The genetic changes of Wilms tumour

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Abstract:
Wilms tumour is the most common renal malignancy of childhood. It is curable in the majority of children, albeit at considerable cost in terms of treatment related late effects in some children. In the small group of 'high risk' Wilms tumours, the prognosis is much worse. Overall, one in ten children with Wilms tumour will still die of their disease despite modern treatment approaches.

The genetic changes underpinning Wilms tumour have been defined by studies of familial cases and more recently, by unbiased DNA sequencing of tumour genomes. Together these have defined the landscape of cancer genes that are operative in Wilms tumour. Many are intricately linked to control of fetal nephrogenesis. Here, we review our current understanding of germline and somatic genetic changes that underlie Wilms tumour.

A – Introduction

A1. Brief overview

1.1 What is it?

Wilms tumour (WT), also known as nephroblastoma, is one of the so-called embryonal tumours of childhood, due to its histological mimicry of stages in nephrogenesis and its early age of onset. It accounts for 90% of childhood renal tumours and constitutes 7% of all childhood cancers(1). Thought to arise from aberrant nephrogenesis, many of the genetic changes underpinning WT occur in genes involved in fetal nephrogenesis(2). Although our understanding of tumourigenesis remains incomplete, the WNT pathway and insulin-like growth factor (IGF) signaling have long been considered to have pathogenic roles.

This review follows recent large scale analyses interrogating the somatic basis of WT. The genetic changes underpinning WT are diverse, driven by an array of almost 40 cancer genes (Table 1). Such diversity is particularly surprising given the monotonous driver landscape of other childhood renal tumours, such as clear cell sarcoma of the kidney (CCSK) or congenital mesoblastic nephroma (CMN). In comparison to adult cancers, the median somatic mutation rate is far lower in WT, 0.17 per million bases

(Mb) versus 1-10 per Mb across adult papillary and clear cell renal cell carcinoma(3,4). Whole exome sequencing has identified recurrent and unique mutations in the microRNA processing genes and the transcription factors SIX1/SIX2(5–8). A recent whole genome sequencing study defined novel mutations in proteins involved in histone modification during nephrogenesis (*BCOR, MAP3K4*), proteins that interact with MYCN (*NONO, MAX*) and proteins involved in transcriptional repression (*BCORL1*), amongst others(9).

1.2 Who gets it?

In almost 90% of cases, WT is a sporadic event occurring in one kidney. There is a narrow developmental window for WT, with a median age of diagnosis around 3 years and 95% of cases diagnosed in children under 10 years(10). Bilateral and multifocal tumours, or WT on a background of a predisposition syndrome, tend to present earlier. This latter group includes children with WT1-associated congenital malformation syndromes (WT-anirida-genitourinary malformation-mental retardation (WAGR), Denys-Drash, Frasier) and other urogenital malformation anomalies(11). Those with WT associated with asymmetric overgrowth (Beckwith-Wiedemann syndrome and isolated hemi-hypertrophy) tend to present at the more typical age. Familial WT pedigrees exist, account for 1-2% of cases and are known to involve several different heritable mutations(12). WT rarely occurs in adults, in whom the prognosis is worse than in children. It is believed that initial misdiagnosis and treatment related toxicity contribute to this poorer outcome(13).

1.2 Epidemiology?

The annual worldwide incidence of WT is approximately 1 in 100,000. The highest incidence rates are found in children of African descent and the rates for WT in East Asian populations is around half that of Caucasian children(1,14). Most countries observe a female predominance of 1.1-1.2:1, though a male prevalence is observed amongst Asian children(15,16).

In the developed world overall survival approaches 90%. There is however significant treatment related morbidity, both acutely and in the long-term. A proportion of children treated with current protocols are at risk of cardiac dysfunction secondary to anthracycline use, subfertility following the use of alkylating agents, second malignancies and radiotherapy-induced toxicity, including organ dysfunction and skeletal abnormalities(17). Almost 15% of children relapse and despite intensive treatment regimens, approximately half of these patients do not survive(18). Furthermore a considerable proportion of relapses occur in patients deemed standard-risk at diagnosis.

The treatment of WT can be considered a success story, with clear management pathways delineated for most children. However, the management of bilateral disease needs continual refinement to optimise renal parenchymal preservation while maximising cure in patients who often have a tumour predisposition syndrome. The

poor prognosis of high-risk tumours and relapsed disease is also a major challenge requiring improved understanding of oncogenesis and development of novel agents to improve outcome. In addition, survival drops significantly in low income countries and in sub-Saharan Africa, to 39%(19). A further priority is to reduce the burden of treatment by identifying low-risk patients in whom further reduction of therapy is feasible while maintaining excellent survival. It is necessary to first provide an overview of these clinical challenges, before exploring how recent advances in our understanding of the genetic landscape of WT may contribute to improved survival.

A2. Main clinical challenges

2.1 Current treatment strategies highlighting the differences between the SIOP and the US approach

There are two different philosophies for managing children diagnosed with a renal tumour. In Europe, the majority of children with WT receive pre-operative chemotherapy in line with Société Internationale d'Oncologie Pédiatrique Renal Tumours Study Group (SIOP-RTSG) protocols(20). Tumours in infants younger than 6 months of age are usually managed with primary nephrectomy, as in this group non-WT renal tumours are a more likely diagnosis. The aims of pre-operative chemotherapy are to treat micrometastases at diagnosis, to evaluate tumour response and to reduce the risk of intra-operative rupture(21). Most children receive actinomycin D (AD) and vincristine (VCR), with the addition of doxorubicin (DOX) in metastatic cases. Chemotherapy is commenced without a confirmatory biopsy in most European countries, owing to the diagnostic likelihood of a renal mass in a child above six months being a WT and the potential risks associated with biopsy(22). Conversely, in North America most children undergo immediate nephrectomy as per the National Wilms' Tumour Study/Children's Oncology Group (COG). This approach provides a chemo-naïve histopathologic diagnosis, and reduces exposing children with benign and non-WT malignant renal tumours to inappropriate cytotoxic chemotherapy. In addition it allows early classification of stage to allow subsequent risk-stratified oncological therapy.

Both groups use stage of disease and histological subtype to stratify post-operative chemotherapy and, for higher risk patients, radiotherapy. SIOP classifies tumours as low- (completely necrotic and cystic), intermediate- (epithelial, stromal, regressive or mixed subtype, including focal anaplasia) or high-risk (blastemal type and diffuse anaplasia). COG characterises histology as favourable (i.e. 'non-anaplastic') or unfavourable (focal and diffuse anaplasia). Blastemal subtype, identified by the percentage of blastema remaining following pre-operative chemotherapy, is classified as high-risk by SIOP. By contrast, COG includes all histological appearances other than the presence of anaplasia in a treatment-naïve tumour as favourable histology. Since 2005, COG have included a molecular marker, loss of heterozygosity (LOH) for alleles spanning chromosomes 1p and 16q (1p36.12p36.11 and 16q22.1q24.3 respectively) into risk stratification, treating children whose tumours have combined 1p/16q LOH with more intensive chemotherapy(23,24). Although the method of

oncogenesis in tumours with combined 1p/16q LOH remains uncertain, this biomarker is significantly associated with risk of relapse and death in all stage disease. Regarding stage, only COG upstages children who have undergone biopsy from stage 1 to stage 3. Uniquely, COG stratification identifies a group of very low risk tumours that do not receive adjuvant cytotoxic treatment, i.e. children younger than 2 years with stage I favourable histology and tumour weight less than 550g as very low-risk(25). All other children receive post-operative chemotherapy with VCR and ACT-D, with the addition of DOX for metastatic disease and stage I high-risk tumours. High-risk tumours with advanced stage are treated with carboplatin (CDC)/ etoposide (ETO)/ cyclophosphamide (CYC)/ DOX. Two year event free and overall survival rates for children treated with the most recent large scale European trial (SIOP-2001) were 87% and 93% respectively, with similar results reported in COG trials(26,27).

2.1 Standard risk children who relapse

Relapse in WT occurs in approximately 15% of treated patients, mostly within two years of diagnosis(18). Common relapse sites include the lung, abdomen and liver, and only rarely does WT disseminate to the bone or brain. Overall survival varies between 10% - 70% depending on initial treatment, relapse site and histology (28–31). Prognostic factors for recurrence are not fully understood and more than half of all relapses occur in patients without known risk factors. In SIOP-2001, relapse rates amongst 3559 children were 26% in high-risk, 11% in intermediate-risk and 5% in low-risk(26). In very low-risk cases, as defined by COG, relapse occurs in up to 15%(32). In this group, only LOH at 11p15 has been reproducibly associated with disease recurrence(25,33). For all histological risk groups, gain of 1q consistently predicts poorer event free survival(34–36). In the COG cohort, gain of 1q is also associated with a reduction in overall. Although this is the most promising molecular biomarker, affecting 28% of all WT, the driver mechanisms underlying gain of 1q remain unknown.

2.2 Anaplasia

Anaplasia, defined as the presence of cells with nuclear enlargement, hyperchromasia and abnormal mitotic figures, is found in less than 10% of WT(37). Diffuse anaplasia (DAWT), classified as high-risk and unfavourable histology by SIOP and COG respectively, is frequently associated with poorer outcome. Somatic mutation of the tumour suppressor gene *TP53* underlies up to 60% of anaplastic tumours(38–40). Mutations are limited to anaplastic regions and are rarely seen in other histological subtypes. However, a recent analysis of fatal tumours found mutant *TP53* in 26% of non-anaplastic cases, suggesting variant *TP53* may be a clonal event preceding the development of anaplasia(41). In advanced stage disease, these mutations are associated with an increased risk of relapse and mortality, when compared to wild-type *TP53* DAWT. Despite this association, genetic testing of tumours is not yet routinely undertaken and all patients with DAWT are stratified to receive more intensive treatment.

2.3 Bilateral tumours

Bilateral or stage V disease, whereby WT or precursor lesions known as nephrogenic rests (NR) affect both kidneys, is found in 5-8% of cases(42). Both kidneys are usually affected simultaneously and only in less than 1% of cases is disease metachronous(1). Patients tend to present under 2 years of age and there is a marked female preponderance. In a recent review of 545 bilateral cases, 22% of children had predisposition syndromes(43). There is a strong association with germline genetic and epigenetic abnormalities, with *WT1* loss and 11p15 loss of imprinting predominating. Management remains challenging, particularly in the context of *WT1* mutation syndromes associated with inherent predisposition to nephropathy and the morbidity associated with persistent hypertension. Both SIOP and COG protocols initiate pre-operative chemotherapy followed by nephron-sparing surgery, with the aim of achieving cure whilst preserving maximal renal function (NSS).

2.4 Long term morbidity, in particular renal and cardiac morbidity

Current treatment protocols leave a proportion of patients at risk of renal and cardiac failure, hypertension, metabolic syndrome, infertility, secondary cancers and abnormal musculoskeletal development(17). The last long-term follow up identified that almost a quarter of survivors experience severe chronic and life-threatening health conditions in adulthood, although this cohort was treated as far back as the 1980s(44). The incidence of end stage renal failure (ESRF) stands at 1% for unilateral disease, increasing to 10% for patients with bilateral WT(45). Highest rates of ESRF are found in patients with DDS and WAGR syndrome, at 74% and 36% respectively. The risk of congestive cardiac failure is related to the cumulative dose of DOX administered, ranging from about 5% for patients receiving DOX during initial treatment to 17% for relapsed cases(46). Females and infants are particularly susceptible and risk is potentiated by both pulmonary and abdominal radiotherapy. To avoid cardiotoxicity, DOX is no longer recommended for the treatment of small volume (<500 mL) stage II-III intermediate-risk histology WT (20,47). Similarly, pulmonary radiotherapy can be omitted for lung lesions that demonstrate complete response to chemotherapy(48). Although both approaches carry a minimal increased risk of relapse, second remission is usually achieved.

2.5 Wilms in low- and middle income countries

Over 80% of all childhood cancers are diagnosed in children living in low and middle-income countries(49). This significant cancer burden in resource poor settings is associated with poorer outcomes. Even across Europe, there is some variation in overall survival rates, down to 83.9%(50). In sub-Saharan Africa failure of treatment most commonly results from abandonment. As a consequence, in this region overall survival ranges from 11-61%(8). Improvements in survival through international collaboration have been demonstrated in several centres, with adoption of amended SIOP protocols, better supportive care and the establishment of multidisciplinary teams(51,52).

B – Main sections and subsections

B1. Cancer genes operative in Wilms tumour

2.1 Nephrogenesis

The definitive kidney anlage, metanephros, forms at around the fifth week of gestation from the intermediate mesoderm, through a sequence of reciprocal and complex tissue interactions(53). The earliest stage involves the interaction between the ureteric bud, a caudal outpouching of the Wolffian duct, and the metanpehric mesenchyme. As the ureteric bud invades the metanephric blastema, the cells condense and undergo mesenchymal to epithelial transition (MET), leading to early tubule formation. These early tubules will eventually become the glomerular podocytes, proximal and distal tubules and loop of Henle. The ureteric bud, itself induced to branch, forms the collecting duct system. It has long been thought that WT arises from the metanpehric mesenchyme, with gene expression correlating with early nephrogenesis(54). Recently, molecular profiles of WT with classic triphasic histology (blastemal, epithelial and stromal elements) have also matched those of the ureteric bud(55). Furthermore, many of the mutated genes found in WT are key regulators of the entire process (Figure 1).

2.2 Germline predisposition to Wilms

In up to 15% of cases, WT occurs on a background of a predisposition syndrome or germline mutation in cancer-risk genes (Table 2)(56,57).

The first gene to be implicated in tumorigenesis was *WT1* at 11p13. It encodes a zinc finger DNA-binding transcription factor that is non-redundant for urogenital development and glomerular function(58,59). There is no recurrent loci for somatic *WT1* mutations in WT. Mechanisms of WT1 inactivation include mutations affecting the DNA binding domain and mutations producing truncated proteins that lack this domain completely(60). WT1 is expressed in the metanephric and condensing mesenchyme, and its loss results in a spectrum from complete renal agenesis to disrupted differentiation depending on stage of nephrogenesis(59,61,62). Over 1000 genes appear to be regulated by the two major isoforms of WT1, many of which are essential for renal development and are themselves mutated in WT(63).

The constellation of urogenital malformation, renal failure and WT susceptibility occurs in the following syndromes, all with constitutional abnormalities in the *WT1* gene. WAGR syndrome (WT, anirida, genital anomaly and retardation) is caused by microdeletion of 11p13, including the *WT1* locus and the adjacent aniridia gene *PAX6*. Risk of WT development is around 50% and children present earlier with a higher incidence of bilateral tumours(64). Similarly, bilateral disease occurs in 20% of children with DDS, a syndrome characterised by ambiguous genitalia and nephropathy secondary to diffuse mesangial sclerosis(65). Missense mutations in the DNA-binding domain of *WT1* underlie DDS(66). Mutations that alter *WT1* splicing

cause Frasier syndrome, phenotypically similar to DDS but with focal segmental glomerulosclerosisis and a predisposition to gonadoblastoma(67). The association of *WT1* with intralobar nephrogenic rests (ILNR) suggests somatic *WT1* loss may be an early event(68).

A second WT locus was subsequently identified at 11p15. Paternal uniparental disomy or maternal *H19* epimutation both result in biallelic expression of *IGF2* and overactivation of the IGF signalling pathway (50). Abnormal methylation at 11p15 is the most common genomic change found in WT, uniformly present in multi-sampled tumours and found in perilobar nephrogenic rests (PLNR) (70,71). Multiple germline epigenetic and genetic changes at 11p15 are responsible for Beckwith Wiedmann Syndrome (BWS). BWS is an overgrowth syndrome with increased risk of embryonal tumours including WT, neuroblastoma, hepatoblatoma and rhabdomyosarcoma. WT develops in 20% of cases, with highest risk in uniparental disomy or H19 hypermethylation(72). The most common epigenetic subgroup (hypomethylation of *KvDMR1*) carries no increased risk of WT. Another generalised overgrowth syndrome with susceptibility to WT is the X-linked Simpson Golabi–Behmel syndrome. Mutations occur in the *GPC3* gene, encoding an extracellular proteoglycan involved in promoting Wnt signalling(73).

Disruption of miRNA biogenesis, through germline mutations in *DIS3L2* is the basis of Perlman syndrome(74). This is a rare overgrowth syndrome with susceptibility to WT, over half of which are bilateral. Mutations in the miRNA processing gene *DICER1* underlie the pleiotropic cancer susceptibility DICER1 syndrome and have been identified as a cause of familial WT(75). Two further predisposition loci were found by genetic linkage studies of affected families, occurring at 17q21(*FWT1*) and 19q13 (*FWT2*), although the genes have yet to be characterised(76,77). Finally, WT susceptibility occurs in several tumour predisposition syndromes including in Li-Fraumeni (*TP53*) and Fanconi anaemia (*BRCA2, PALB2*)(11).

2.3 *Recent advances in our understanding of somatic and germline changes*

Until a few years ago, the only known somatic mutations were those involving *WT1*, LOH at 11p15, the Wnt pathway (*AMER1*, *CTNNB1*) and the oncogene *MYCN*. Of these genes, only mutations in *MYCN* have clinicopathological association, predicting poor outcome in several childhood embryonal cancers including WT, neuroblastoma, medulloblastoma and rhabdomyosarcoma(78–81). Mutations in *CTNNB1* are frequently found to occur at serine 45, a functionally critical phosphorylation residue necessary for beta-catenin degradation(82,83). Recently, mutations in *MLLT1* have been identified, often occurring alongside variant *CTNNB1*(84). MLLT1 orchestrates transcription during nephrogenesis.

Applying unbiased tumour genome sequencing has revealed further cancer genes that harbor likely driver mutations in WT. Whole exome sequencing has identified alterations in the epigenetic remodelers SMARCA4 and ARID1A, members of the

BAF chromatin remodeling complex, with variants also found in medulloblastoma and atypical teratoid rhabdoid tumour (ATRT)(85–87). MicroRNA biogenesis and the miRNA processing genes *DROSHA, DICER1, DGCR8, XPO5* and *TARBP2* have too been implicated(5). *DROSHA* and *DICER1* mutations lead to reduced expression of the tumour-suppressor Let7 family and failure of epithelial differentiation. WT specific oncogenes that have been discovered include *SIX1* and *SIX2*, encoding transcription factors with a non-redundant role in renal development(8,88).

More recently, whole genome sequencing of 117 WT has added further candidates to the genetic landscape of WT(9). WT-related cancer genes now include those involved in histone modification during nephrogenesis (*BCOR, MAP3K4, BRD7, CREBBP* and *HDAC4*) and those that play a crucial role in transcriptional repression (*BCORL1*). BCOR and the homologous BCORL1 are ubiquitously expressed and postulated to have tumour suppressor function, with both somatic mutations and fusion transcripts identified in several other cancers(89–91). Internal tandem duplications (ITDs) of *BCOR* are the sole driver in a proportion of CCSK(92).

In addition, *NONO* and *MAX* have been implicated; both genes encoding proteins that interact with MYCN, with MAX expression appearing to correlate with clinical outcome in neuroblastoma(93–95). Alterations in *ACTB* (β-actin), another component of the BAF complex and *ASXL1*, a polycomb group protein, were also identified. Polycomb proteins are recruited by WT1, leading to downregulation of Pax2 expression, a transcriptional regulator with a vital role in urogenital development(96).

As well as representing a genetically diverse group, WT have been shown to display intra-tumoural diversity(70). Such micro-diversity has been associated with higher histological risk, advanced stage and poorer outcome in a study of 44 chemotherapy-exposed SIOP tumours(97). Copy number variants (CNVs) are common and the following are not uniformly spatially distributed, gain of 1q, gain of 2p24 (*MYCN* locus) and 17p13 loss (*TP53*)(9,41,70). Loss of 17p13 is predominantly associated with anaplastic tumours, which display a characteristically unstable cancer genome with additional loss of 4q and 14q(98). Gain of 2p24 (*MYCN*) is also associated with anaplasia, and has been reported as both a somatic and germline event(80).

Germline mutations occur in around 10% of patients with non-syndromic WT. The recent COG study identified a number of novel, putative WT predisposition genes including *CHEK2, EP300* and *ARID1A*(9). *CHEK2* is a tumour suppressor gene contributing to hereditary breast cancer and germline mutations have been found in high grade paediatric brain tumours(99,100). Germline events in another breast cancer risk gene, *PALB2*, were preferentially associated with diffuse anaplastic WT. Biallelic mutations in *PALB2* underlying Fanconi anaemia subtype FA-N have been previously identified in familial WT(101). Another recently identified candidate tumour suppressor gene is *REST*, with inactivating mutations predisposing to WT(102).

REST, a transcriptional repressor, is essential for embryogenesis and truncations in the protein occur in several other cancers including neuroblastoma(103). A second gene with a role in maintaining embryonic stem cell pluripotency is *CTR9*. Constitutional CTR9 mutations are present in several WT families(104,105). Homozygous loss of function mutations in *TRIP13* were found in children with WT on a background of mosaic variegated anapleuoidy syndrome(106).

2.4 MicroRNA processing genes

Mutations in several miRNA processing genes (miRNAPGs), including *DROSHA*, *DICER1*, *DGCR8*, *XPO5* and *TARBP2*, have been found in sporadic WT, in chemotherapy-naïve tumours and in tumours exposed to neoadjuvant agents(5,8,87,88). The mutational hotspot in the metal-binding RNase IIIb domain of *DROSHA* (E1147K) appears to be unique to WT, and has not been found in other childhood or adult cancers (Table 3). Recurrent mutations in the RNA binding domains of *DROSHA*, *DGCR8* and *DICER1* variant tumours lead to impaired miRNA biogenesis. Global downregulation of mature miRNAs, including the Let7 family, occurs in *DROSHA* mutants, with partial loss is seen in *DICER1* tumours(6). Let7 miRNA processing is suppressed by Lin28b. Overexpression of this RNA-binding protein during nephrogenesis leads to WT formation in mice(107). Copy number gain of *LIN28B* and loss of *Let7* are respectively seen in 25% and 46% of WT, and interestingly, cluster separately to *miRNAPG* variant tumours in gene but not miRNA expression(9). A reduction of the miR-200 family is also seen alongside *miRNAPG* mutations. These miRNA have a crucial role in MET in the developing kidney. Their downregulation is thought to lead to failure of the process(108). Mutations in *miRNAPG* are associated with pre-therapy blastemal histology, PLNR and aberrant imprinting at 11p15(88). The high frequency of LOI at 11p15 observed in tumours with combined *miRNAPG* and *SIX1/SIX2* alterations suggest multiple events are responsible for WT tumourigenesis in blastemal subtype. This combination, although infrequent, is associated with both relapse and poor outcome.

2.5 Unique (i.e. Wilms specific) cancer genes SIX1/SIX2

The three studies to have identified mutations in *SIX1/SIX2* all found a recurrent Q177R mutation in the DNA-binding homeodomain of these transcription factors, resulting in a glutamine to arginine substitution(7–9). Recurrent hot spot mutations in SIX1/SIX2 are unique to WT. Mutations in a different loci within the homeobox of *SIX1* occur in branchio-oto-renal syndrome, characterized by a spectrum of kidney abnormalities but with no increased risk of WT(109). SIX1 and SIX2 are key regulators of nephrogenesis. *SIX1* loss leads to mesenchymal apoptosis in *SIX1*-knockout mice(110). *SIX2* activity maintains the mesenchyme progenitor population in an undifferentiated blastema state(111). Cell cycle genes are upregulated in both *SIX1* and *SIX2* mutant WT. SIX2 overexpression in renal cell lines correlates with a higher percentage of cells in the S-phase(7,8). This cumulative evidence suggests that *SIX1/SIX2* have oncogenic function in a subset of tumours, driving proliferation of the metanephric mesenchyme. In WT, *SIX1/SIX2* mutations have been associated with

high-risk blastemal type in SIOP tumours and with the presence of undifferentiated blastema in chemo-naïve samples(7,8). Although the high allele frequency of *SIX* mutations suggests they may be an early event, an analysis of 8 paired primary-relapse samples found it to also occur de-novo(112).

2.6 Comparison of genetics of Wilms tumours with the other renal tumours of childhood

The remaining 10% of non-WT renal tumours most frequently include CCSK, malignant rhabdoid tumour of the kidney (MRTK), renal cell carcinoma (RCC) and the relatively benign CMN. CCSK has a similar age distribution to WT but is not associated with familial or predisposition syndromes. There are two non-concurrent genetic events that underlie the majority of CCSK tumours; internal tandem duplications (ITDs) of *BCOR* and translocation t(10;17)(q22;p13), resulting in fusion of *YWHAE* and *NUTM2B/E*(92,113,114). Although ITDs in *BCOR* have not been observed in WT, somatic mutations were found in *BCOR* and the closely related *BCORL1*(9). The Xp11 translocation-RCC are the most common subtype of RCC, and involve a fusion between the transcription factor *TFE3* (Xp11) and several genes including *ASPL* (17q25), *PRCC* (1q21) and *PSF* (1p34)(115). There are a multitude of rarer fusion partners, of which only *NONO* (Xq13) has also been implicated as a WT-related cancer gene. The peak incidence of RCC is in adolescence and around 15% of patients have previously received chemotherapy(116). Complete surgical resection is the only realistic curative therapy, and the use of multi-targeted receptor tyrosine kinase inhibition is reserved for metastatic or relapsed cases with only anecdotal evidence of efficacy. MRTK tends to occur under 2 years of age and 95% of patients have bialleic mutations in *SMARCB1*, another subunit of the BAF chromatin remodeling complex(117). A third of children have germline alterations in *SMARCB1* which acts as an additional poor prognostic indicator for a disease with an already dismal outlook(118). CMN is usually diagnosed in infancy and has an impressive five-year survival approaching 95%. Recurrent translocations, resulting in a fusion protein between the growth factor receptor NTRK3 and the transcription factor ETV6, are observed in the cellular and mixed subtypes of CMN(119).

B2. Peculiarities of Wilms that require some thinking

3.1 Genetic epidemiological differences in incidence and Wilms tumour sub-types around the world

There is epidemiological evidence to suggest the observed difference in WT incidence exists between races rather than geographical areas. The highest annual rates are seen in children of African descent (10 cases per million), the lowest in Asian populations (3 cases per million) and in Caucasians, the incidence is 6-9 per million(14,15,120). Hispanic children are noted to have a lower incidence of WT than Caucasian children and this risk varies within the population, depending on maternal birthplace(121,122). These observations and the increasing repertoire of germline WT predisposition genes

suggest genetic or epigenetic mechanisms are responsible for the observed ethnic disparity. Loss of imprinting at 11p15 and PLNR are more frequently identified in Caucasians than in both Japanese and American-born Asian children(123). Conversely, analysis of bilateral tumours from Japanese children reveals a far higher incidence of constitutional *WT1* anomalies(124). There is also apparent variation in histological subtype between races. Registration of anaplastic histology was 4.9% in the Japan Wilms' Tumor Study Group compared to 10.8% in the American National Wilms Tumor Study 5(125). Japanese children with anaplastic tumours had a lower stage of disease and good outcomes, but the number of cases was too small for direct prognostic comparison. Although a recent meta-analysis of published WT research identified mutations in *WT1* and *WTX* as more prevalent in non-Caucasians, with the reverse true for *CTNNB1,* the differences in prevalence were not statistically significant(126). Several genome wide association studies have identified polymorphisms that infer WT susceptibility, including *HACE1*, *BARD1*, 2p24, 11q14, but none of these investigations have been carried out in a cohort with mixed ethnicity(127–129).

3.2 Specific and near exclusive age predilection of Wilms to early childhood

In addition to the racial disparity observed in WT incidence, age at diagnosis varies and in the US, black children are diagnosed later than their Caucasian and Asian counterparts(10). WT predominantly occurs in early childhood, with a median age of diagnosis at 3 years for sporadic WT and 2 years for bilateral or multifocal cases. There is accumulating evidence to suggest that aberrant nephrogenesis may be an initiating step in tumourigenesis, explaining the narrow developmental window of WT. The first clue is that some WTs are accompanied by the persistence of embryonic tissue, ILNRs and PLNRs, otherwise not normally present in the postnatal kidney. Furthermore in a subset of WT, methylation profiles vary during tumour evolution from NRs(130). Gene expression profiles segregate WT into five clinically-relevant groups, each one coupled to a developmental stage of nephrogenesis(131). The link is further supported by the mapping of cell subpopulations in fetal kidneys and WT. $NCAM^{+}CD133^{-}$ represent renal stem cells in fetal kidneys and blastema in WT(132). $NCAM^{+}CD133^{+}$ and $NCAM^{-}CD33^{+}$ define immature and mature epithelia respectively. Finally, the ever-increasing number of WT related genes with pivotal roles in the developing kidney supports the hypothesis that WT are inextricably linked to renal organogenesis.

C How can this new knowledge of somatic cancer genes in Wilms lead to novel treatments?

Although largely curable in the developed world, identifying novel therapeutics remains a priority for the WT subgroups with poor prognosis. A recent study highlighted that only around 19% of children with relapse/refractory WT were recruited to early phase trials over the past decade(133). The outcome for patients enrolled in previous trials of targeted therapy remains dismal. COG is aiming to

address this by matching biological agents to actionable mutations, through its TARGET initiative(134). There are several promising avenues, particularly those involving somatic variants found in patients with relapse and/or fatal tumours.

One potential candidate is the oncogene *MYCN* as it is ubiquitously associated with poor outcome in many childhood cancers. MYCN was considered an 'undruggable' target prior to the advent of inhibitors of Aurora-A kinase (AURKA), which block the interaction between the two proteins resulting in MYCN degradation(135). Only 13% of WT have variant MYCN. In a recent phase II study of alisertib, an AUKRA inhibitor, 8 out of 10 WT patients had progressive disease(133). Objective response has been demonstrated with alisertib, as a single agent and as combination therapy in ATRT and neuroblastoma, respectively(136,137). In neuroblastoma cell lines, MYCN inactivation and growth arrest is seen with inhibition of RAS(138). The *RAS* superfamily (*H-RAS, K-RAS, N-RAS*) are the most mutated oncogenes in human cancer and have remained another elusive target(139). Although mutations in *RAS* are rarely observed in WT, RAS expression is associated with increased WT size and identified in patients with the combination of variant *SIX* and *miRNAPG*(88,140). In mice, K-RAS activation on a background of β-catenin stabilisation leads to metastatic renal tumours that closely resemble WT epithelial histology(141).

With the recent identification of mutations in epigenetic remodelers in WT, and their interaction with histone deacetylases (HDAC), inhibitors of the latter might be another promising avenue. Transient response to single agent vorinostat, an HDAC inhibitor, was demonstrated in a child with refractory anaplastic embryonal rhabdomyosarcoma harboring mutations in *BCOR* and *ARID1A*(142). A further potential target is *TP53,* given the prevalence of *TP53* mutants in both anaplastic and non anaplastic fatal tumours(41). There are currently no paediatric trials targeting *TP53.* Adult early phase trials are ongoing; to test both *TP53* recombinant adenoviral human gene therapy and inhibitors of MDM2/MDMX, negative regulators of *TP53*(143). Another recent phase II trial of interest is the CD56-binding antibody-drug conjugate, lorvotuzumab mertansine (144). CD56 (NCAM-1) is enriched in blastema and $CD56^{+}$ cells may act as cancer stem cells in a subset of tumours(145).

A more complete understanding of the genetic changes that drive WT development and progression has helped to identify potentially actionable mutations. Whether these will translate into improved survival for children with refractory, relapsed or high-risk disease remains to be seen. Our knowledge of the biological heterogeneity of WT continues to drive improvements in risk stratification through the introduction of molecular biomarkers. The next SIOP study/trial aims to validate the clinical utility of several of these promising candidates including 1q gain(20). Despite the discovery of almost 40 WT genes, the candidate genes driving oncogenesis in tumours with gain of 1q remain unknown. The outstanding objective remains to salvage the proportion of WT patients that relapse whilst, at the other end of the spectrum, to identify children with excellent prognosis in whom omission of therapy is a viable option. Further

elucidating the underlying genetic landscape will hopefully make personalised therapy for each child with WT the norm.

Conflicts of Interest
None

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Figure 1: Figure placing cancer genes in nephrogenesis

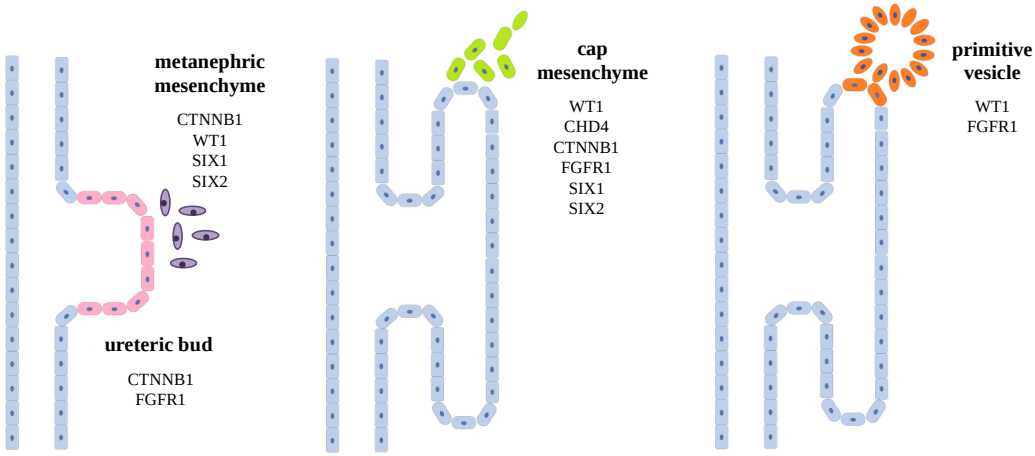

Table 1: Somatic cancer genes identified in Wilms tumour, with prevalence > 1%

Genetics	Copy number variation	Point mutation	Prevalence	Clinicopathological associations
WT1 (11p13)	✓	✓	10-20%	early event, found in ILNR associated with stromal histology
CTNNB1 (3p21)	✓	✓	15%	late event, not in NR associated with non-anaplastic histology
AMER1 (Xq11)	✓	✓	15-20%	no clinicopathological associations
IGF2 (11p15)	✓	✓	69%	early event, found in PLNR associated with epithelial /blastemal histology
TP53 (17p13)	✓	✓	70%	reduced EFS and OS rarely found in tumours without diffuse anaplasia
MYCN (2p24)	✓	✓	13%	reduced EFS and OS associated with anaplastic histology
miRNAPG	✓	✓	15-18%	found in PLNR *DGCR8* has a female bias (88% of cases) reduced EFS/OS when concurrent with *SIX1/2*
SIX1 (14q23), *SIX2* (2p21)	✓	✓	7-18%	found in PLNR reduced EFS/OS when concurrent with miRNAPG
SMARCA4 (19p13)	✓	✓	4.5%	not known
MLLT1 (19p13)	✓	✓	4%	early event, found in ILNR; younger age
BCORL1 (Xq26)	✓	✓	3.8%	not known
COL6A3 (2q37)	✓	✓	3.2%	not known
NF1 (17q11)	✓	✓	2.9%	not known
BCOR (Xp11)	✓	✓	2.6%	not known
NONO (Xq13)	✓	✓	2%	not known
ARID1A (1p36)	✓	✓	1.8%	not known
MAP3K4 (6q26)	✓	✓	1.7%	not known
MAX (14q23)	✓	✓	1.7%	not known
ASXL1(20q11)	✓	✓	1.7%	not known
BRD7 (16q12)	✓	✓	1.5%	not known
FGFR1 (8p11)	✓	✓	1.4%	not known
HDAC4 (2q37)	✓	✓	1.2%	not known
CHD4 (12p13)	✓	✓	1.2%	not known
ACTB (7p22)	✓	✓	1.1%	not known

Table 2: Wilms predisposition syndromes

WT risk	**Syndrome**	**Genetics**
High >20%	WAGR	*WT1* deletion
	DDS	*WT1* missense mutation
	Perlman	*DIS3L2* mutation
	Fanconi anaemia	Biallelic *BRCA2* mutation/ PALB2 mutation
	Mosaic variegated aneuploidy	Biallelic *BUB1B/TRIP13* mutation
Moderate 5 – 20%	Frasier	*WT1* intron 9 splice mutation
	BWS	Uniparental disomy or H19 epimutation
	Simpson Golabi Behmel syndrome	*GPC3* mutation
Low < 5%	Bloom	Biallelic *BLM* mutation
	DICER1 syndrome	*DICER1* mutation
	Li Fraumeni	*TP53* mutation
	Isolated hemihypertrophy	variable
	Hyperparathyroidism-jaw tumour syndrome	*CDC73/ HRPT2* mutation
	Mulibrey nanism	*TRIM37* mutation
	PIK3CA-related segmental overgrowth	*PIK3CA* mutation

Table 3: Recurrent intragenic mutations found in Wilms tumour(146).

Gene	**Recurrent mutation**	**Number of WT cases**	**Hotspot identified in other cancers (number of cases)**
CTNNB1	*S45F*	35	soft tissue (441) hepatocellular carcinoma (78) colon carcinoma (77) adrenocortical carcinoma (42)
MYCN	*P44L*	34	neuroblastoma (4) endometrial carcinoma (4) basal cell carcinoma (4) glioma (3) medulloblastoma (1)
DROSHA	*E1147K*	85	nil
DGCR8	*E518K*	50	thyroid carcinoma (2)
SIX1	*Q177R*	29	nil
SIX2	*Q177R*	23	nil
MAP3K4	*G1366R*	6	colon carcinoma (3) malignant melanoma (2) acute myeloid leukaemia (1)
MAX	*R60Q*	15	endometrial carcinoma (4) colon carcinoma (4) glioma (3) acute myeloid leukaemia (2) medulloblastoma (1)

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