

Genetic Predisposition to Wilms Tumor

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Richard H. Scott and Nazneen Rahman

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R.H. Scott • N. Rahman (✉)
Section of Cancer Genetics, Institute of Cancer
Research, 15 Cotswold Road, Sutton,
Surrey SM2 5NG, UK
e-mail: ScottR3@gosh.nhs.uk;
nazneen.rahman@icr.ac.uk

Abstract

Wilms tumor is a primarily sporadic disease, with only 1–2 % of affected individuals having a relative with Wilms tumor. However, bilateral Wilms tumors occur in approximately 5 % of cases, and Wilms tumor has been reported in association with more than 50 different genetic disorders, pointing to an underlying predisposition in further individuals. There is conclusive evidence of an increased risk of Wilms tumor in only a small number of disorders, including familial Wilms tumor, the *WT1*-related syndromes, certain overgrowth disorders including Beckwith-Wiedemann syndrome and a small number of other cancer predisposition syndromes. The identification of the molecular defects that underlie these Wilms predisposition syndromes clarifies the risks of Wilms tumor risks and assists in the targeting of Wilms surveillance to those at increased risk. For example, in some disorders such as the 11p15-overgrowth disorders, it has emerged that only a subset of individuals are at increased risk of Wilms tumor. The discovery of further Wilms predisposition alleles is set to continue and will improve our ability to identify and manage those at increased risk of Wilms tumor.

2.1 Introduction

Wilms tumor is primarily a sporadic disease with only 1–2 % of individuals with the tumor having a relative with Wilms tumor (Breslow et al. 1996). However, a number of strands of evidence indicate that underlying constitutional predisposition accounts for a substantial proportion of cases.

Firstly, Wilms tumors are frequently multifocal. Disease is bilateral in 5 % of cases and unilateral-multicentric in 10 % (Dinkel et al. 1988; Breslow et al. 1993; Ritchey et al. 2005). Precursor lesions – nephrogenic rests – are present in surrounding renal tissue in 40 % of cases (25 % perilobar; 15 % intralobar) (Beckwith et al. 1990).

Secondly, a wide range of syndromes, congenital anomalies and constitutional chromosome abnormalities have been reported in association with Wilms tumor (Scott et al. 2006a). Data from the British National Registry of Childhood Tumors showed that ~9 % of individuals with Wilms tumor have a congenital malformation and one study of long-term survivors of childhood cancer found a syndrome diagnosis in 23 of 136 (17 %) of those with Wilms tumor

(Narod et al. 1997; Merks et al. 2005). This is the highest proportion seen in any malignancy. Conclusive evidence exists of an increased risk of Wilms tumor for only a minority of conditions reported in association with Wilms tumor (Table 2.1). In many of the other conditions reported, the rare co-occurrence of Wilms tumor is likely due to chance.

Identification of the underlying molecular basis of Wilms predisposition has furthered understanding of Wilms tumor predisposition. In some syndromes, for example, those caused by 11p15 abnormalities, evidence has emerged that an increased risk of Wilms tumor occurs only in a subset of individuals (Scott et al. 2006a; Gaston et al. 2001). In addition, it has emerged that some genetic defects originally identified in individuals with syndromic Wilms tumor also account for a proportion of cases with apparently sporadic isolated ('non-syndromic') disease, for example, 11p15 abnormalities and *WT1* mutations (Little et al. 2004; Scott et al. 2008).

The underlying cause of the large majority of Wilms tumors, including bilateral and familial cases, remains unexplained, and it is likely that further strongly predisposing genetic defects remain to be identified. It is also likely

Table 2.1 Conditions in which there is strong evidence of an increased risk of Wilms tumor

| |
|--|
| <i>High risk (≥20%)</i> |
| Familial Wilms tumor |
| <i>WT1</i> deletions (including WAGR syndrome) ^a |
| <i>WT1</i> truncating mutations and pathogenic missense mutations (including Denys-Drash syndrome) |
| Perlman syndrome |
| Fanconi anaemia subtype D1 (biallelic <i>BRCA2</i> mutations) and subtype N (biallelic <i>PALB2</i> mutations) |
| Mosaic variegated aneuploidy |
| <i>Moderate risk (5–20%)</i> |
| <i>WT1</i> intron 9 splice mutations (Frasier syndrome) |
| 11p15-overgrowth caused by <i>H19</i> DMR hypermethylation or paternal UPD 11p15 ^b |
| Beckwith-Wiedemann syndrome without an 11p15 defect |
| Simpson-Golabi-Behmel syndrome caused by <i>GPC3</i> deletions or mutations |
| <i>Low risk (≤5%)</i> |
| Isolated hemihypertrophy without an 11p15 defect |
| Bloom syndrome |
| Li-Fraumeni syndrome and Li-Fraumeni-like syndrome |
| Mulibrey nanism |
| Hereditary hyperparathyroidism-jaw tumor syndrome |
| Trisomy 18 |
| Trisomy 13 |
| 2q37 deletions |

^aWAGR syndrome, Wilms tumor-aniridia-genitourinary abnormalities-growth retardation syndrome

^b11p15-overgrowth caused by *H19* DMR hypermethylation or paternal UPD 11p15 includes individuals with Beckwith-Wiedemann syndrome, isolated hemihypertrophy as well as other presentations such as non-syndromic Wilms tumor

that lower-penetrance predisposition alleles exist, such those that have been identified in neuroblastoma and a number of adult malignancies (Capasso et al. 2009).

2.2 Conditions with an Increased Risk of Wilms Tumor

2.2.1 Familial Wilms Tumor

At least 50 familial Wilms tumor pedigrees are known (N Rahman, unpublished observation). Most families manifest with non-syndromic disease, and the underlying cause of the majority

remains unknown. A minority are caused by syndromes described in the subsequent sections: *WT1* mutations/deletions (four families), 11p15 defects (two families), mosaic variegated aneuploidy (two families) and biallelic *BRCA2* mutations (one family) (Scott et al. 2008; Yunis and Ramsay 1980; Pelletier et al. 1991; Kaplinsky et al. 1996; Zirn et al. 2005; Sparago et al. 2007; Hanks et al. 2004; Reid et al. 2007).

An autosomal dominant non-syndromic familial Wilms tumor gene, *FWT1*, has been mapped to 17q21 but has not yet been identified (Rahman et al. 1996, 1998). Wilms tumor in *FWT1*-linked families tends to be diagnosed at a later age and more advanced stage than sporadic Wilms tumor (median age at diagnosis 6 years). The penetrance of *FWT1* is only ~30 %, and the wild-type allele is not lost in tumors (Rahman et al. 1997). These features suggest that *FWT1* does not operate as a classical tumor suppressor gene.

A second autosomal dominant non-syndromic Wilms tumor predisposition gene, *FWT2*, has been proposed to lie at 19q13 (McDonald et al. 1998). The evidence favouring this locus is inconclusive as no single family with a LOD score >3 has been identified. Although combining the LOD score of five smaller families gave a score >3, families unlinked at 19q13 were excluded from the analysis.

Several families not linked to *FWT1*, *FWT2*, *WT1* or 11p15 exist, indicating that further genetic heterogeneity in familial Wilms tumor exists (Rapley et al. 2000). A small number of families have been reported which show predisposition to both Wilms tumor and neuroblastoma, another embryonal tumor (Abbaszadeh et al. 2010). The gene(s) causing this previously unrecognised cancer syndrome are currently unknown.

2.2.2 *WT1*-Associated Syndromes

Constitutional monoallelic (heterozygous) mutations or deletions in the *WT1* gene cause predisposition to Wilms tumor. The gene behaves as a classical tumor suppressor gene, and the

wild-type allele is inactivated in tumors occurring in individuals with constitutional monoallelic mutations or deletions. The median age of Wilms tumor diagnosis in such individuals is younger than in unselected Wilms tumor case series (approximately 1 year in *WT1*-associated syndromes; 3–4 years in unselected Wilms cases). Tumors are more frequently bilateral (38 % in *WT1*-associated syndromes; 5 % in unselected Wilms cases), and intralobar nephrogenic rests (ILNRs) are more frequently present. The tumors often show stromal predominant histology (Royer-Pokora et al. 2004).

Constitutional *WT1* defects are associated with a range of overlapping phenotypes, manifesting various combinations of three features: Wilms tumor predisposition, genitourinary abnormalities and renal dysfunction. A number of genotype-phenotype correlations have emerged.

2.2.2.1 WAGR Syndrome

WAGR (Wilms tumor-aniridia-genitourinary abnormalities-mental retardation) syndrome is found in approximately 7–8 per 1,000 individuals with Wilms tumor (Breslow et al. 2003). It manifests with complete or partial aniridia, ambiguous external genitalia/cryptorchidism in males and intellectual impairment. Additionally, there is a high risk of renal failure, which affects ~40 % of individuals by the age of 20 years (Breslow et al. 2000). The condition is caused by monoallelic deletions at 11p13 encompassing the *WT1* and *PAX6* genes. Deletion of *WT1* results in Wilms tumor predisposition and deletion of *PAX6* results in aniridia (Muto et al. 2002). Approximately 30 % of individuals with aniridia harbour *WT1*-*PAX6* deletions. Many of the remainder harbour point mutations or intragenic deletions of *PAX6*. Individuals with isolated *PAX6* defects are not at increased risk of Wilms tumor. A number of individuals have been reported with deletions or chromosomal aberrations that delete *WT1* but not *PAX6* (Royer-Pokora et al. 1991; Baird et al. 1992). These manifest with Wilms tumor predisposition and genitourinary abnormalities but not aniridia.

2.2.2.2 Denys-Drash Syndrome

Denys-Drash syndrome classically describes the combination of Wilms tumor, nephropathy and genitourinary abnormalities in males that are severe enough to result in pseudohermaphroditism (Denys et al. 1967; Drash et al. 1970). The nephropathy is usually a characteristic mesangial sclerosis, presenting with hypertension and proteinuria and typically progressing to renal failure requiring renal replacement therapy prior to the age of 10 years (Eddy and Mauer 1985). Genitourinary abnormalities in XY individuals are very common but vary in severity from mild hypospadias to female genitalia with streak gonads. Some XX individuals have gonadal dysgenesis, but the majority have normal genitourinary development. Most individuals with classical Denys-Drash syndrome harbour de novo missense *WT1* mutations targeting critical residues in the zinc finger domains that are responsible for DNA binding of the *WT1* protein. These mutations are thought to act in a dominant-negative manner to result in this more severe phenotype (Royer-Pokora et al. 2004).

2.2.2.3 Frasier Syndrome

Frasier syndrome is the association of nephropathy, gonadal dysgenesis and gonadoblastoma (Frasier et al. 1964). The nephropathy is typically a focal segmental glomerulosclerosis which progresses to renal failure by the second or third decade of life (Demmer et al. 1999). Genitourinary abnormalities in XY individuals are severe and sex reversal is common. The syndrome is caused by mutations in intron 9 of *WT1* that alter splicing and prevent formation of *WT1* isoforms that normally include a linker of three amino acids (KTS) between the third and fourth zinc finger domains (Barboux et al. 1997).

2.2.2.4 Non-syndromic Wilms Tumor and Other Presentations of *WT1* Mutations

WT1 mutations have also been reported in individuals with one or two of the three features of *WT1*-associated syndromes, for example, with Wilms tumor and cryptorchidism, with isolated ('non-syndromic') Wilms tumor or with isolated

nephropathy (Kohler et al. 2001). These individuals are more likely to harbour intragenic truncating mutations than missense mutations in the zinc finger domains. Most germline *WT1* mutations are de novo, but rare families have been reported with *WT1* defects that have presented with familial Wilms tumor (Little et al. 2004; Yunis and Ramsay 1980; Pelletier et al. 1991; Kaplinsky et al. 1996; Zirn et al. 2005).

2.2.2.5 The Risk of Wilms Tumor with *WT1* Mutations

The risk of Wilms tumor in individuals with *WT1* deletions, truncating mutations or pathogenic missense mutations targeting the zinc finger domains is probably at least 50 % (Royer-Pokora et al. 2004; Muto et al. 2002). Missense variants outside the zinc finger domains may be rare non-pathogenic polymorphisms, and caution should be exercised in their interpretation, particularly if they are not de novo.

The risk of Wilms tumor in individuals with *WT1* intron 9 splice mutations (Frasier syndrome) is considerably lower than for other mutations. Only four of 66 individuals (6 %) reported with Frasier syndrome developed Wilms tumor (Coppes et al. 1993; Barbosa et al. 1999; Loirat et al. 2003). However, the risk of gonadoblastomas is high in Frasier syndrome, whereas these tumors are rare in individuals with other classes of *WT1* mutation.

2.2.3 Overgrowth Syndromes

Childhood overgrowth syndromes are a heterogeneous group of disorders characterised by pre- and/or postnatal overgrowth often in association with other abnormal phenotypic features. It has previously been assumed that a wide variety of overgrowth disorders predispose to cancer in childhood including Wilms tumor. In part, this may be because high birth weight has been identified as a possible risk factor for Wilms tumor in a number of mainly population-based studies (Leisenring et al. 1994; Heuch et al. 1996; Yeazel et al. 1997; Schuz et al. 2001; Jepsen et al. 2004). However, as understanding of specific

overgrowth disorders has improved, it has emerged that only a small subset of overgrowth syndromes predispose to Wilms tumor. Wilms tumor risk of children with overgrowth should therefore be evaluated on the basis of the specific syndrome rather than a collective basis.

2.2.3.1 11p15-Overgrowth Including Beckwith-Wiedemann Syndrome and Hemihypertrophy

Growth-promoting constitutional epigenetic and genetic abnormalities at the imprinted 11p15 region cause a spectrum of overgrowth phenotypes (Scott et al. 2008; Weksberg et al. 2005). The classical 11p15-overgrowth phenotype is Beckwith-Wiedemann syndrome (Weksberg et al. 2005; Thorburn et al. 1970; Elliott and Maher 1994). It is characterised by pre- and postnatal overgrowth, macroglossia, anterior abdominal wall defects, ear lobe creases and posterior helical pits, neonatal hypoglycaemia and hemihypertrophy (growth asymmetry). Non-malignant renal tract abnormalities also occur, including nephromegaly, renal cysts, medullary sponge kidney, medullary dysplasia and hydronephrosis. The overall risk of childhood cancer associated with Beckwith-Wiedemann syndrome has been estimated to be 4–21 %. Wilms tumor is the most frequently occurring childhood tumor, reported in 1–8 % of individuals (Sotelo-Avila et al. 1980; Elliott et al. 1994; Wiedemann 1997; DeBaun and Tucker 1998; Goldman et al. 2002). Perilobar nephrogenic rests (60 %) and bilateral disease (17 %) are seen more frequently than in unselected Wilms series (15 and 5 % respectively) (Ritchey et al. 2005; Beckwith et al. 1990; Porteus et al. 2000). Approximately 75 % of individuals fulfilling diagnostic criteria for Beckwith-Wiedemann syndrome have an identifiable 11p15 defect (Weksberg et al. 2005).

A substantial proportion of individuals with 11p15 defects do not fulfil the diagnostic criteria of Beckwith-Wiedemann syndrome. These individuals typically manifest with more subtle physical phenotypes such as isolated hemihypertrophy (Merks et al. 2005; Martin et al. 2005; Shuman et al. 2006; Bliet et al. 2008). This is in keeping

with the recognised association between isolated hemihypertrophy and Wilms tumor. A prospective study of 168 patients with isolated hemihypertrophy identified ten tumors in nine individuals including five with Wilms tumor (3 %) (Hoyme et al. 1998). It is notable that tumors occur at similar frequency in the larger and smaller kidney in asymmetric individuals. Approximately 20 % of individuals with hemihypertrophy have an identifiable 11p15 defect (Martin et al. 2005; Shuman et al. 2006; Blik et al. 2008).

Constitutional 11p15 Defects Cause Non-syndromic Wilms Tumor

More recently, it has emerged that some individuals with constitutional 11p15 defects manifest with non-syndromic Wilms tumor. A study of 437 British children with non-syndromic Wilms tumor found 11p15 defects in 12 (3 %) (Scott et al. 2008). These individuals could not be reliably distinguished from unselected cases based on physical phenotypic or histological features. As with individuals with Beckwith-Wiedemann syndrome, bilateral disease was more frequent in this group.

The Risk of Wilms Tumor with Constitutional 11p15 Defects

The detailed exposition of the 11p15 region and these defects is beyond the scope of this chapter. Briefly, the 11p15 region contains a number of growth-controlling genes that show imprinted (i.e. parent-of-origin-specific) expression at 11p15 (Weksberg et al. 2005; Rahman 2005). The genes are arranged in two independent domains (imprinted domain 1 and imprinted domain 2), each controlled by differential DNA methylation at an imprinting control region (the H19 DMR at domain 1 and KvDMR at domain 2).

A variety of epigenetic and genetic defects have been reported that disrupt the region to result in a net increase in the expression of growth-promoting genes. Isolated KvDMR hypomethylation is the commonest cause of Beckwith-Wiedemann syndrome, accounting for approximately 50 % of cases. Paternal uniparental disomy of 11p15, which results in KvDMR

hypomethylation and H19 DMR hypermethylation, is found in 20 % of cases. Isolated H19 DMR hypermethylation is found in approximately 5 % of cases. Maternally inherited *CDKN1C* mutations are found in a further 5 % of Beckwith-Wiedemann syndrome cases. A small number of cases are caused by duplications 11p15. These include interstitial paternal duplications encompassing only the *IGF2/H19* locus, as well as larger duplications extending to the 11p telomere as part of an unbalanced reciprocal chromosome translocation (Weksberg et al. 2005; Russo et al. 2006; Algar et al. 2007).

A number of studies have revealed strong epigenotype-Wilms tumor risk correlations in 11p15-overgrowth disorders. Studies of large numbers of individuals with Beckwith-Wiedemann syndrome and individuals with hemihypertrophy have each found a strong association between defects that result in H19 DMR hypermethylation and Wilms tumor risk (Merks et al. 2005; Gaston et al. 2001; Martin et al. 2005; Shuman et al. 2006; Blik et al. 2008; Blik et al. 2001, 2004; Weksberg et al. 2001; DeBaun et al. 2002; Cooper et al. 2005). These defects include isolated hypermethylation of the H19 DMR and UPD 11p15 and result in biallelic expression of *IGF2*. It has been assumed that it is biallelic *IGF2* expression which drives Wilms predisposition in these individuals. No individual to date has been identified with Wilms tumor and isolated KvDMR hypomethylation, despite this accounting for approximately 50 % of cases of Beckwith-Wiedemann syndrome. This strong correlation is confirmed by study of Wilms tumor case series, which has identified only 11p15 defects resulting in H19 DMR hypermethylation (Scott et al. 2008).

The risk of Wilms tumor in individuals with features of 11p15-overgrowth but with no detectable 11p15 defect is dependent on their clinical presentation. The risk of Wilms tumor in individuals fulfilling diagnostic criteria for Beckwith-Wiedemann syndrome is likely to be moderately increased (>5 %), while the risk for those with isolated hemihypertrophy is likely to be low (<5 %) (Scott et al. 2006a).

It should be noted that there is no evidence of an increased risk of Wilms tumor in individuals

with 11p15-growth retardation disorders such as Silver-Russell syndrome. This is in keeping with the observation that the molecular defects at 11p15 observed in these individuals result in *H19* DMR hypomethylation/reduced *IGF2* expression and are therefore reciprocal to those seen in 11p15-overgrowth disorders (Gicquel et al. 2005).

Heritability of 11p15 Defects

The majority of 11p15 defects are apparently isolated epigenetic abnormalities. These are typically non-heritable and therefore manifest with sporadic rather than familial disease. A small number of individuals have been identified with heritable genetic defects, usually *H19* DMR microdeletions or microinsertions, that cause *H19* DMR hypermethylation (Scott et al. 2008; Sparago et al. 2004; Cerrato et al. 2008). To allow accurate counselling regarding familial recurrence risks, 11p15 testing should be targeted to detect these heritable defects, for example, by using MS-MLPA (spell out in full). The risk of Wilms tumor in relatives of those with 11p15 defects is low assuming this group of defects have been eliminated.

2.2.3.2 Perlman Syndrome

Perlman syndrome is a rare autosomal recessive overgrowth disorder with high mortality in infancy. It is characterised by prenatal overgrowth with polyhydramnios, visceromegaly, cryptorchidism, facial dysmorphism, developmental delay, renal dysplasia and Wilms tumor (Perlman et al. 1973). It is caused by biallelic mutations in *DIS3L2* gene (Astuti et al. 2012). Nine of 29 (31 %) reported cases developed Wilms tumor (Perlman et al. 1975; Neri et al. 1984; Greenberg et al. 1986; Grundy et al. 1992; Henneveld et al. 1999; Fahmy et al. 1998; Chitty et al. 1998; Piccione et al. 2005; Alessandri et al. 2008). No other tumors have been reported. Of note, nephroblastomatosis or renal hamartomas have been reported in all but one of the infants born at term. Of the nine individuals that survived beyond 28 days, six developed Wilms tumor.

2.2.3.3 Simpson-Golabi-Behmel Syndrome

Simpson-Golabi-Behmel syndrome is an X-linked recessive overgrowth disorder characterised by coarse facial features, cardiac abnormalities, polydactyly, accessory nipples and, in some individuals, learning difficulties. Renal dysplasia or nephromegaly have been reported in approximately 30 % of cases, and other renal abnormalities described include hydroureter and hydronephrosis (Mariani et al. 2003). The condition is caused by loss of function mutations or deletions of *glypican-3* (*GPC3*) located at Xq26 (Pilia et al. 1996; Li et al. 2001). Such mutations are identifiable in about 70 % of affected individuals. The cause of the remainder is unknown. *GPC3* is a cell surface proteoglycan that modulates the effects of several growth factors and interacts with the Wnt pathway (Grisaru et al. 2001; Song et al. 2005).

Of the 51 cases with *GPC3* mutations reported with the condition, three (6 %) developed Wilms tumor (Hughes-Benzie et al. 1996; Lindsay et al. 1997; Rodriguez-Criado et al. 2005; Young et al. 2006; Romanelli et al. 2007; Sakazume et al. 2007; Li and McDonald 2009). Other embryonal tumors have been reported in a small number of cases. There is no evidence of increased risk of Wilms tumor in females carrying *GPC3* mutations/deletions or in individuals affected with a clinical diagnosis of Simpson-Golabi-Behmel syndrome without a *GPC3* mutation/deletion.

2.2.4 Other Tumor Predisposition Syndromes

There is evidence to support an increased risk of Wilms tumor associated with a small number of additional tumor predisposition syndromes.

2.2.4.1 Fanconi Anaemia Types D1 and N

Fanconi anaemia refers to a group of recessive chromosome breakage disorders with overlapping clinical and cellular phenotypes. Clinically, it is characterised by short stature, microcephaly, radial ray defects, hyper- and hypopigmented

skin lesions and bone marrow failure. Myelodysplasia and acute myeloid leukaemia are common in childhood, and there is an increased risk of solid tumors of the head and neck in adulthood (Tischkowitz and Hodgson 2003). Cells from individuals with Fanconi anaemia show increased chromosome breakage to DNA cross-linking agents. It is this feature which allows confirmation of the diagnosis of Fanconi anaemia through the analysis of the response of peripheral blood lymphocytes to agents such as diepoxybutane (DEB). At least 13 subtypes of Fanconi anaemia have been described and 13 causative genes identified (Reid et al. 2007; Tischkowitz and Hodgson 2003; Thompson 2005). Two subtypes of Fanconi anaemia, subtypes D1 and N, show a high risk of Wilms tumor and other childhood solid tumors.

Heterozygous monoallelic mutations in *BRCA2*, which is involved in double-strand break DNA repair, cause high-penetrance predisposition to breast cancer and ovarian cancer in adulthood, but not to childhood cancers. Biallelic (homozygous or compound heterozygous) mutations in *BRCA2* cause Fanconi anaemia type D1. Affected children are less likely to have skeletal abnormalities than most Fanconi anaemia subtypes, and their cells often show spontaneous chromosome breakage (Howlett et al. 2002; Reid et al. 2005; Meyer et al. 2005). The cancer spectrum is also distinctive, with a greatly increased risk of childhood solid tumors including Wilms tumor, as well brain tumors. Ten of 32 individuals (30 %) reported with biallelic *BRCA2* mutations developed Wilms tumors (Reid et al. 2005; Meyer et al. 2005; Reid 2008).

Biallelic mutations in *PALB2*, which encodes a *BRCA2* interacting protein, cause Fanconi anaemia type N (Reid et al. 2007; Xia et al. 2006, 2007). Unlike *BRCA2*, heterozygous monoallelic mutations in *PALB2* cause only a modest (approximately twofold) increase in breast cancer risk, and increased risk of ovarian cancer has not been observed (Rahman et al. 2007). However, the phenotype seen with biallelic *PALB2* mutations is very similar to that caused by biallelic *BRCA2* mutations. The cancer spectrum is strikingly similar, with frequent occurrence of Wilms tumor

and other childhood solid tumors. Three of eight individuals (38 %) reported with biallelic *PALB2* mutations developed Wilms tumor (Reid et al. 2007; Reid 2008).

There is no evidence to suggest that there is an increased risk of Wilms tumor in other subtypes of Fanconi anaemia.

2.2.4.2 Mosaic Variegated Aneuploidy

Mosaic variegated aneuploidy is a rare autosomal recessive disorder characterised by constitutional mosaicism for gains and losses of whole chromosomes. Biallelic mutations in *BUB1B* – which encodes BUBR1, a key component of the mitotic spindle checkpoint – cause approximately half of cases (Hanks et al. 2004). The clinical features of the condition are variable and include developmental delay, microcephaly, CNS malformations, cataracts, congenital heart defects and other malformations. Childhood cancers are frequently reported in the condition, including Wilms tumor, leukaemia and rhabdomyosarcoma. Wilms tumor has occurred in nine (19 %) of 47 cases (N Rahman, unpublished observation) (Hanks et al. 2004; Nakamura et al. 1985; Kajii et al. 1998, 2001; Kawame et al. 1999; Matsuura et al. 2000; Jacquemont et al. 2002; Furukawa et al. 2003).

2.2.4.3 Bloom Syndrome

Bloom syndrome is an autosomal recessive DNA repair disorder caused by biallelic mutations in the *BLM* gene, which encodes a DNA helicase important in the response to aberrant recombination between sister chromatids and homologous chromosomes (Ellis et al. 1995). Diagnosis of the condition can be made through the analysis of peripheral blood lymphocytes following exposure to bromodeoxyuridine (BrdU). Clinically, the condition is characterised by short stature, microcephaly, sun-sensitivity and characteristic telangiectatic skin lesions in sun-exposed areas. In some cases, learning difficulties are also a feature. An increased frequency of a number of cancers has been reported, principally in adulthood (German 1997). Wilms tumor has been reported in a number of individuals and is known to have occurred in eight of 267 individuals (3 %) in the Bloom syndrome registry (J German, personal

communication) (German 1997; Cairney et al. 1987; Berger et al. 1996; Jain et al. 2001; The Bloom's Syndrome Registry 2010).

2.2.4.4 Li-Fraumeni Syndrome

Li-Fraumeni is an autosomal dominant tumor predisposition disorder which is characterised by a high incidence of a range of tumors including breast cancer, sarcomas, adrenocortical carcinoma and brain tumors (Li et al. 1988). Approximately 70 % of families with classical Li-Fraumeni syndrome harbour heterozygous, monoallelic mutations in *TP53* – a key regulator of cell cycle arrest, apoptosis and DNA repair (Birch et al. 1994; Evans et al. 2002). Wilms tumor is not one of the cardinal tumors seen in the condition and is not included in the diagnostic criteria of Li-Fraumeni syndrome. However, it has been reported in at least 7 families with *TP53* mutations and in several Li-Fraumeni or Li-Fraumeni-like families without *TP53* mutations (Li and Fraumeni 1982; Hartley et al. 1993; Bardeesy et al. 1994; Evans et al. 1998; Verselis et al. 2000; Chompret et al. 2000; Birch et al. 2001; Olivier et al. 2002). Of note, five of the seven *TP53* mutations were splice site mutations despite splice mutations accounting for only 4 % of all reported germline *TP53* mutations, and it is possible that Wilms tumor risk is influenced by the type of *TP53* mutation. However, overall, the risk of Wilms tumor appears to be low, both in families with *TP53* mutations and in mutation-negative families with classical Li-Fraumeni syndrome or a Li-Fraumeni-like phenotype.

2.2.4.5 Mulibrey Nanism

Mulibrey nanism (MUScle-LIVer-BRAIN-EYE nanism) is an autosomal recessive disorder characterised by short stature, facial dysmorphism, muscle wasting, hepatomegaly, J-shaped sella turcica radiographically and distinctive yellow spots on the retina (Karlberg et al. 2004a, b). Hepatic hamartomas and ovarian fibrothecomas are also seen. The condition is caused by biallelic mutations in the *TRIM37* gene, which has ubiquitin E3 ligase activity (Avela et al. 2000). At least 130 individuals with mulibrey nanism have been reported, of whom six (4–5 %) have developed

Wilms tumor (Karlberg et al. 2004a; Simila et al. 1980; Seemanova and Bartsch 1999; Karlberg et al. 2009).

2.2.4.6 Hyperparathyroidism-Jaw Tumor Syndrome

Hyperparathyroidism-jaw tumor syndrome is an autosomal dominant disorder caused by heterozygous, monoallelic mutations in the *HRPT2* gene, which is thought to be involved in RNA elongation (Carpten et al. 2002). It is characterised by parathyroid tumors and fibro-osseous lesions of the maxilla and mandible (Jackson et al. 1990). More than 150 individuals from more than 50 families have been reported (Kakinuma et al. 1994; Teh et al. 1996; Wassif et al. 1999; Tan and Teh 2004; Mizusawa et al. 2006; Masi et al. 2008; Iacobone et al. 2009). A variety of renal abnormalities and tumors occur including renal cysts, renal cortical adenomas, benign mixed epithelial-stromal renal tumors and papillary renal cell carcinomas. Wilms tumor has been reported in three individuals (<2 %), including one individual who apparently developed bilateral Wilms tumor at the age of 53 years.

2.2.5 Constitutional Chromosome Abnormalities

Abnormalities at 11p13 (*WT1*) and 11p15 are the most frequent constitutional chromosome abnormalities associated with Wilms tumor. There is evidence of Wilms tumor predisposition in a small number of other chromosome disorders.

2.2.5.1 Trisomy 18

Trisomy 18 (Edwards syndrome) occurs in approximately 1 in 13,000 live births (Nielsen and Wohler 1991). It is associated with multiple congenital malformations and has high infant mortality, with 90 % of individuals dying before the age of 1 year. Renal malformations including horseshoe kidney are present in the majority of cases (Kinoshita et al. 1989). There have been at least 12 cases of Wilms tumor in individuals with trisomy 18 (Geiser and Schindler 1969;

Shanklin and Sotelo-Avila 1969; Miller 1971; Karayalcin et al. 1981; Sheng et al. 1990; Faucette and Carey 1991; Olson et al. 1995; Kullendorff and Wiebe 1997; Anderson et al. 2003). In addition, perilobar nephrogenic rests and/or nephroblastomatosis have been reported in a number of cases without Wilms tumor (Bove et al. 1969). The median age of diagnosis of Wilms tumor in trisomy 18 (5 years) is higher than in sporadic disease. Given the high early mortality of trisomy 18, the risk of Wilms tumor to long-term survivors is clearly increased.

2.2.5.2 Trisomy 13

Trisomy 13 (Patau syndrome) occurs in approximately 1 in 10,000 live births. Like trisomy 18, it is associated with multiple congenital malformations including renal abnormalities (Nielsen and Wohler 1991). It has a high early mortality, with a median survival of 1 week. Two cases of Wilms tumor have been reported in trisomy 13, one of which arose in a horseshoe kidney (Olson et al. 1995; Sweeney and Pelegano 2000). Nephroblastomatosis was also identified in one foetus following termination at 24 weeks of gestation [cite 1] ADD REF. Given the very high mortality of trisomy 13, it is likely that there is an increased risk to those that survive the early neonatal period.

2.2.5.3 2q37 Deletion

Three individuals with constitutional terminal deletions of chromosome 2q37 have been reported with Wilms tumor. Two had isolated deletions of 2q37 with a centromeric breakpoint at 2q37.1 (Conrad et al. 1995; Viot-Szoboszalai et al. 1998). A further child had a paternally inherited unbalanced translocation resulting in monosomy 2q37-qter and trisomy 15q22-qter (Olson et al. 1995). The location of the breakpoint within 2q37 was not reported. Almost 100 individuals have been reported with 2q37 deletions (Casas et al. 2004; Falk and Casas 2007). The most frequent centromeric breakpoint is 2q37.3. In approximately a quarter of cases, the deletion extends to 2q37.1. The overall risk of Wilms tumor may be as high as 3 % (two of 66). However, it is possible that the

risk is primarily in those in which the deletion extends to 2q37.1 and who may be at higher risk.

2.3 Conditions in Which Wilms Tumor Predisposition Is Unclear or Uncertain

In addition to the conditions described above in previous sections of this chapter, Wilms tumor has been reported in association with a substantial number of other genetic disorders (Scott et al. 2006a). For some, relatively common, disorders in which few cases of Wilms have been reported, it is likely that the occurrence(s) of Wilms tumor is coincidental and not because of a predisposition. For example, fragile-X syndrome, Marfan syndrome and tuberous sclerosis are all relatively common and readily diagnosed genetic disorders in which only a single case of Wilms has been reported (Newbold et al. 1982; Grether et al. 1987; Drouin et al. 1992). Only six cases of trisomy 21 (Down) syndrome have been reported with Wilms tumor despite the condition affecting approximately 1 in 800 live births (Fabia and Drolette 1970; Kusumakumary et al. 1995; Spreafico et al. 2007). Seven individuals with neurofibromatosis type 1 have been reported (Ito et al. 1997). However, neurofibromatosis type 1 occurs in approximately 1 in 3,000 individuals and a number of population-based, cohort and cancer registry studies have failed to detect an association with Wilms tumor (Sorensen et al. 1986; Huson et al. 1988; Friedman and Birch 1997; Walker et al. 2006).

For other disorders, the possibility of a small increased risk of Wilms tumor cannot be excluded. For example, four individuals with Turner syndrome (45,XO) were reported in one American Wilms tumor case series (Olson et al. 1995). However, no case was found in a British series of 400 cases and only one case was found in a Danish series of 597 individuals (Hasle et al. 1996; Swerdlow et al. 2001). It is likely therefore that the absolute Wilms tumor risk in Turner syndrome is close to that of the general population.

In the case of Sotos syndrome, an overgrowth disorder caused by heterozygous monoallelic mutations in *NSDI*, molecular testing has clarified the risk of Wilms tumor. The syndrome can be difficult for those without experience of the condition to diagnose on clinical grounds alone. A number of individuals with a clinical diagnosis of Sotos syndrome were reported with Wilms tumor, and it had been thought that the risk was appreciable in the condition. Following the introduction of molecular testing for the condition, it has emerged that the risk of Wilms tumor is very low (Tatton-Brown et al. 2005).

In the case of the rarer disorders reported on one or only a small number of occasions with Wilms tumor and the many reported individuals with Wilms tumor with a presentation that is not readily classifiable, it is hard to be certain whether the occurrence of Wilms tumor represents a predisposition or a coincidental finding. These conditions are not set out individually here, but the interested reader is referred to Table 2 in Scott et al. (2006a).

Similarly, a number of discrete chromosomal abnormalities have been reported on one occasion in association with Wilms tumor (Table 2.2). It is likely that in some of these, the chromosomal defect targets a Wilms predisposition gene. For example, two individuals have been reported with overlapping abnormalities that result in copy number gain at chromosome 15q (Hu et al. 2002; Schluth et al. 2005). This region contains the *IGF1R* gene, which may underlie predisposition to Wilms tumor in these individuals. One child with bilateral Wilms tumor was reported with a de novo apparently balanced reciprocal chromosome translocation with breakpoints at 5q21 and 6q21 (Table 2.2) (Hoban et al. 1997; Slade et al. 2010). The 6q21 breakpoint transects the *HACE1* gene and would be predicted to truncate the gene product. This, and the subsequent identification of a further child with unilateral Wilms tumor harbouring a truncating point mutation in *HACE1*, identified *HACE1* as a likely Wilms predisposition gene (Slade et al. 2010). This study found that *HACE1* mutations are rare in Wilms tumor and are likely to make only a small contribution to Wilms tumor predisposition.

2.4 Wilms Tumor Surveillance in Predisposed Individuals

Surveillance for Wilms tumor is recommended in children at substantially increased risk, and Wilms tumor surveillance has become widespread. However, there is limited evidence regarding its efficacy and the balance of risks and benefits of Wilms tumor surveillance (Scott et al. 2006b). This has resulted in the use of different surveillance strategies in different countries and even different units within the same country as well as the inclusion of children at different levels of risk. In some cases, children close to population risk have been enrolled in surveillance.

Because of the high survival rate in Wilms tumor, it is unlikely that surveillance will lead to a substantial decrease in mortality. However, surveillance may identify tumors at a more favourable stage. This could be important because the resultant reduced intensity of chemotherapy and radiotherapy is likely to result in reduced long-term treatment-related morbidity. There have been three small retrospective evaluations of Wilms tumor surveillance published, only one of which reported a significant difference in stage distribution between screened and unscreened individuals (Green et al. 1993; Craft et al. 1995; Choyke et al. 1999). It is notable that three of 15 screened individuals in this study had false-positive scans that resulted in further imaging and major surgery, indicating that significant negative sequelae of surveillance can occur. In addition, the anxiety and practical difficulties associated with regular surveillance can be appreciable.

Although there is no clear evidence that surveillance results in a significant decrease in mortality or tumor stage, tumors detected by Wilms tumor surveillance would be anticipated to be on average smaller than tumors that present clinically. In Germany, where abdominal ultrasound in children is common and 10 % of Wilms tumors are diagnosed prior to symptoms, there are some data to suggest that asymptomatic tumors are of lower stage than those that present due to clinical symptoms (N Graf, personal communication). On this basis, it is felt reasonable to offer surveillance

Table 2.2 Constitutional chromosome abnormalities reported in association with Wilms tumor

| Karyotype | Comment | Clinical features | Reference |
|--|---|---|--|
| t(1;16)(p22;p13.2) | Apparently balanced | Unilateral Wilms | Olson et al. (1995) |
| del(1)(p36pter) | | Unilateral Wilms | Scott et al. (2006a) |
| del(1)(p36pter) dup(1)(q24qter) | De novo unbalanced translocation with breakpoints at 1p36 and 1q24. Mosaic in amniocytes and normal renal tissue. Present in all tumor cells examined | Bilateral Wilms, agenesis corpus callosum, cardiac malformations, facial dysmorphism, developmental delay | Mark et al. (2005) |
| dup(1)(q27.2;q27.3) | | | Bache et al. (2006) |
| t(1;7)(q42;p15) | Apparently balanced, de novo | Unilateral Wilms, nephrogenic rest contralateral kidney, bilateral radial aplasia, short tibiae and fibulae; transient thrombocytopenia | Hewitt et al. (1991) |
| del(2)(p11.2p12) | Maternally inherited | Speech delay, mildly dysmorphic | Barber et al. (2005) |
| t(5;6)(q21;q21) | Apparently balanced, de novo, <i>HACE1</i> interrupted at 6q21; see text | Bilateral Wilms | Hoban et al. (1997), Slade et al. (2010) |
| t(7;19)(q11.2;q13.3) | Apparently balanced, de novo | Bilateral Wilms, thick corpus callosum, large cisterna magna, facial dysmorphism | Cavicchioni et al. (2005) |
| t(7;13)(q36;q13) | Apparently balanced, de novo | Unilateral Wilms, facial dysmorphism, developmental delay, umbilical hernia, testicular ectopia | Bernard et al. (1984) |
| 8p+ | Additional material of unknown origin at 8p | Wilms in a single kidney | Olson et al. (1995) |
| del(9)(q22q32) | De novo, encompasses <i>PTCH</i> | Synchronous rhabdomyosarcoma, features of Gorlin syndrome | Alvarez-Franco et al. (2000) |
| t(9;12)(q22.3;q15) | Apparently balanced, de novo | | Betts et al. (2001) |
| del(11)(q14.1q21) | De novo | Horseshoe kidney, nephrogenic rests | Stratton et al. (1994) |
| del(12)(q11q13.1) | De novo, LOH 12q in tumor | Unilateral Wilms, growth retardation, developmental delay, facial dysmorphism | Rapley et al. (2001) |
| dup(12)(q24.3qter) del(22)(q13.3qter) | Inherited from mother with balanced t(12;22)(q24.3;q13.3) | Unilateral Wilms, overgrowth, developmental delay | Turner et al. (2001) |
| Tetrasomy 15q24.3-qter | Mosaic in lymphocytes | Unilateral Wilms, developmental delay, arachnodactyly, facial dysmorphism | Schluth et al. (2005) |
| Tetrasomy 15q25.3-qter | Mosaic constitutionally, present in all tumor cells | Bilateral, arachnodactyly, overgrowth, craniosynostosis | Hu et al. (2002) |
| Ring chromosome of unknown origin | Mother and two children with ring chromosome | Both children developed Wilms, one unilaterally, one bilaterally | Kakati et al. (1991) |

to children at substantially increased risk of Wilms tumor (Scott et al. 2006b).

In the United Kingdom, surveillance is performed by renal ultrasound scanning, and, given the rapid tumor doubling time, this is recommended to be performed at 3–4-month intervals (Scott et al. 2006b). Alternative methods of

surveillance have been proposed and used, including regular parental examination for abdominal masses and CT or MRI scanning. However, renal ultrasound scan is the preferred modality because it is sensitive to relatively small tumors and does not require sedation to perform (Schmidt et al. 2003).

In the United Kingdom, it is recommended that children at >5 % risk of Wilms tumor are offered this surveillance (Table 2.1) (Scott et al. 2006b). Screening begins at syndrome diagnosis and continues to cover the age range of diagnosis of at least 90–95 % of tumors for the predisposing syndrome. For the *WT1*-associated syndromes, Fanconi anaemia types D1 and N, mosaic variegated aneuploidy and Perlman syndrome virtually all tumors occur before 5 years and thus surveillance is not recommended beyond this age. Surveillance is recommended to continue to 7 years for individuals with constitutional 11p15 defects, Simpson-Golabi-Behmel syndrome and those from familial Wilms tumor pedigrees in which Wilms tumor has occurred above the age of 5 years.

2.5 Future Directions

2.5.1 Identification of Further High-Penetrance Predisposition Alleles

Despite the successes in the clinical and molecular delineation of Wilms tumor predisposition syndromes, further high-penetrance Wilms tumor predisposition alleles remain to be identified. The cause of the majority of familial Wilms tumor pedigrees remains unknown. The causative gene(s) are likely to be identifiable using linkage-based approaches and/or next-generation sequencing techniques. The genes underlying some recognised syndromic Wilms tumor predisposition syndromes also remain to be identified, for example, *BUB1B* mutation-negative mosaic variegated aneuploidy cases. In addition, it is likely that there are other Wilms tumor predisposition syndromes that are as yet unrecognised as illustrated by the recent emergence of Fanconi anaemia type add types as a new, highly penetrant Wilms predisposition syndrome. Next-generation sequencing approaches may be particularly applicable to gene identification in these rare syndromes, which may not be amenable to linkage analysis.

Some cases of bilateral Wilms tumor are accounted for by known Wilms predisposition

genes, most notably *WT1* and 11p15. However, the majority remain unexplained and the underlying predisposition alleles remain to be identified (Little et al. 2004; Scott et al. 2008). In some cases, the underlying allele will be identifiable using the approaches above. However, recent evidence suggests that in some cases the underlying predisposition may be caused by a mosaic, tissue-specific defect at 11p15 which has arisen early during development such that it is present in the precursors of both kidneys (N Rahman, unpublished observation). Further investigation of this possibility is warranted.

2.5.2 Clarification of Wilms Tumor Risks and Identification of Further Genotype-Tumor Risk Correlations

The study of larger number of individuals with known Wilms tumor predisposition syndromes or syndromes where predisposition remains uncertain will improve estimates of the risk of Wilms tumor in these conditions. Accurate estimation of risk is difficult in the absence of large, prospective trials. These are rarely possible in the disorders in question, which are rare and in some cases difficult to diagnose before the occurrence of Wilms tumor. This is particularly problematic in conditions where Wilms tumor is a diagnostic criterion. It is likely that for many syndromes, cases with tumors are more likely to be reported than those without. This reporting bias is likely to have led to an overestimate of Wilms tumor risk. The availability of cheaper molecular testing and its application in a wider range of clinical presentations may assist by improving diagnosis of cases without Wilms tumor (or prior to its diagnosis), as it has in the *WT1*- and 11p15-related disorders (Little et al. 2004; Scott et al. 2008; Kohler et al. 2001; Martin et al. 2005).

Molecular analysis of larger number of cases also has the potential to detect further genotype-tumor risk correlations. The success in this regard in 11p15-overgrowth disorders points to the importance of these findings in targeting Wilms surveillance to those at highest risk and allowing the release of individuals at low risk from unnecessary surveillance (Scott et al. 2008).

2.5.3 Identification of Further Common, Low-Penetrance Predisposition Alleles

Following the advent of high-density SNP array technology and the development of the required statistical expertise, genome-wide association studies have been performed in a wide range of disorders (Donnelly 2008). These large case-control experiments have identified common low-penetrance predisposition alleles for a wide range of disorders including a number of cancers. Typically, odds ratios for disease seen with alleles identified by such studies are between 1.2 and 2.0. Of particular relevance is the genome-wide association study led by John Maris at the Children's Hospital of Philadelphia which has identified low-penetrance predisposition alleles for the childhood embryonal tumor neuroblastoma (Maris et al. 2008; Capasso et al. 2009; Diskin et al. 2009). In 2012, a genome-wide association study of British and American Wilms tumor cases identified loci at chromosome 2p24.3 and chromosome 11p14.1 at which common variants are associated with increased risk of Wilms tumor (Turnbull et al. 2012). The risk variants at these loci had odds ratios for disease of approximately 1.2 and 1.4 respectively. The mechanism by which the risk association of these loci is conferred remains unclear. At 2p24, the most likely candidate genes for the effect include *DDX1* and *MYCN*. At 11p14.1, the most likely candidate is *DLG2*. Further sequencing studies and functional analyses may assist in determining mechanism of these effects. Further genome-wide association studies may identify further such common, low-penetrance predisposition alleles.

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