Syndromic Wilms' Tumor

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5.1 Introduction

Anomalies, either isolated or as part of a syndrome, occur in approximately 10% of children with Wilms' tumor (WT). WT1 and WT2 genes on chromosome bands 11p13 and 11p15.5 act as tumor suppressors and play multiple roles during kidney and gonad development. Several other genes include WTX (on chromosome X), CTNNB1 (chromosome 3), and TP53 (chromosome 17) among others. The genes with their mutations and epigenetic defects associated with tumorigenesis of WT have been described elsewhere.

Among the various syndromes, the moderate to high-risk conditions include WAGR syndrome, Denys-Drash syndrome (DDS), familial WT, Perlman syndrome, and Frasier syndrome. These syndromes may be causative for WT in up to 7–15% of children. There is at the best an anecdotal association between a variety of other clinical scenarios also in patients with WT; these include Li-Fraumeni syndrome, Down syndrome, Marfan syndrome, and the neurofibromatosis group of syndromes. For common urological conditions like horseshoe kidney, multicystic dysplastic kidney, cryptorchidism, and hypospadias. There is very little data to corroborate the increased risk of WT association with these conditions.

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5.2 Incidence and Genetic Penetrance

The median age of diagnosis of WT is 3–4 years, and it is extremely rare in patients about the age of 15 years [1]. Most cases of WT are unilateral and unifocal in nature, and only ~5% affect bilateral kidneys [2]. WT is essentially a sporadic disease, with familial cases contributing only 1–2% of the incidence [3].

There are several syndromes and clinical and genetic conditions which have been reported to be associated with WT and with varying frequency of ~ 9–17%. Either an epigenetic modification or a germline anomaly during the early development is hypothesized to be the cause of these associations [4, 5]. However, only a small number of conditions have any definitive evidence of an increased risk of developing WT. The association with several other conditions is serendipitous at best. Non-syndromic bilateral WT and familial cases are probably explained by low-penetrance predisposition alleles as seen in several other malignancies like neuroblastoma [6]. Most of these cases remain unexplained, suggesting predisposition variants at other genetic loci [7].

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5.3 Syndromes and Clinical Conditions

Several conditions with risk of developing WT have been reported, and these can be classified as low, moderate, and high risk (Table 5.1) [8].

These conditions with risk of developing WT can broadly be studied under five groups:

1. WT1-associated phenotypes
2. Overgrowth syndromes
3. Familial WT
4. Other tumor predisposition syndromes
5. Constitutional chromosomal disorders

Table 5.1 Conditions with an increased risk of WT [8]

High risk (>20%)
• WT1 deletions (including WAGR syndrome)
• Truncating and pathogenic missense WT1 mutations (including Denys-Drash syndrome)
• Familial WT
• Perlman syndrome
• Mosaic variegated aneuploidy
• Fanconi anemia D1/biallelic BRCA2 mutations
Moderate risk (5–20%)
• WT1 intron 9 splice mutations (Frasier syndrome)
• Beckwith-Wiedemann syndrome caused by 11p15 uniparental
• Disomy, isolated H19 hypermethylation, or of unknown cause
• Simpson-Golabi-Behmel syndrome caused by GPC3 mutations/deletions
Low risk (<5%)
• Isolated hemihypertrophy[a]
• Bloom syndrome
• Li-Fraumeni syndrome/Li-Fraumeni-like syndrome
• Hereditary hyperparathyroidism-jaw tumor syndrome
• Mulibrey nanism
• Trisomy 18
• Trisomy 13
• 2q37 deletions

[a]Individuals with hemihypertrophy caused by 11p15 uniparental disomy or isolated H19 hypermethylation are at moderate risk

5.4 WT1-Associated Phenotypes

WT1 is somatically inactivated in patients developing WT. Since WT1 is essential for the embryogenesis of the kidney, it may cause the lowering of the median age of diagnosis of WT in these children (median age 1 year) in comparison to the normal population (median age 3–4 years). These tumors are more likely to be bilateral and multifocal (up to 38% in associated syndromes). These tumors are commonly stromal rich and contain intralobar nephrogenic rests (ILNRs) [9]. WT1 defects have different phenotypes, which usually manifest as WT, genitourinary malformations, and renal dysfunction.

5.4.1 WAGR Syndrome

WAGR (WT, aniridia, genitourinary malformations, intellectual disability, previously mental retardation) syndrome was one of the first syndromes to be associated with WT (Fig. 5.1).

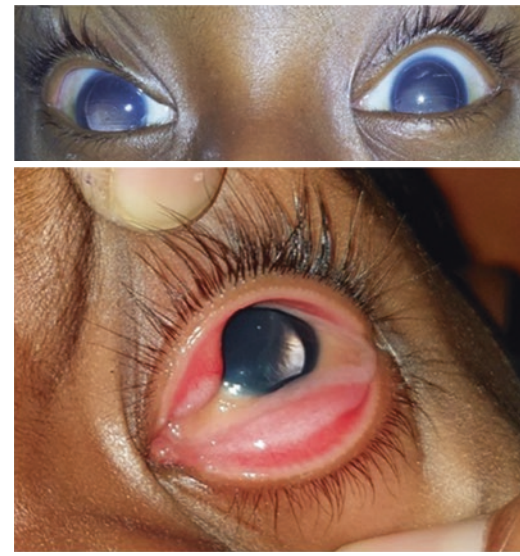

Fig. 5.1 Aniridia (a component of WAGR syndrome) (Picture courtesy Prof S. Kumaravel, JIPMER, Puducherry)

Deletion of PAX6 causes aniridia, and WT1 deletion causes genitourinary malformations and WT. Microdeletions encompassing WT1 are seen in 33% of patients with aniridia [10].

Risk stratification for individuals with WAGR syndrome ranges from 45 to 60%. These patients are diagnosed at an earlier age and have a greater preponderance of harboring bilateral disease in comparison to other syndromes. Ninety percent develop WT by the age of 4 years and 98% by the age of 7 years [11]. They have a favorable histology and are associated with a higher incidence of ILNR.

There is an increased risk of developing end-stage renal disease (ESRD) in this group, and almost 40% individuals develop renal failure before the age of 20 years. Patients developing WT reported to have a survival rate of 48% after the age of 27 years [12].

5.4.2 WAGRO Syndrome

WAGR associated with obesity comprises of the WAGRO syndrome [13]. It has a variable phenotype. Of all the components aniridia is the most consistent [14]. Intellectual impairment is associated with over 70% WAGRO patients along with several neurological and metabolic disorders like obesity. They are commonly noted to have genitourinary disorders such as cryptorchidism, hypospadias, uterine anomalies, and streak gonads.

Obesity ("O" for obesity) is the differentiating feature between WAGRO syndrome and WAGR. In WAGRO syndrome, the deletion of the short arm of chromosome 11 is to the larger extent, involving the brain-derived neurotrophic factor (BDNF) gene. Deletion of BDNF gene is associated with symptoms of polyphagia, developing by the second year of life leading to obesity in all children by 10 years of age [15].

5.4.3 Denys-Drash Syndrome

Denys-Drash syndrome (DDS) is defined as an association of diffuse mesangial sclerosis leading to proteinuria and renal failure along with ambiguous genitalia (Fig. 5.2), which in a male may be 46XY disorder of sexual development (DSD) and a high risk of developing WT [16, 17]. Children with this condition have a germline point mutation in WT1 exon eighth or ninth. These mutations target important residues in the zinc finger domains that are essential for DNA binding of the WT1 protein. There may be other variants of aberrations in cases without renal failure [9].

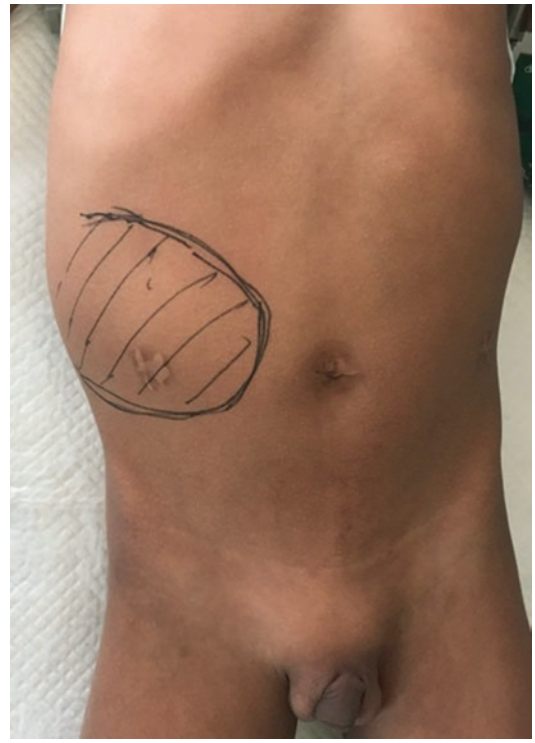

Fig. 5.2 Denys-Drash syndrome with ambiguous genitalia and WT

The incidence of children with DDS who go on to develop WT may be as high at 74%, but some workers believe that even this is underreported. Most of these children may die of ESRD before the potential development of WT [18].

5.4.4 Frasier Syndrome

Frasier syndrome (FS) characteristically has gonadal dysgenesis (476XY) DSD, gonadoblastoma, and nephropathy (focal segmental glomeru-

losclerosis) [19]. The genito-urinary malformations in males are usually severe. Initially thought to be a separate entity from DDS, more researchers believe that FS and DDS are two extremes of a phenotypic spectrum [20, 21]. Heterozygous single-nucleotide variants in the WT1 intron 9 donor splice site are the predominant type of alteration observed in individuals with FS. The risk stratification for these individuals to develop WT is moderate (5–20%).

5.4.5 Other WT1 Phenotypes

There may be clinical conditions with only one or two of the cardinal features of WT1 phenotypes, like WT and cryptorchidism and WT and nephropathy. Only about 2% of non-syndromic WT patients have germline WT1 gene mutations. The risk of developing WT in patients with microdeletions and missense mutations affecting zinc finger domains is significantly high—up to 50% in some series [9].

5.5 Overgrowth Syndromes

Overgrowth syndromes in children are a heterogeneous group of conditions which have antenatal or postnatal overgrowth usually associated with other abnormal clinical conditions. These syndromes were thought to have an association with an increased incidence of WT; however in view of recent understandings, it is now known that only a few specific syndromes predispose to WT. There should be a tailored approach instead of a generalization of WT association in overgrowth syndromes.

5.5.1 Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) is a disorder, associated with pre- and post-natal overgrowth, anterior abdominal wall defects, macroglossia, earlobe creases, and hypoglycemia with hemihypertrophy (Fig. 5.3). There may be associated CAKUT, nephrolithiasis, and embryonal tumors (WT, hepatoblastoma, neuroblastoma, rhabdomyosarcoma) [22]. The incidence is 1 in 14,000 [23].

BWS is a result of mutations, epigenetic abnormalities, and aberrations at 11p15.5. Most patients with 11p15 defects may not fulfill the criteria of BWS even though they may have features like isolated hemihypertrophy [24].

The risk of developing WT in patients of BWS is difficult to ascertain because of the carried genotypical and phenotypical presentations in the

Fig. 5.3 Macroglossia and hemihyperplasia in Beckwith-Wiedemann syndrome in a case of WT (Picture courtesy Prof. S. Kumaravel, JIPMER, Puducherry)

entire spectrum of this disease. Approximately 7% of children with BWS develop WT. Defects that cause an increase in growth promoters are related with a higher risk of WT in BWS patients (Disomy of 11p15.5 or gain of methylation); about 25% of these individuals go on to harbor WT. In patients with BWS with WT, 81% will develop the tumor by five years and almost 93% by 8 years [25].

Isolated hemihypertrophy may have an association with various other syndromes such as Proteus, Klippel-Trenaunay-Weber, and Cutis marmorata telangiectatica congenita. The association of these with WT is around 3% [26].

5.5.2 Simpson-Golabi-Behmel Syndrome

It is an X-linked overgrowth syndrome in which patients may present with skeletal and cardiac malformations, coarse facial features, accessory nipples, and intellectual impairment. About one-third of patients may have associated renal dysplasia [27].

Mutations or deletions of glypican-3 (GPC3) at Xq26 are seen in 70% of individuals affected. The risk stratification for WT is moderate, with about 9–10% incidence. There is low penetrance for other embryonal tumors [28].

5.5.3 Perlman Syndrome

It is an autosomal recessive overgrowth disorder identified by antenatal overgrowth with polyhydramnios, visceromegaly, cryptorchidism, facial dysmorphism, developmental delay, renal dysplasia, and WT [29]. The genetic aberration is unclear; however, it may be similar to Simpson-Golabi-Behmel syndrome due to GPC3 mutation. Renal hamartomas or WT (33%) or both are seen in the majority of reported cases. Five of the eight patients who survived the neonatal period went on to develop WT [30].

5.5.4 Sotos Syndrome

It is an overgrowth syndrome associated with facial, extremity, and cognitive abnormalities [31].

5.6 Familial Wilms' Tumor

Sporadic WT running in families has an incidence of 1–2%. The genetic defects are not well identified; however, WT1 mutations, mosaic variegated aneuploidy, and biallelic BRCA2 mutations are seen in specific families [32].

FWT1, an autosomal dominant gene on chromosome 17q21 and another gene FWT2 at chromosome 19q13, have been identified. The exact loci have not been mapped as yet. It is interesting to note that the penetrance of FWT1 mutation is about 30%, and WT in these families are diagnosed at a delayed age (median: 6 years) [33]. Several families without linkages to WT1, FWT1, and FWT2 exist, suggesting that significant genetic heterogeneity and penetrance is a complex phenomenon.

5.7 Other Tumor Predisposition Syndromes

Mutations in more than 70 genes are associated with benign and malignant tumors, of which only a few have an increased risk of WT.

5.7.1 Bloom Syndrome

This is an autosomal recessive chromosomal illness characterized by short stature, hypo- and hyper-pigmented skin lesions which may be photosensitive, immunodeficiency, and a specific facial appearance. This syndrome has proven association with different malignancies, developing tumors in up to 50% of patients. Around 200 cases have been reported, and this condition has a low penetrance for WT (approximately 3%) [34, 35].

5.7.2 Mosaic Variegated Aneuploidy

Mosaic variegated aneuploidy is an autosomal recessive disorder associated with mosaicism for deletions and additions of whole chromosomes. Clinical features may include microcephaly, growth retardation, developmental delay, cataracts, and congenital heart defects. Biallelic mutations in BUB1B are thought to be the specific genetic defect in this disorder. This syndrome is associated with embryonal and hematological cancers. About one-fourth of cases have an associated WT [36].

5.7.3 Fanconi Anemia

Fanconi anemia is usually diagnosed in children with short stature, microcephaly, "radial-ray" defects, skin lesions, and bone marrow failure. These patients are prone to myelodysplastic syndrome and acute myeloid leukemia. There are several overlapping clinical and cellular phenotypes associated with recessive chromosomal breakage. More than 13 subtypes have been identified, and D1 and N subtypes have an increased association with WT.

Biallelic BRCA2 mutations cause Fanconi anemia subgroup D1 [37]. There is an associated risk of solid tumors and brain tumors in these patients. About 40% may have an associated WT.

5.7.4 Other Syndromes

Li-Fraumeni syndrome, Mulibrey nanism, and hereditary hyperparathyroidism-jaw tumor syndrome are other conditions with low penetrance. These are associated with less than 5% of WTs in these patients [38–40].

5.8 Constitutional Chromosomal Disorders

Trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome), and 2q37 deletion are other constitutional chromosomal disorders with preponderance for WT. Trisomy 18 and 13 are associated with early death in the neonatal period and infancy. Given the early mortality in both of these conditions, there will be a significant increase in association with WT in survivors.

5.9 Conditions with Uncertain Association with WT

There is a significantly large number of conditions associated with WT, where the increased risk of tumor is at best implausible. Various congenital abnormalities and syndromes such as Down syndrome, Marfan syndrome, tuberous sclerosis, and Turner syndrome have reported WT. There is little evidence to link these genetically [41].

Clinically relevant conditions like horseshoe kidney and multicystic dysplastic kidney have no or very little risk of developing WT. [42] Cardiac defects have an unknown risk association of developing WT, which remains most likely minuscule [43]. Cervical ribs are also reported to associate with WT; however, data from a case-control study suggests otherwise [44].

5.10 Evaluation and Surveillance in Predisposed Children

5.10.1 Evaluation

Evaluation of the predisposed child should begin with a detailed history and a detailed physical examination. Most syndromes will have characteristic clinical markers, which aid in narrowing down the syndromic associations. Adequate time must be spent on a family history to look for clues of genetic penetrance and aberrations in the family. Radiological features specific to conditions like nephrogenic rests must be taken into consideration while deciding the management algorithm in these patients.

Genetic testing even though not easily available in the developing world must be sought to narrow down the mutations and aberration. This may aid in emphatically diagnosing specific syndromes associated with WT.

5.10.2 Molecular Genetic Testing

Individuals who have physical, radiological, and histological features suggestive of a predisposition should undergo genetic testing. Any WT in a family member should be taken seriously, and genetic testing is recommended. A geneticist should be an integral part of the multidisciplinary team deciding the management strategies.

Molecular genetic testing includes various gene analyses like single-gene testing, gene-targeted deletion/duplication analysis, methylation studies, use of a multigene panel, and chromosomal microarray. Clinical features should guide the selection of test.

5.10.3 Surveillance

There are various strategies for surveillance; however, the efficacy of these is not well established. Surveillance of predisposed individuals is recommended even though it may not lead to a significant decrease in the mortality of WT. The basic premise of surveillance is to have early detection of WT so as to reduce the intensity of various adjuvant therapies.

Both in the United Kingdom and in the European Union, surveillance is offered to patients at a >5% risk of WT. Renal ultrasound is by far the easiest and commonest tool applied for screening. As WT can be a rapidly growing disease, an ultrasound abdomen is recommended to be performed every 3–4 months [45]. Screening should begin as soon as a syndrome is thought of and should cover the age range so as to cover at least up to 95% of tumors for the associated syndrome.

For the WT1-associated syndromes, Fanconi anemia types D1 and N, mosaic variegated aneuploidy, and Perlman syndrome, virtually all tumors occur before 5 years, and thus surveillance may be stopped after this age is achieved. For children with Simpson-Golabi-Behmel syndrome, familial WT families, and similar genotypic defects like 11p15, the tumors may occur even beyond 5 years. It is recommended to keep these individuals for 7–10 years of follow-up.

5.11 Surgical and Medical Management in Syndromic Patient

5.11.1 Oncological Management

Mutations in WT1 and associated genes influence the surgical and oncological treatment of patients. Chemotherapy regimens must be tailored to the renal function and the weight of the individual patient. There is a significantly high risk of chronic kidney disease (CKD) in syndromes associated with WT1 mutation. This can reach up to 80% for Denys-Drash and 50% for WAGR syndrome [46]. This future progression to ESRD with nephropathies must be kept in mind by the oncologist when deciding the types and dosages of chemotherapeutic drugs.

Perioperative management needs to be looked at carefully in the setting of conditions like hypertension and proteinuria, which may predispose to thrombotic events.

5.11.2 Nephron-Sparing Surgery (NSS) in Syndromic WT

It is believed that NSS is the logical step in managing syndromic patients of WT. This approach helps clinicians prevent or delay the development of chronic kidney disease, which can occur due to intrinsic renal dysfunction (associated with WT1 syndromes) or cumulative insults like hypertension, hyperfiltration, etc. that suffered over a long time.

A substantial number of patients with DDS and FS, tend to progress to ESRD as mentioned earlier. NSS is recommended in patients with bilateral tumors without ESRD to delay the onset of renal failure or the requirement of dialysis. Patients diagnosed with unilateral WT and have point mutations in exons 8-9/intron 9 are inherently at higher risk of progressing to ESRD. There may be some merit in performing an NSS in these patients; however, some workers recommend bilateral nephrectomy with a renal transplant cohort [47].

Patients with DDS who develop ESRD after undergoing NSS for WT should be counseled to undergo total nephrectomy before renal transplantation in order to prevent recurrences under immunosuppressive therapy. It is recommended to have an interval of about two years for renal transplantation after completing the treatment for WT.

It is imperative to strike a fine balance between conservative treatment, NSS, nephrectomy, and oncological safety in these patients.

5.12 Future Directions

There have been considerable advances in the molecular and genetic diagnosis of WT and associated syndromes over the past few decades. In spite of these advancements, several new genes and high penetrance alleles need to be identified and remain to be identified. Newer technology like next-generation sequencing may aid in detecting further genotypes and even low penetrance alleles.

Identifying newer therapeutics, especially in poor prognostic subgroups, is the need of the hour. Targeting epigenetic modifiers and the advent of promising monoclonal antibodies remains to be assessed for the management of WT in the future.

Children with syndromic WT carry a huge burden of disease in terms of cancer predisposition, renal failure, gonadal deficiency, and infertility. As the clinical and genetic associations are better established, experts may be able to offer prime quality and individually customized care to these patients with syndromic WT in the future.

References

1. Hentrich MU, Meister P, Brack NG, Lutz LL, Hartenstein RC. Adult Wilms' tumor. Report of two cases and review of the literature. Cancer. 1995;75:545–51.
2. Ritchey ML, Shamberger RC, Hamilton T, Haase G, Argani P, Peterson S. Fate of bilateral renal lesions missed on preoperative imaging: a report from the National Wilms Tumor Study Group. J Urol. 2005;174:1519–21. https://doi.org/10.1097/01.ju.0000179536.97629.c5.
3. Breslow NE, Olson J, Moksness J, Beckwith JB, Grundy P. Familial Wilms' tumor: a descriptive study. Med Pediatr Oncol. 1996;27:398–403. https://doi.org/10.1002/(SICI)1096-911X(199611)27:5<398::AID-MPO2>3.0.CO;2-H.
4. Dome JS, Huff V. Wilms tumor predisposition. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle: University of Washington; 2003.
5. Merks JH, Caron HN, Hennekam RC. High incidence of malformation syndromes in a series of 1,073 children with cancer. Am J Med Genet A. 2005;134:132–43. https://doi.org/10.1002/ajmg.a.30603.
6. Tolbert VP, Coggins GE, Maris JM. Genetic susceptibility to neuroblastoma. Curr Opin Genet Dev. 2017;42:81–90. https://doi.org/10.1016/j.gde.2017.03.008.
7. Weksberg R, Brzezinski J. Identifying new Wilms' tumour predisposition genes. Lancet Child Adolesc Health. 2019;3:285–7. https://doi.org/10.1016/S2352-4642(19)30064-1.
8. Scott RH, Stiller CA, Walker L, Rahman N. Syndromes and constitutional chromosomal abnormalities associated with Wilms tumor. J Med Genet. 2006;43:705–15. https://doi.org/10.1136/jmg.2006.041723.
9. Royer-Pokora B, Beier M, Henzler M, Alam R, Schumarjer V, Weirich A, et al. Twenty-four new cases of WT1 germline mutations and review of the literature: genotype/phenotype correlations for Wilms tumor development. Am J Med Genet. 2004;127:249–57. https://doi.org/10.1002/ajmg.a.30015.
10. Muto R, Yamamori S, Ohashi H, Osawa M. Prediction by FISH analysis of the occurrence of Wilms tumor in aniridia patients. Am J Med Genet. 2002;108:285–9. https://doi.org/10.1002/ajmg.10094.
11. Beckwith JB. Nephrogenic rests and the pathogenesis of Wilms tumor: developmental and clinical considerations. Am J Med Genet. 1998;79:268–73.
12. Breslow NE, Norris R, Norkool PA, Kang T, Beckwith JB, Perlman EJ, et al. Characteristics and outcomes of children with the Wilms tumor-aniridia syndrome: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2003;21:4579–85. https://doi.org/10.1200/JCO.2003.06.096.
13. Ferreira M, Almeida Júnior I, Kuratani D, Rosa R, Gonzales J, Telles L, et al. WAGRO syndrome: a rare genetic condition associated with aniridia and additional ophthalmologic abnormalities. Arq Bras Oftalmol. 2019;82:336–8. https://doi.org/10.5935/0004-2749.20190065.
14. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. WAGR syndrome: a clinical review of 54 cases. Pediatrics. 2005;116:984–8. https://doi.org/10.1542/peds.2004-0467.
15. Han JC, Liu QR, Jones M, Levinn RL, Menzie CM, Jefferson-George KS, et al. Brain- derived

neurotrophic factor and obesity in the WAGR syndrome. N Engl J Med. 2008;359:918–27. https://doi.org/10.1056/NEJMoa0801119.
16. Denys P, Malvaux P, Van den BH, Tanghe W, Proesmans W. Association of an anatomopathological syndrome of male pseudohermaphroditism, Wilms' tumor, parenchymatous nephropathy and XX/XY mosaicism. Arch Fr Pediatr. 1967;24:729–39.
17. Drash A, Sherman F, Hartmann WH, Blizzard RM. A syndrome of pseudohermaphroditism, Wilms' tumor, hypertension, and degenerative renal disease. J Pediatr. 1970;76:585–93. https://doi.org/10.1016/s0022-3476(70)80409-7.
18. Mueller RF. The Denys-Drash syndrome. J Med Genet. 1994;31:471–7. https://doi.org/10.1136/jmg.31.6.471.
19. Frasier S, Bashore R, Mosier H. Gonadoblastoma associated with pure gonadal dysgenesis in monozygous twins. J Pediatr. 1964;64:740–5. https://doi.org/10.1016/s0022-3476(64)80622-3.
20. Finken MJ, Hendriks YM, van der Voorn JP, Veening MA, Lombardi MP, Rotteveel J. WT1 deletion leading to severe 46XY gonadal dysgenesis, Wilms tumor and gonadoblastoma: case report. Horm Res Paediatr. 2015;83:211–6. https://doi.org/10.1159/000368964.
21. Koziell A, Charmandari E, Hindmarsh PC, Rees L, Scambler P, Brook CG. Frasier syndrome, part of the Denys Drash continuum or simply a WT1 gene associated disorder of intersex and nephropathy? Clin Endocrinol. 2000;52:519–24. https://doi.org/10.1046/j.1365-2265.2000.00980.x.
22. Thorburn MJ, Wright ES, Miller CG, Smith-Read EH. Exomphalos-macroglossia-gigantism syndrome in Jamaican infants. Am J Dis Child. 1970;119:316–21. https://doi.org/10.1001/archpedi.1970.02100050318006.
23. Choyke PL, Siegel MJ, Sotelo-Avila C, De Baun MR. Nonmalignant renal disease in pediatric patients with Beckwith-Wiedemann syndrome. Am J Roentgenol. 1998;171:733–7. https://doi.org/10.2214/ajr.171.3.9725306.
24. Bliek J, Maas S, Alders M, Merks JH, Mannens M. Epigenotype, phenotype, and tumors in patients with isolated hemihyperplasia. J Pediatr. 2008;153:95–100. https://doi.org/10.1016/j.jpeds.2007.12.022.
25. Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2010;18:8–14. https://doi.org/10.1038/ejhg.2009.106.
26. Hoyme HE, Seaver LH, Jones KL, Procopio F, Crooks W, Feingold M. Isolated hemihyperplasia (hemihypertrophy): report of a prospective multicenter study of the incidence of neoplasia and review. Am J Med Genet. 1998;79:274–8.
27. Mariani S, Iughetti L, Bertorelli R, Coviello D, Pellegrini M, Forabosco A, et al. Genotype/phenotype correlations of males affected by Simpson-Golabi-Behmel syndrome with GPC3 gene mutations: patient report and review of the literature. J Pediatr Endocrinol Metab. 2003;16:225–32. https://doi.org/10.1515/jpem.2003.16.2.225.
28. Song HH, Shi W, Xiang YY, Filmus J. The loss of glypican-3 induces alterations in Wnt signaling. J Biol Chem. 2005;280:2116–25. https://doi.org/10.1074/jbc.M410090200.
29. Perlman M, Levin M, Wittels B. Syndrome of fetal gigantism, renal hamartomas, and nephroblastomatosis with Wilms' tumor. Cancer. 1975;35:1212–7.
30. Henneveld HT, van Lingen RA, Hamel BC, Stolte-Dijkstra I, van Essen AJ. Perlman syndrome: four additional cases and review. Am J Med Genet. 1999;86:439–46.
31. Lapunzina P. Risk of tumorigenesis in overgrowth syndromes: a comprehensive review. Am J Med Genet C Semin Med Genet. 2005;137:53–71. https://doi.org/10.1002/ajmg.c.30064.
32. Reid S, Renwick A, Seal S, Baskcomb L, Barfoot R, Jayatilake H, et al. Biallelic BRCA2 mutations are associated with multiple malignancies in childhood including familial Wilms tumour. J Med Genet. 2005;42:147–51. https://doi.org/10.1136/jmg.2004.022673.
33. Rahman N, Abidi F, Ford D, Arbour L, Rapley E, Tonin P, et al. Confirmation of FWT1 as a Wilms' tumour susceptibility gene and phenotypic characteristics of Wilms' tumour attributable to FWT1. Hum Genet. 1998;103:547–56. https://doi.org/10.1007/pl00008708.
34. Cairney AE, Andrews M, Greenberg M, Smith D, Weksberg R. Wilms tumor in three patients with Bloom syndrome. J Pediatr. 1987;111:414–6. https://doi.org/10.1016/s0022-3476(87)80469-9.
35. Llis NA, Groden J, Ye TZ, Straughen J, Lennon DJ, Ciocci S, et al. The Bloom's syndrome gene product is homologous to RecQ helicases. Cell. 1995;83:655–66. https://doi.org/10.1016/0092-8674(95)90105-1.
36. Kajii T, Kawai T, Takumi T, Misu H, Mabuchi O, Takahashi Y, et al. Mosaic variegated aneuploidy with multiple congenital abnormalities: homozygosity for total premature chromatid separation trait. Am J Med Genet. 1998;78:245–9. https://doi.org/10.1002/(sici)1096-8628(19980707)78:3<245::aid-ajmg7>3.0.co;2-o.
37. Meyer S, Fergusson WD, Oostra AB, Medhurst AL, Waisfisz Q, deWinter JP, et al. A cross-linker-sensitive myeloid leukemia cell line from a 2-year-old boy with severe Fanconi anemia and biallelic FANCD1/BRCA2 mutations. Genes Chromosomes Cancer. 2005;42:404–15. https://doi.org/10.1002/gcc.20153.
38. Yart A, Gstaiger M, Wirbelauer C, Pecnik M, Anastasiou D, Hess D, et al. The HRPT2 tumor suppressor gene product parafibromin associates with human PAF1 and RNA polymerase II. Mol Cell Biol. 2005;25:5052–60. https://doi.org/10.1128/MCB.25.12.5052-5060.2005.
39. Olivier M, Eeles R, Hollstein M, Khan MA, Harris CC, Hainaut P. The IARC TP53 database: new online mutation analysis and recommendations to users. Hum Mutat. 2002;19:607–14. https://doi.org/10.1002/humu.10081.

40. Karlberg N, Jalanko H, Perheentupa J, Lipsanen-Nyman M. Mulibrey nanism: clinical features and diagnostic criteria. J Med Genet. 2004;41:92–8. https://doi.org/10.1136/jmg.2003.014118.
41. Fabia J, Drolette M. Malformations and leukemia in children with Down's syndrome. Pediatrics. 1970;45:60–70.
42. Narchi H. Risk of Wilms' tumour with multicystic kidney disease: a systematic review. Arch Dis Child. 2005;90:147–9. https://doi.org/10.1136/adc.2004.051243.
43. Stiller CA, Lennox EL, Wilson LM. Incidence of cardiac septal defects in children with Wilms' tumour and other malignant diseases. Carcinogenesis. 1987;8:129–32. https://doi.org/10.1093/carcin/8.1.129.
44. Merks JH, Smets AM, Van Rijn RR, Kobes J, Caron HN, Maas M, et al. Prevalence of rib anomalies in normal Caucasian children and childhood cancer patients. Eur J Med Genet. 2005;48:113–29. https://doi.org/10.1016/j.ejmg.2005.01.029.
45. Scott RH, Anne Murray A, Baskcomb L, Turnbull C, Loveday C, Al-Saadi R, et al. Stratification of Wilms tumor by genetic and epigenetic analysis. Oncotarget. 2012;3:327–35. https://doi.org/10.18632/oncotarget.468.
46. Lange J, Peterson SM, Takashima JR, Grigoriev Y, Ritchey M, et al. Risk factors for end stage renal disease in non-WT1-syndromic Wilms tumor. J Urol. 2011;186:378. https://doi.org/10.1016/j.juro.2011.03.110.
47. Auber F, Jeanpierre C, Denamur E, Jaubert F, Schleiermacher M, Patte C, et al. Management of Wilms tumors in drash and frasier syndromes. Pediatr Blood Cancer. 2009;52:55–9. https://doi.org/10.1002/pbc.21759.