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Congenital abnormalities and clinical features associated with Wilms' tumour: A comprehensive study from a centre serving a large population

A. Ng[a], *A. Griffiths*[a], *T. Cole*[b], *V. Davison*[b], *M. Griffiths*[b], *S. Larkin*[b], *S.E. Parkes*[a], *J.R. Mann*[a,*], *R.G. Grundy*[c]

[a]*Department of Paediatric Oncology, Birmingham Children's Hospital, B4 6NH, UK*
[b]*Department of Clinical Genetics and the Regional Cytogenetics Unit, Birmingham Women's Hospital NHS Healthcare Trust, B15 2TG, UK*
[c]*Department of Child Health, University of Nottingham, Nottingham NG7 2UH, UK*

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ABSTRACT

Altogether 156 children treated for Wilms' tumour (WT) between 1970 and 1998 were studied. Sixty-six children, selected only by their attendance at clinic, were carefully examined and the findings compared to those from a case note review of 90 children. Congenital abnormalities were present in 45% of the examined cohort, in 19% of the case notes review group and in 30% overall. Novel findings included the association of WT with Marshall Smith syndrome, developmental delay in 3 of 4 cases of WT (one bilateral) and 1 sibling from consanguineous Pakistani families and another sibling also had leukaemia. The possibility of rare DNA repair or cancer predisposing disorders among these 4 families requires further study. Careful examination and history taking of an unselected patient cohort revealed a higher than expected incidence of clinical abnormalities which may be overlooked if not specifically sought.

1. Introduction

One of the fascinating aspects of Wilms' tumour (WT) is the association between congenital abnormalities, specific genetic abnormalities and tumourigenesis. Clinical and genetic analyses of these rare patients have provided the clues that lead to our current, though still incomplete, understanding of the molecular pathogenesis of this tumour.

The WT predisposition syndromes can be broadly divided into four groups: those involving genes on chromosome 11p13 controlling development of the kidney, eye and genitourinary tract; the overgrowth syndromes; familial WT; and DNA repair defects. A previous large study suggested that congenital anomalies are found in about 14% of patients with WT and are twice as common in children with bilateral tumours.[1] Four to eight percent of patients with WT have genitourinary anomaly, representing a twofold increase over the general population rate.[1] Sporadic aniridia is associated with a greatly increased risk of developing WT at an early age.[2,3] Children with the complex phenotype including sporadic Aniridia, Genitourinary abnormalities and Retardation of growth and development, known as the AGR triad, have a 50% chance of developing WT.[4] The full phenotype is termed the WAGR syndrome. Constitutional cytogenetic studies in children with the WAGR syndrome provided one of the clues that led to the isolation of the *WT1* gene from 11p13.[5] *WT1* plays a crucial role in genitourinary and renal development.[6] Mutations inactivating both copies of this gene are detectable in most

* *Corresponding author:* Tel.: +44 (0)121 455 8643; fax: +44 (0)121 333 8241.
E-mail address: jillmann@doctors.org.uk (J.R. Mann).
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but not all WT arising in patients with the WAGR or Denys–Drash syndrome, but are only detected in 5–10% of sporadic WT.[7]

Three important overgrowth syndromes, Beckwith–Wiedemann,[8,9] Perlman,[10] and Simpson–Golabi–Behmel[11] syndromes, and isolated hemihypertrophy are associated with an increased risk of developing WT. Furthermore, an epidemiological study has shown a link with increased birth weight in children subsequently diagnosed with WT.[12]

Autosomal recessive DNA repair disorders including mosaic variegated aneuploidy, biallelic *BRCA2* mutations, and cancer predisposing syndromes such as Li–Fraumeni have also been associated with the development of WT.[13–15]

Information on the incidence of congenital abnormalities in WT has mostly been collected from large multi-institutional therapeutic studies.[1,4,16,17] In this paper, we report the findings of a detailed study of patients attending a single centre which serves a large population.

2. Patients and methods

Children attending the long-term follow-up clinic at Birmingham Children's Hospital (BCH) with a diagnosis of WT made between 1970 and 1988 were invited in an unselected manner to take part. A standard form was used to record clinical details and examination findings. The information sought included detailed family pedigree at least to grandparents, pre/perinatal history including birthweight, anterior abdominal wall defects and hypoglycaemia. The clinician (A.G., J.R.M., paediatric oncologists +/− T.C., clinical geneticist) completed a comprehensive examination, prompted by the details listed on the form, particularly looking for abnormalities of the limbs, skin, musculoskeletal and genitourinary systems, and neurodevelopment. These congenital abnormalities included those of abnormal embryogenesis and minor variants.[22] Limb asymmetry was defined as a discrepancy in leg length or circumference of more than 2 cm. Overgrowth features included limb asymmetry, and height/weight over 95th centiles.

Constitutional karyotype was performed if not previously done and DNA was stored. If available the medical notes on all other patients with WT treated at BCH during the same period were scrutinised and information was extracted according to the form. Approval was obtained from the South Birmingham Local Research Ethics Committee for this study.

3. Results

During the study period, 171 WT cases were treated, of whom 147 are alive and well with a median follow-up of 12 years. Sixty-six unselected patients attending clinics were examined and data recorded according to the study form. For comparison medical notes on 90 other WT patients were reviewed and data were extracted using the same form. This group included 13 deceased cases whose notes were still available. The notes of 15 other patients were either incomplete or unavailable for review. Overall, 156 cases (133 Caucasian, 13 Asian, 3 Afro-Caribbean, 7 other ethnic groups) were assessed. Congenital abnormalities were recorded in 45% of the examined cohort, in 19% of the notes review group and in 30% of both groups combined. The rates of abnormalities by ethnic groups were Caucasian 28% (37 of 133), Asian 62% (8 of 13) and Afro-Caribbean 66% (2 of 3). Details are summarised in Tables 1–3.

3.1. *Clinical abnormalities associated with WT*

There were 4 children with WAGR syndrome (cases 1–3 and 5), 1 child without obvious clinical signs of WAGR who was mosaic for 11p13 deletion (case 4) and 1 child with Denys–Drash syndrome (case 6). Clinical abnormalities affecting the genitourinary (cases 7–14), gastrointestinal (cases 15–18), cardiovascular (cases 19, 24, and 25), respiratory tracts (cases 20 and 21), skeleton (cases 10, 25, and 26), spine (case 25), or developmental delay (cases 27–32 and 48) were found without recognised genetic syndromes. Eleven patients had overgrowth features, including 4 with limb asymmetry and 7 with height/weight above 95th centiles. Of the latter 7 cases, 4 had measurements greater than 3 standard deviations (SD) and 2 had birthweight more than 2SD above the mean (cases 36, 37, 40, and 41). All these cases, together with the specific overgrowth syndromes (including Marshall Smith), are listed in Table 3.

Table 1 – Demographics of the whole assessed cohort

	Examined		Case note review		All assessed cases	
	No.	%	No.	%	No.	%
Gender						
Male	35	53	50	56	85	55
Female	31	47	40	44	71	45
Ethnicity						
Caucasian	53	80	80	89	133	85
Asian	9	14	4	4.5	13	8
Afro-Caribbean	1	1.5	2	2	3	2
Other	3	4.5	4	4.5	7	5
Laterality of WT						
Unilateral	59	89	83	92	142	91
Bilateral	7	11	7	8	14	9

No., number; WT, Wilms' tumour.

Table 2 – Comparison of clinical abnormalities in the examination and note review cohorts

Clinical features	Total no.	Examined no.	Notes review no.	Percentage of examined cohort	Percentage of notes cohort	Ethnicity			Gender	
						C	A	AC	M	F
WT1 mutation syndromes	6	4	2	6	2	5	1	–	4	2
Overgrowth syndromes	3	3	0	5	0	2	–	1	1	2
Overgrowth features	11	10	1	15	1	11	–	–	6	5
Genitourinary anomalies	8	4	4	6	4	7	1	–	5	3
Gastrointestinal and abdominal defect	4	2	2	3	2	4	–	–	4	0
Cardiovascular and respiratory abnormalities	6	2	4	3	4	5	1	–	6	0
Skeletal/spinal anomalies	3[a]	0	3	0	3	3	–	–	1	2
Developmental delay	6	5	1	8	1	1	5	–	2	4
All abnormalities and syndromes	47	30	17	45	19	37	8	2	29	18

No., number; C, Caucasian; A, Asian; AC, Afro-Caribbean.
a One girl also had absent uterus.

Four patients were the offspring of consanguineous Pakistani parents (Pedigrees 1–4, Fig. 1). The propositus in one of these families had bilateral WT. Three of these 4 cases had developmental delay (cases 29, 30, and 32) and 1 had aortic stenosis (case 19). Three siblings of these 4 cases also had developmental delay (case 29) or pulmonary atresia (case 19) or acute lymphoblastic leukaemia (ALL) (case 19).

3.2. *Familial WT*

A Caucasian family was found with histologically proven WT affecting 4 members and hemihypertrophy in a cousin (Pedigree 6, Fig. 1; case 47).

3.3. *WT and other tumours*

We identified 5 families (3 Caucasian and 2 Pakistani) with a history of another malignancy in 1 or more family members presenting in childhood. Each of the Pakistani families (Pedigrees 3 and 5) had a case of ALL affecting a sibling or first cousin, and the Caucasian families (Pedigrees 7–9) are shown in Fig. 1. There were 3 Caucasian individuals, siblings or first cousins, who had brain tumours (cases 7 and 48) in childhood or a teenage cancer (case 49). Another Caucasian girl with unilateral WT and her sister also developed a thyroid adenoma in adolescence (Pedigree 10, case 51).

In addition, the biological fathers of a boy with bilateral WT and WAGR syndrome (case 1) and a girl with unilateral WT (case 52) developed a meningioma and a pineal tumour, respectively. The first cousin of a girl with unilateral WT also developed a brain tumour in adult life (case 53). All 3 are Caucasian and none of the Caucasian families were consanguineous.

Overall, in 4% of families these were paediatric cancers in first, second or third degree relatives (Tables 3 and 4).

3.4. *Genetic analyses*

Blood samples for cytogenetic/molecular genetic analysis were obtained from 59 of the 66 patients in the examined group and 15 of 90 in the notes review group. All the peripheral blood karyotypes were normal except in 4 children with deletion of 11p13 and one who was mosaic for 11p13 deletion. Molecular analysis had confirmed the diagnosis of the patient with Simpson–Golabi–Behmel syndrome[23] and the baby with Denys–Drash syndrome, who had *WT1* mutation.

Tumour cytogenetic results were available in 32 of the 66 patients in the examined group and 21 of the 90 patients in notes review group. Among these, 3 tumours had 11p13 deletion, 3 had loss of chromosome 16, 2 cases had loss of chromosome 1, and 11 had hyperdiploid karyotypes. Cytogenetic analysis failed in 12 cases.

4. Discussion

Detailed assessment of an unselected group of children with WT has detected a higher level of congenital and other abnormalities than has generally been reported from large multi-institution studies.[1,2,4,16–19] Our series included over 75% of all WT cases diagnosed in West Midlands residents during 1970–1998. We found that among children with WT treated at our centre who underwent careful clinical examination 45% had abnormalities, compared with 19% in the group where information was obtained by thorough case notes review. Our findings suggest that information gathered only from clinical records may underestimate the prevalence of abnormalities because they may be missed unless are specifically looked for. Furthermore, some abnormalities may not reveal themselves (e.g. absent uterus with primary amenorrhoea) until years after the diagnosis of WT. These factors may account for the lower prevalence reported (10–22%) from information collected at the time of entry of patients into national WT trials.[1,4,16,17,20] However, it is also possible that patients without additional abnormalities are less likely to be attending long-term follow-up clinics, so a lower prevalence of abnormalities in these cases is not unexpected.

The abnormalities detected in our survey included overgrowth features (7%), genitourinary tract malformation (5%) and other anomalies such as cardiac, skeletal, respiratory and gastrointestinal tract defects. Most of our patients with clinical abnormalities did not have a syndrome for which the genetic basis is known, such as those associated with

Table 3 – Description of associated clinical abnormalities and childhood tumours in affected individuals and close relatives

Case	Group	Gender	Ethnicity	Age at diagnosis (year)	Age examined (year)	WT laterality	Blood karyotype	Clinical abnormalities/ phenotype or cancer
1	E	M	C	2	7	Bilateral	46,XY,del(11)(p13p15.1)	WAGR, father had meningioma in adult life
2	E	M	C	0.8	1	Bilateral	46,XY,del(11)(p13p13)	WAGR
3	E	M	A	1.5	21	Bilateral	46,XY,del(11)(p13p14.2)	WAGR
4	E	F	C	1	5	Unilateral	Mosaic for 46,XX,del (11)(p13p13)	Wedge of pale pigmentation in one iris
5	N	M	C	3	26	Bilateral	46,XY,del(11)(p13p13)	WAGR
6	N	F	C	0.1	0.1	Bilateral	46,XX, *WT1* mutation	Denys–Drash syndrome
7	E	F	C	3	25	Unilateral	Not available	Horseshoe kidney, first cousin had ependymoma, daughter with hemihypertrophy, sisters and first cousin had congenital heart disease
8	E	M	C	1.5	2.5	Unilateral	Not available	Undescended testes, foreskin abnormality
9	E	F	A	5	5.5	Bilateral	46,XX	Streak ovaries but normal uterus and external genitalia
10	E	F	C	2	13	Unilateral	Not available	Absent uterus, normal vagina and ovaries; cervical hemivertebra, scoliosis and bilateral dislocated hips (possibly MURCS association)
11	N	M	C	1	9	Unilateral	Not available	Ectopic testis
12	N	M	C	2	24	Unilateral	46,XY	Varicocele
13	N	M	C	2	21	Unilateral	Not available	Varicocele
14	N	F	C	3	4	Unilateral	46,XX	Horseshoe kidney, acrofacial dysostosis
15	E	M	C	5	23	Unilateral	46,XY	Umbilical hernia
16	E	M	C	3	3	Unilateral	46,XY	Malrotation of gut
17	N	M	C	3	7	Unilateral	Not available	Meckel's diverticulum
18	N	M	C	5	9	Unilateral	Not available	Bilateral inguinal hernia
19	E	M	A	1	14	Unilateral	Not available	Aortic stenosis, brother had acute lymphoblastic leukaemia, sister had congenital heart disease, consanguineous family
20	E	M	C	2	2	Unilateral	Not available	Juvenile laryngeal papillomatosis
21	N	M	C	1.5	2	Unilateral	Not available	Choanal hypoplasia
22	N	M	C	4	9	Unilateral	Not available	Micrognathia, large and prominent ears
23	N	M	C	2	15	Unilateral	Not available	Pulmonary stenosis
24	N	M	C	4	9	Unilateral	Not available	Ventricular septal defect
25	E	F	C	4	20	Unilateral	Not available	Spina bifida, hydrocephalus, scoliosis
26	E	M	C	5	12	Unilateral	Not available	Deformity of the right costal cartilages
27	E	F	A	7	22	Unilateral	46,XX	Psychomotor delay
28	E	F	C	4	12	Unilateral	Not available	Psychomotor delay, macrocephaly
29	E	M	A	3	14	Unilateral	46,XY	Developmental delay, sister had developmental delay, consanguineous family
30	E	M	A	3	22	Unilateral	46,XY	Developmental delay, height and weight < third centiles, consanguineous family
31	E	F	A	9	14	Unilateral	46,XX	Severe deafness
32	N	F	A	0.4	7	Bilateral	Not available	Global developmental delay, microcephaly, consanguineous family

(*continued on next page*)

Table 3 – *continued*

Case	Group	Gender	Ethnicity	Age at diagnosis (year)	Age examined (year)	WT laterality	Blood karyotype	Clinical abnormalities/ phenotype or cancer
33	E	F	C	4	24	Unilateral	46,XX	Beckwith–Wiedemann syndrome
34	E	F	C	6	7	Unilateral	46,XX	Marshall Smith Syndrome
35	E	M	AC	7	21	Unilateral	*GPC3* deletion	Simpson–Golabi–Behmel syndrome
36	E	M	C	7	11	Unilateral	Not available	Height and weight > 97th centiles (3.5SD)
37	E	M	C	5	15	Unilateral	46,XY	Height and weight >95th centiles (3.6SD)
38	E	M	C	1.5	3	Unilateral	46,XY	Height and weight > 95th centiles
39	E	M	C	2	5	Unilateral	46,XY	Height and weight >95th centiles
40	E	M	C	3	15	Unilateral	46,XY	Height and weight >97th centiles (3.6SD)
41	E	F	C	2	3	Unilateral	Not available	Height and weight > 97th centiles (3.9SD)
42	E	F	C	8	9	Unilateral	46,XX	Height and weight >95th centiles
43	E	F	C	3	11	Unilateral	46,XX	Limb asymmetry
44	E	F	C	3	25	Unilateral	46,XX	Limb asymmetry
45	E	F	C	3	29	Unilateral	46,XX	Limb asymmetry
46	N	M	C	3.5	9	Unilateral	Not available	Limb asymmetry
47	E	M	C	7	16	Unilateral	46,XY	Familial Wilms' tumour, hemihypertrophy (cousin)
48	E	M	C	0.8	10	Unilateral	Not available	Developmental delay, brain tumours (brother and first cousin)
49	E	M	C	4.5	17	Unilateral	Not available	Teenage cancer (first cousin)
50	E	F	A	2.5	14	Bilateral	Not available	Acute lymphoblastic leukaemia (first cousin)
51	E	F	C	3	15	Unilateral	46,XX	Thyroid adenoma (proband and sister)
52	E	F	C	1	13	Unilateral	Not available	Pineal tumour in adult life (father)
53	N	F	C	2	23	Unilateral	Not available	Brain tumour in adult life (first cousin)

E, examined group; N, notes review group; M, male; F, female; C, Caucasian; A, Asian; AC, Afro-Caribbean.

overgrowth and *WT1* mutation and this finding is similar to that of other reported series.[1,4,16,17] It is also pertinent to note that previously reported associations including horseshoe kidney, gut malrotation and skeletal defects were documented in our series. The possibility of a link of WT to other more complex disorders such as acrofacial dysostosis (case 14) has not been reported, but merits further consideration.[21] Merks and colleagues[22] recently reported a higher incidence of malformation syndrome, including new syndrome-tumour associations, in a large cohort of children with cancer examined by geneticists skilled in clinical morphology. They identified developmental delay, asymmetric growth and abnormalities affecting the genitourinary tract, skeleton, face, palate, skin; as well as association with recognised and suspected genetic syndromes in their cohort of 136 patients with WT. Although not all of our patients were assessed by a clinical geneticist, known genetic syndromes were found in 11% of the group who underwent careful examination. This figure was lower than the 16.9% among the WT patients in Merks' study, but the latter also included cases with suspected genetic syndromes.

A range of overgrowth features was detected in our series. Four children were found to have limb asymmetry and there was one case each of Beckwith–Wiedemann and Simpson–Golabi–Behmel syndromes.[23] One child whose Marshall Smith syndrome has been reported[24] had unilateral WT; the occurrence of her WT was recently mentioned in a review of the UK Children Cancer Study Group's database.[25] We have been unable to find any previous report of WT associated with this overgrowth syndrome. Seven other children without recognisable overgrowth disorders had height and weight over the 95th centile and 4 of them had childhood measurements greater than 3SD above the mean. The latter would be expected in only approximately 1 case in every 250 individuals. In contrast, only 1 child in the cohort had growth measurements less than –2SD. It is recognised that children with over-

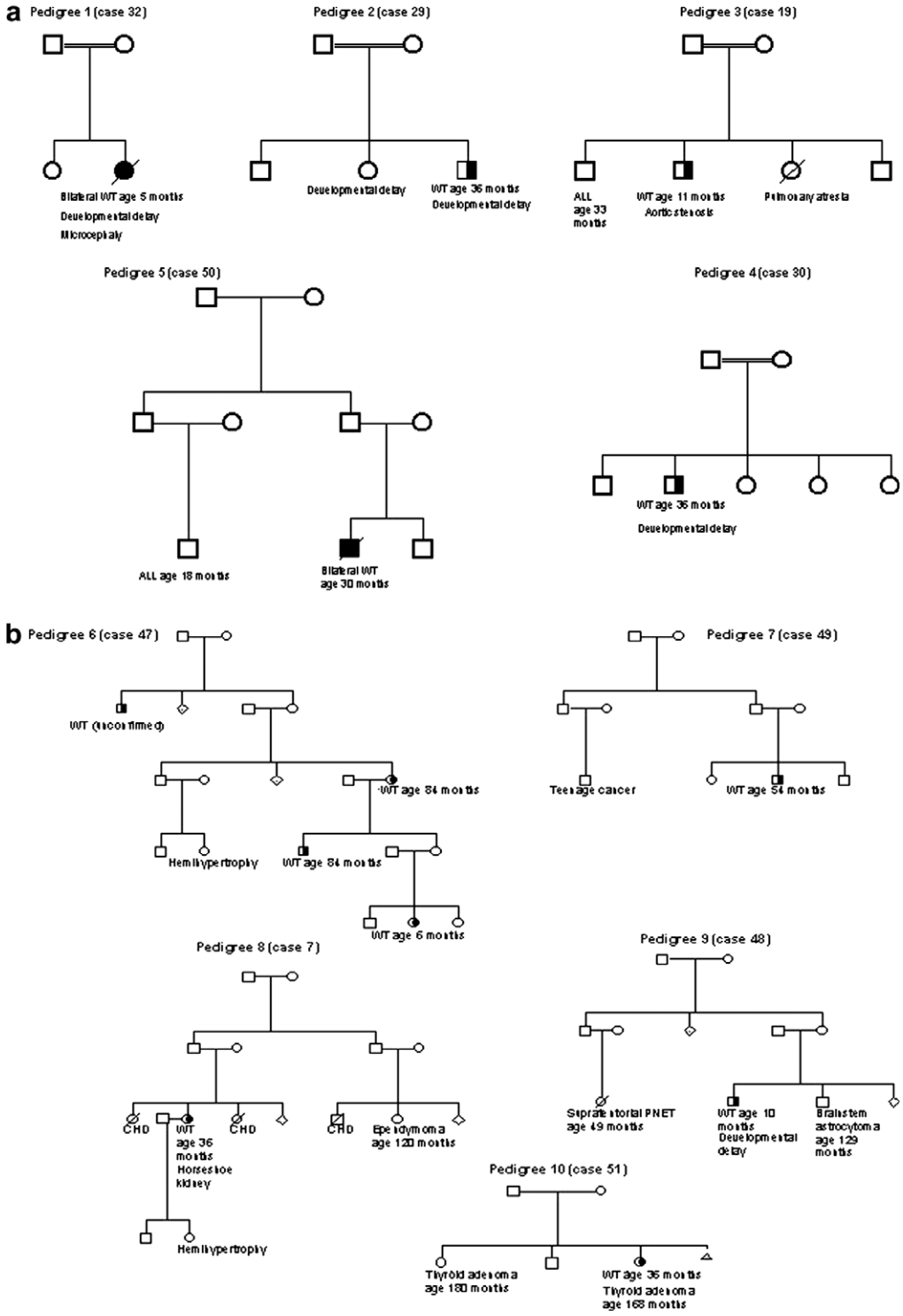

Fig. 1 – Family pedigrees showing familial Wilms' tumour, consanguineous parents, and other paediatric tumours. *Note:* Pedigree 1–5 – Pakistani families (consanguineous families 1–4). Pedigree 6 – Familial Wilms' tumour. Pedigree 7–10 – families with other paediatric and adolescent tumours. WT, Wilms' tumour; ALL, acute lymphoblastic leukaemia; PNET, primitive neuroectodermal tumour; CHD, congenital heart disease. Shaded symbol, bilateral WT; half-shaded symbol, unilateral WT.

growth syndromes may show regression to mean height and weight over time. We therefore reviewed the birth weight data of this cohort and this was found to have a normal distribution, but errors due to maternal recall, secular changes and ethnicity make the data difficult to interpret further. The question of why WT occurs in the overgrowth syndromes presently remains unanswered, but nevertheless our data are not incompatible with other epidemiological data that

Table 4 – Cancer associated with Wilms' tumour (WT)

Type of cancer	No. of cases in family	No. of WT index cases	Percentage of assessed WT cases (%)	Laterality		Gender of WT index cases		Ethnicity of WT index cases	
				Unilateral	Bilateral	M	F	Caucasian	Asian
Familial WT	3	1	1	1	0	1	0	1	0
Paediatric brain tumours	3	2	4 (when only	2	0	1	1	2	0
Teenage cancer	1	1	paediatric cancer	1	0	1	0	1	0
ALL	2	2	is included)	1	1	1	1	0	2
Thyroid adenoma[a]	2	1		1	0	0	1	1	0
Adult brain tumours	3	3		2	1	1	2	3	0

ALL, acute lymphoblastic leukaemia; No., number; M, male; F, female.
a Index case developed a thyroid adenoma as well at teenage.

increased birth weight is associated with a greater risk of WT.[12] The wide range of clinical phenotypes associated with WT and overgrowth highlighted by our study suggests that the 'growth excess' and association with WT could be due to a threshold effect or a common component of a complex multifactorial pathway.

Consistent with previous reports, congenital abnormalities in our series were found in a larger proportion of bilateral (43%) than unilateral (29%) cases.[1,4,16,17] Although the numbers are small, we also found that a much greater proportion of Asian than Caucasian patients with WT had abnormalities (62% compared with 28%), particularly global developmental delay without recognised genetic syndromes (in 5 of 13 Asians as compared with 1 of 133 Caucasians). We considered whether consanguinity might have played a role in the aetiology of these abnormalities and of the Wilms' and other tumours in the Asian families. The rate of consanguinity, 4/13 (31%), was lower than that reported by Bundey and Alam[26] in this population (60–70%) but the numbers are small, so they may not be significant. Structural or developmental abnormalities in the patients, and/or childhood tumours/abnormalities in their siblings or first cousins, were present in 5 of the 9 children with WT from non-consanguineous families, compared with in all 4 of those whose families were consanguineous. This might suggest that consanguinity, and therefore recessive genes, could account for some cases of WT and be associated with additional clinical features. Powell and colleagues[27] reported an excess of congenital abnormalities in Pakistani Muslim children with cancer compared with non-Muslim Asian and Caucasian children. The relative excess detailed in that paper was partly accounted for by inherited genetic factors, such as autosomal recessive disorders associated with parental consanguinity. Of the 8 Asian cases with WT and associated features in our series (Table 2), 7 are of Pakistani Muslim origin. In light of recent knowledge, further investigations to exclude a DNA repair disorder may be warranted, especially if associated anomalies are present.[21,22]

Congenital malformations may be markers of an underlying genetic predisposition that may increase the risk of childhood cancer. Some 5–13% of childhood cancer patients have been reported to have malformations.[18,19,27] We have found abnormalities in 30% of our patients with WT. Moreover, careful documentation of family histories has also revealed that a higher proportion (4%) of families had members with other paediatric cancers than <1–2% reported elsewhere.[28,29] We also identified a case of familial WT.[30,31]

Our study highlights the importance of documenting family history at follow-up clinics, as new information about cancer in the families was often identified thereby. Some of these reports had important genetic implications. We also recommend that enquiry should be made about possible parental consanguinity in all cases of WT, and whether there are other family members with developmental delay and other abnormalities. In WT cases from consanguineous families, caution should be taken when providing figures on the risk of cancer in other children as historical data may be inappropriate. Although these results will need to be verified by a detailed population-based study with a larger cohort, clinicians should be aware of the potential association with other cancers and the necessity of careful clinical assessment and follow-up in children with WT.

Conflict of interest statement

None declared.

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