# 6 Familial Non-syndromic Wilms' Tumor

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## 6.1 Introduction

A patient with Wilms' tumor (WT) is considered to have a familial disease if at least one family member has confirmed diagnosis of WT. The familial cases of WT (FWT) are not associated with the syndromes or cancers and account for only 1–2% of all cases [1]. They generally present at an earlier age, and the frequency of bilateral disease is more than sporadic cases [1]. FWTs are found in twins, siblings, successive generations, and consanguinity which suggests the possibility of a monogenic determination [2–4].

## 6.2 Epidemiology of FWT

Most of the WT families are small affecting one or two family members. The disease often occurs in siblings, cousins, and other relatives, but only one-tenth of the kindreds involve affected parents [5, 6]. The siblings or cousins having WT are usually related to each other by an unaffected carrier [1, 5–7]. The age of onset in FWT is earlier than in sporadic cases (35 months vs 44.7 months in cases with unilateral tumors and 16 months vs 32 months in patients with bilateral tumors) and they have an equal male to female incidence [5, 6]. The frequency of bilateral disease in FWT increases to around 16% [5, 7], and the cases of bilateral and metastatic disease aggregate within specific families [5]. The age at onset, penetrance, and the frequency of bilateral tumors are heterogeneous in WT families. This is because the predisposition to WT is due to an autosomal dominant allele with incomplete penetrance which is estimated between 25 and 60% [1, 6, 8].

## 6.3 Risk of WT in Kindreds of WT Families

The risk of transmission of WT to children of individuals who survived the disease is estimated as follows [6]:

1. The risk of transmission of the tumor to offspring is 30% if one parent had unilateral WT [6].
2. The risk of transmission of the tumor to offspring is 40% if one parent is a known case of familial WT [6].
3. The risk of transmission of the tumor to offspring is 50% if one parent had bilateral WT [6].
4. If two or more children have WT without any affected parents, the parents are considered unaffected gene carriers, and the risk of transmission of tumor in prospective children is 30% [6].

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The risk of recurrence of WT is small among relatives. In siblings, it is estimated to be less than 0.4%, in uncles and aunts around 0.06%, and 0.04% in first cousins [9].

## 6.4 Pathology of Familial WT

The histopathology features of FWT are not remarkably different from those of nonfamilial cases, although some predisposition genes are associated with particular histology. Husong et al. reported the presence of neural elements in all four affected members of a WT family [10].

## 6.5 Genetics and Molecular Biology

Initially, WT was considered to occur due to the loss of function of a single gene as per Knudson's two-hit hypothesis [1], but now several genes are implicated in tumorigenesis of WT. There are several mutations of WT genes, areas of loss of genetic material, and allelic uniqueness (loss of heterozygosity (LOH)) which have been identified to be responsible for tumorigenesis. The mutations of the *WT1* gene located at 11p13 have been implicated as a predisposing factor in some families, but it was excluded in most of the WT families. The linkage analysis has ruled out the role of genes at 11p15, 16q, and 1q for most of the familial WT [11, 12].

Two other FWT genes are recognized: FWT1 at 17q12–q21 and *FWT2* at 19q13.4 [13, 14]. Nevertheless, the role of other unidentified familial WT genes is to be sought as many of the WT families are not attributed to either of these loci [12, 14–16].

### 6.5.1 WT1 Gene

This was the first gene to be found responsible for the WT occurrence. It regulates the transcription of growth factors, growth factor receptors, and other transcription factors that are responsible for cell growth, differentiation, and apoptosis. The *WT1* mutations, whether truncation, deletions, or missense mutation, are required on both the alleles for tumorigenesis [16]. However, the presence of germline *WT1* mutations has been noted in only 4–6% cases of FWT [16, 17]. The tumors being homozygous for paternally derived alleles indicate a paternal origin of the WT mutation [16].

The constitutional *WT1* mutations have been implicated for tumorigenesis in three other WT families: first, a male child with WT and urogenital malformations with the paternal inheritance of *WT1* mutation from the affected father [18]; second, the three sisters with a paternal inheritance from their unaffected father [19]; and third, three affected members with WT and aniridia due to translocation t(2;11)(q32;p13) [20]. However, the direct sequence analysis of *WT1* has excluded the *WT1* mutation in most WT families as a predisposing factor [11, 16].

### 6.5.2 Familial Predisposition Gene

The linkage analysis of two WT families revealed the role of a putative tumor gene at the 17q12-21 locus which was named *FWT1* [13]. Moreover, the LOH at 19q was noticed in individuals from two families, and their predisposition was not linked to 17q locus. This suggested that mutations at two different loci; a germline predisposing mutation and a somatic mutation at the second locus are responsible for tumorigenesis in FWT. The subsequent studies demonstrated the role of inherited WT gene *FWT2* at 19q13.3-q13.4 in five WT families [14].

In *FWT1*-linked families, the average age of presentation was 5 years (2–12 years) which is older than the average age of sporadic tumors [12, 13]. Also, these *FWT1*-linked patients present at a significantly *later stage than* sporadic WT [12]. The age of presentation and laterality were found to be variable in patients with the *FWT2* gene [14].

### 6.5.3 Novel Predisposition Genes for Familial WT

In the last decade, several novel predisposition genes have been implicated in the tumorigenesis of FWT. In a recent exome sequencing study involving FWT, one-third were found to have constitutional mutations in *WT1*, *CTR9*, *REST*, *TRIM28*, *H19* hypermethylation (IGF2 locus), *CDC73*, *BRCA2*, and *NYNRIN* [17]. The *REST* and *TRIM28* mutations were most common being present in 8% of families, followed by *WT1* in 6% of families. The *CTR9* mutations and *H19* hypermethylation were found in 5% and 3% of families, respectively. The *CDC73* mutation and biallelic mutations of *BRCA2* and *NYNRIN* genes were found in one family each [17].

The *CTR9* (Cln 3-requiring 9) gene is an important unit of the RNA polymerase-associated factor complex (PAF1c) which is paramount in the regulation of RNA polymerase II. It is identified as a predisposition gene for WT and functions as a tumor suppressor gene [21]. The *CTR9* gene is sited at 11p15.3 and encrypts a 1173 amino acid protein. It is demonstrated in fetal and adult kidneys and is responsible for embryonic organogenesis and maintenance of embryonic cell pluripotency [22].

The *REST* gene encoding RE1-silencing transcription factor was detected as a tumor suppressor gene in four familial and nine nonfamilial cases [23]. It is a zinc-finger transcription factor that helps in cellular differentiation and embryogenesis [24]. The age of presentation is earlier in familial cases than in sporadic cases. The inheritance of mutation is maternal in most cases, and the tumors are triphasic in histology [23].

The *TRIM28* gene or KAP1 (Krüppel-Associated Box (KRAB)-Associated Protein 1) or TIF1-β (transcriptional intermediary factor 1 β) situated at chromosome 19q13.43 has been identified as a predisposing gene in families of WT [17, 25, 26]. It is involved in maintaining the genome stability, repair of DNA, and embryogenesis [27]. The mutations are transmitted from the mother with incomplete penetrance. Most of the patients have epithelial histology which carries a favorable prognosis [17, 25, 26]. Thus, *TRIM28* expression is a possible marker to identify a group of tumors with an excellent prognosis [25]. It may lead to both unilateral and bilateral tumors, and most of the patients exhibit perilobar nephrogenic rests (PLNR) [26]. The immunohistochemistry of tumor tissue shows loss of TRIM28 protein and loss of heterozygosity (LOH) of *TRIM28* suggesting it to be a classical tumor suppressor gene [25, 26].

The truncating mutations of *FBXW7* (F-box and WD repeat domain containing 7) and *KDM3B* genes also predispose to WT [17]. Both of them are pleiotropic cancer predisposition genes; *FBWX7* is found to be associated with osteosarcoma, extra-renal rhabdoid, and multiple childhood and adult cancers, while *KDM3B* is associated with WT, hepatoblastoma, acute myeloid leukemia, and Hodgkin's lymphoma [17]. The *KDM3B* and *NYNRIN* (NYN Domain and Retroviral Integrase Containing) mutations may also cause nonmalignant conditions, particularly intellectual disability [17].

## 6.6 Genetic Counseling and Surveillance

The presence of a relative with WT is sufficient to implicate the genetic predisposition of WT. The molecular testing is indicated in such individuals and includes single gene analysis, gene-targeted deletion/duplication analysis, methylation studies, whole genome, and whole exon sequencing [28]. All patients with a genetic predisposition (bilateral or multifocal tumors, syndromic babies, with associated congenital anomalies and familial WT) and the offspring of affected parents with unilateral or bilateral disease and those with a carrier parent should receive genetic counseling and surveillance [6, 28]. The surveillance includes molecular genetic testing and a three-monthly abdominal ultrasound until the age of 8 years to detect the tumors at an early stage [28]. The aim is to detect tumors in the early stages when they have a better prognosis as compared to advanced-stage tumors.

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