearances suggest an underlying defect in cell cycle control and, early on, it was found that the majority of anaplastic Wilms tumours harbour *p53* mutation [37]. The *p53* mutation is usually confined to the anaplastic region, whether the anaplasia is defined as focal or diffuse [38]. This suggests that *p53* mutation is acquired during clonal evolution of Wilms tumour. This is consistent with a comparative genomic hybridisation study that showed loss of 17p as the most significant DNA copy number abnormality acquired between diagnosis and relapse [39]. Both anaplasia and *p53* mutation were found at relapse in one case with initial favourable histology.

Since not all anaplastic Wilms tumour have detectable *p53* mutation, other changes that might affect the pathway have been looked for. Amplification of *MDM2*, a *p53* antagonist, was not found in a small series [37]. Stabilisation of the *p53* protein, as shown by positive immunohistochemistry, is found mostly in metastatic or relapsing Wilms tumours of any histology, and is only associated with anaplasia or *p53* mutation in the minority of cases [40]. More recent gene expression profile analysis of a series comprising 5 anaplastic and 21 favourable histology tumours showed an association of underexpression of *p21* and relapse [41]. However, dysregulation of *p53* target genes has not been a consistent finding in other analyses of prognostic gene expression profiles in favourable histology Wilms tumours [42, 43]. This suggests that abnormalities of *p53* are largely restricted to anaplastic Wilms tumour and may be acquired during clonal evolution in relapsing, initially favourable histology tumours.

The phenomenon of 'nuclear unrest' has been described as a possible intermediate stage between favourable histology and anaplastic Wilms tumour [44]. There is nuclear enlargement similar to that seen in anaplasia but no abnormal mitotic figures and no increase in *p53* staining on immunohistochemistry. Note that increased *p53* staining is a variable feature of anaplastic Wilms tumour and therefore cannot be used as an absolute criterion for distinguishing this from nuclear unrest. Nuclear unrest appears to be associated with an increased relapse rate while overall survival is

unaffected [44]. Hence, the clinical relevance of this phenomenon awaits its better molecular characterisation and analysis in larger series. It should be noted that the diagnosis of anaplasia in Wilms tumour is a difficult one. The presence or diffuse nature of anaplasia was not recognised by the institutional pathologist in nearly half of the cases classified as diffuse anaplasia by the review panel in a recent large international trial [5].

## 5. PROGNOSTIC BIOMARKERS IN WILMS TUMOURS

In the current decade, the two major international groups running clinical trials in childhood renal tumours have each introduced a novel prognostic factor into risk stratification. The predominantly European SIOP investigators have defined a new 'high risk' pathological subtype, based on histological response to pre-nephrectomy chemotherapy [45]. This 'blastemal type', where a high proportion of viable undifferentiated blastemal cells survive chemotherapy, is selected for intensified post-operative chemotherapy according to tumour stage (SIOP WT 2001 trial protocol). The Children's Oncology Group (COG) of North America uses a different treatment approach of initial nephrectomy followed by post-operative chemotherapy whose intensity is adapted to chemo-naïve tumour stage and histology. Based on the results of their recent prospective biomarker trial (the NWTSG 5 trial), the COG renal tumour trials now apply the molecular marker of combined loss of heterozygosity (LOH) covering fairly large genomic regions of chromosomes 1p (8 Mb) and 16q (25 Mb), to allocate tumours to more intensive regimens [46]. Both groups classify tumours with diffuse anaplasia (~ 5% of cases), as 'high risk'. The current COG trials have moved focal anaplasia into the high risk category whereas it remains in the intermediate risk group in the SIOP trial. Both of these decisions are based on relatively small numbers of cases and may change as more outcome data become available.

### 5.1. Prognostic Significance of Allelic Imbalance/Loss of Heterozygosity

Use of loss of heterozygosity assays (LOH) to determine areas of allele loss has shown that the majority of Wilms tumours have few or no changes and these tend to be restricted to a few loci, principally at 11p, 1p, 16q, 11q and 22q [29, 47-51]. The clinical prognostic value of LOH 1p/16q was established in nearly 2,000 tumours treated by immediate surgical removal. This gave a relative risk (RR) of relapse of approximately 2-fold for LOH at either locus alone in stage I and II tumours, whereas combined 1p/16q LOH was associated with a RR for relapse of 2.88 [46]. These low stage tumours are treated with only 18 weeks chemotherapy with vincristine and actinomycin D. In higher stage tumours, which receive additional doxorubicin and radiotherapy, LOH for either region alone was not significant but combined LOH remained associated with an adverse RR for relapse of 2.41. Hence, the COG investigators decided to use only combined LOH 1p/16q as a biomarker for risk stratification across all stages.

In a retrospective analysis of 452 Wilms tumours treated by either immediate nephrectomy or pre-operative chemotherapy, isolated LOH 16q was associated with an equally adverse relative risk of relapse, 2.6 fold, as found for

combined LOH 1p/16q and was considerably more frequent (14.6% c.f. 2.6%, respectively) [52]. A similar effect has been seen in 225 tumours treated in previous SIOP trials [49]. Both studies showed an association of LOH 16q with anaplasia but were too small to analyse the relative risk of relapse within stage I tumours only.

Although utilised clinically as a biomarker, the mechanisms by which LOH 1p or 16q might be directly responsible for tumour resistance remain unknown. In all studies, the regions of LOH have been large in the majority of tumours. Mutational screening of candidate genes selected on the basis of their putative role in nephrogenesis or location within rare regions of homozygous loss have so far failed to pinpoint the critical genes involved in either 1p36 or 16q21-24 [53, 54]. It is possible that LOH at these loci is not always the driving factor but a marker of change elsewhere in the genome. For example, cytogenetic analyses of Wilms tumours have shown an association of 16q loss with 1q gain due to unbalanced translocation [55].

## 5.2. The Search for Additional Biomarkers in Wilms Tumour

Neither the SIOP nor COG treatment approaches have yet succeeded in defining a prognostic biomarker that is sufficiently sensitive or specific to identify the majority of patients with poor outcome: 'high risk' histology (blastemal type or diffuse anaplasia) is found in only ~ 25% of all relapses with the SIOP approach, and combined LOH 1p/16q occurs in only ~ 10% of all relapses with the COG approach. It is likely that multiple prognostic factors will be required to accurately define the highest risk group. Conversely, there is a need to more reliably identify patients whose current treatment can be safely reduced, e.g. by omission of doxorubicin, as in the current SIOP WT 2001 trial.

In the past, many studies of individual genes were underpowered and hence could not take account of established prognostic factors such as age, stage and histology. The large size of the NWTSG 5 trial sample collection permitted a well designed case-cohort analysis of the prognostic impact of telomerase activity [56]. This showed a correlation of increased expression of telomerase components with adverse relapse free but not overall survival. However, the ultimate test of telomerase activity, the TRAP assay, could not confirm this correlation, perhaps due to the higher failure rate and the inherent variability in an *in vitro* test of enzymatic activity.

Subsequently, several groups have taken a whole genome approach to the identification of prognostic biomarkers in Wilms tumour [41-43]. To date, it has been difficult to define a reproducible molecular signature predictive of relapse. Genomic copy number appears a better classifier than expression profiling [43]. This may be due to the complexity of cellular composition of Wilms tumour, with retention of expression patterns reflecting embryonic counterparts [57]. Several studies have shown a strong association between gain of the whole or part of chromosome 1q and adverse outcome [55, 58-60]. Such copy number abnormalities of 1q are a frequent finding (~ 40% of cases), but the region of gain is generally very large. Other analyses have highlighted alterations of insulin-like growth factor II signalling and retinoic acid pathways as of potential

prognostic significance [42, 61, 62]. These are of particular interest as therapies are already in clinical use against these agents. Gain of the *MYCN* oncogene has also been described in Wilms tumour and is associated with, but not restricted to, the diffuse anaplastic subtype [63]. The observed levels of copy number gain are generally modest, though occasional cases show high level gain comparable with that seen in neuroblastoma. However, much further research remains to be done before any of these potential biomarkers could be used for treatment decision making.

## 6. MOLECULAR PATHOLOGY OF NON-WILMS TUMOURS

Apart from clear cell sarcoma of kidney (CCSK), all of the other non-Wilms tumour entities have seen major progress in defining their biology. However, due to the small numbers comprising each subtype, these molecular changes have been more useful in diagnosis rather than prognostication.

The cellular subtype of mesoblastic nephroma shares the same balanced translocation that forms the fusion gene, *ETV6-NTRK3*, as is seen in congenital fibromatosis [64]. Identification of this fusion gene may be useful in predicting chemosensitivity in inoperable tumours [65]. Virtually all malignant rhabdoid tumours of kidney have been shown to carry *hSNF5/INI1* mutations, whose presence is most easily assessed by immunohistochemistry to confirm absence of protein expression [66]. Paediatric renal cell carcinomas frequently involve translocations of the *TFE3* gene at Xp11.2, which may assist in diagnosis of some of the more atypical cases [67]. CCSK remains somewhat of an enigma, with its cell of origin still not defined. In a survey of c-KIT expression in nearly 300 renal tumours, CCSK were the only group to commonly show expression, but without mutation [68]. More striking was the finding of deregulation of *EGFR* in CCSK, with all cases showing strong overexpression and two individual cases with gene amplification and mutation, respectively [69]. As might be expected from their differing histogeneses, the non-Wilms renal tumours of childhood can be distinguished from each other and from Wilms tumour by their expression profiles [70].

## 7. CONCLUSIONS

Much progress has been made in understanding the molecular basis of the various renal tumours of childhood in the last decade. However, to date, the impact on clinical practice has been limited mainly to improved diagnostic classification. There is a continued need for translational research to identify better biomarkers that predict response to therapy and long term outcomes. Understanding the biological pathways that underlie 'high' and 'low' risk tumour behaviour and how these relate to histological subtypes will be key to the introduction of targeted therapies, that should improve efficacy and reduce toxicity of current treatments.

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