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REVIEW

The Wilms' tumour 1 gene as a factor in non-syndromic hypospadias: evidence and controversy

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Summary

Hypospadias is one of the most frequent congenital anomalies of the male external genitalia. Its pathogenesis is due to largely unknown or poorly understood genetic factors and is further complicated by environmental—intrauterine—risk factors. One of the genes currently in focus by molecular biologists and clinicians studying syndromic forms of hypospadias is the Wilms' tumour 1 (*WT1*) gene. There is controversy over whether *WT1* defects are also responsible for isolated hypospadias. In this review, we briefly cover the role of WT1 as a transcription factor and discuss proposed pathogenic pathways leading to hypospadias, outlining possible directions for research. We assess available evidence on the gene's mutations and polymorphisms recently suggested in the background of the disease, and examine the putative role of WT1-associated proteins. We also review relevant aspects of genome-wide association studies carried out so far, and raise some points to consider in future efforts.

Key words: Hypospadias; *WT1* gene; rs2234583; *WTIP* gene; *WTAP* gene.

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1. INTRODUCTION

Hypospadias is a congenital malformation of the penis characterised by a failure of urethral groove closure resulting in a meatus on the ventral surface. While it is a very common congenital abnormality seen in male genitalia, different authors have reported wildly divergent data on its prevalence (ranging from 2 to 43 out of 10,000 live births), possibly due to geographical variation of risk factors and different methods of ascertainment.[1,2] Some authors have argued that prevalence has increased in the past decades,[3,4] while others found it to be constant.[5,6] True prevalence and possible changes over time are very difficult to estimate; a collaboration of national and international prospective registries may help to overcome controversies.[7] The disease is generally considered to be of multifactorial origin, but it may be due to monogenic (usually dominant) defects in a certain proportion of families typically showing severe, syndromic hypospadias.[8] Even in the more common multifactorial cases, genetic factors may play a larger role in the pathogenesis than intrauterine environmental factors, with an overall heritability estimated at 77%.[9]

Abnormalities in the Wilms' tumour 1 (*WT1*) gene have long been known to cause genetic syndromes associated with hypospadias. WAGR syndrome (Wilms' tumour, aniridia, genitourinary abnormalities, mental retardation) is due to a chromosomal deletion in the 11p13 region that includes *WT1*,[10] while Denys–Drash syndrome (nephropathy, gonadal dysgenesis, Wilms' tumour) and Frasier syndrome (focal glomerular sclerosis and genital or gonadal dysgenesis) are usually caused by point mutations within the *WT1* locus.[11,12] In our paper we discuss controversial evidence on whether altered *WT1* function may produce non-syndromic forms of hypospadias either indirectly through gonadal dysfunction or directly by being involved in urethral development.

2. MUTATIONS OF GENES INVOLVED IN TESTIS DEVELOPMENT ALSO CAUSE HYPOSPADIAS

Complete XY gonadal dysgenesis leads to persistent Müllerian ducts and female-type external genitalia. It is associated with a severe defect in one of the genes playing a crucial role in testis determination, e.g., the *SRY* (sex determining region of Y) or the *DHH* (desert hedgehog) gene.[13] However, gonadal dysgenesis is not a single, well-defined disorder; it should be viewed as a spectrum of abnormalities. Less severe defects may lead to an incomplete dysgenesis featuring normal Müllerian regression with varying testicular descent and external phenotype: hypospadias is a common finding. This means that genes involved in testis determination may also account for non-syndromic hypospadias if they suffer a mutation that damages their function only mildly.[8]

Mutations in genes like *SOX9* (SRY-box 9) and *NR5A1* (nuclear receptor subfamily 5, group A, member 1, encoding steroidogenic factor 1) have been identified as causes of partial gonadal dysgenesis involving hypospadias.[14,15] *WT1* is known to be responsible for cases presented with varying degrees of dysgenesis: a study found *WT1* mutations in 7.5% of Denys–Drash patients showing severe hypospadias and at least one cryptorchid testis and in one of 10 patients with vanishing testes syndrome.[16]

3. WT1: A UNIQUE TRANSCRIPTION FACTOR

The *WT1* gene spans approximately 50 kbp at chromosomal region 11p13 and contains 10 exons: 6 exons encode an N-terminal region rich in proline and glutamine, while 4 exons at the 3′ end determine 4 classic, C2H2 type zinc finger domains (Fig. 1). Between zinc finger 3 and 4, there is a linker

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region that may or may not contain a KTS tripeptide due to alternative splicing, altering the protein's affinity for DNA.[17] The KTS negative isoform may be more efficient as a transcription factor, but WT1 is also known to regulate certain targets post-transcriptionally through protein-RNA and protein-protein (splicing factor) interactions; this function is mainly attributed to the KTS-positive variant.[18,19] Although many other WT1 variants have been identified (a minimum of 36 are theoretically possible[20]), their differing roles remain mostly unknown, a notable exception being an isoprotein translated from an upstream CUG start codon that may account for oncogenicity according to fresh evidence.[21]

WT1 is an essential regulator in the development of the gonads and the genitourinary tract among other tissues and organs.[22] Originally described as a tumour suppressor of Wilms' tumours, it is now suspected that the underlying pathomechanism involves a disruption of the canonical wingless type (Wnt)–β-catenin pathway: genes in renal development stay repressed due to a failure to suppress the translation of a Polycomb protein by WT1 or certain miRNAs.[23]

In gonad development, WT1 fulfills at least two important roles. One is to trigger the expression of steroidogenic factor 1 (Sf1), thereby promoting the survival of the bipotential gonad.[24] Secondly, WT1 is crucial for male sex determination as it activates transcription of *SRY*. Bradford *et al.* showed that the KTS positive isoform plays a major role in the process, explaining sex reversal seen in Frasier syndrome where the ratio of isoproteins changes in favour of the KTS negative variant.[25]

4. CONTROVERSIAL EVIDENCE OF WT1 INVOLVEMENT IN NON-SYNDROMIC HYPOSPADIAS

4.1. Polymorphisms and mutations within the gene

Recently, some large-scale efforts have been made to shed more light on genetic factors in the background of isolated hypospadias. Carmichael *et al.* examined 293 common tag single nucleotide polymorphisms (SNPs) in 624 cases of hypospadias and 844 population-based male controls in California.[26] Within the *WT1* gene, six SNPs (five in introns and one responsible for a synonymous codon in exon 7) were found to be associated with the disease. While the authors reported some odds ratios higher than 1 even in heterozygotes, an approximately two-fold risk was found for genotypes homozygous for the minor allele at each SNP, primarily for severe hypospadias. In another recent study, genome-wide association analyses performed on large Northern European populations of hypospadias patients and controls found no significant association with any known SNPs in *WT1*.[27] It is worth noting that neither of these studies have included *WT1* SNP rs2234583—suggested as relevant in non-syndromic hypospadias, as explained below—as it was absent from the microarray used by Geller *et al.*, while Carmichael *et al.* have only studied SNPs with frequent minor alleles.[26,27]

Mutations in *WT1* are well-known causes of syndromic hypospadias, but it is still not settled if they play a role in isolated forms of the disease. An early study aimed to answer that question did not detect a mutation of *WT1* in 35 Swedish patients; however, it should be noted that they only sequenced exons 2–10 of the gene.[28] A few years later, it appeared that exon 1 may be relevant in non-syndromic cases. Wang *et al.* reported a C–T transition in position 390 in two patients, and a G–A transition in position 391 in one patient (and another patient showing a mutation in exon 2).[29] Overall, they found heterozygous *WT1* mutations in four of 90 Chinese patients and none of the 276 unrelated control individuals. Defects in exon 1 were associated with more severe (penoscrotal or penile) hypospadias, while the single exon 2 mutation was observed in a mild, glandular case. Exons 1 and 2 encode the N-terminal part of a region rich in proline and glutamine[30] (see also Section 3). As shown in Fig. 1, early *in vitro* studies on the region identified a putative dimerisation domain, an RNA-binding domain and a domain possibly regulating transcriptional activation and repression,[31] but recent evidence points more at the importance of zinc finger 1 and the KTS tripeptide in RNA-

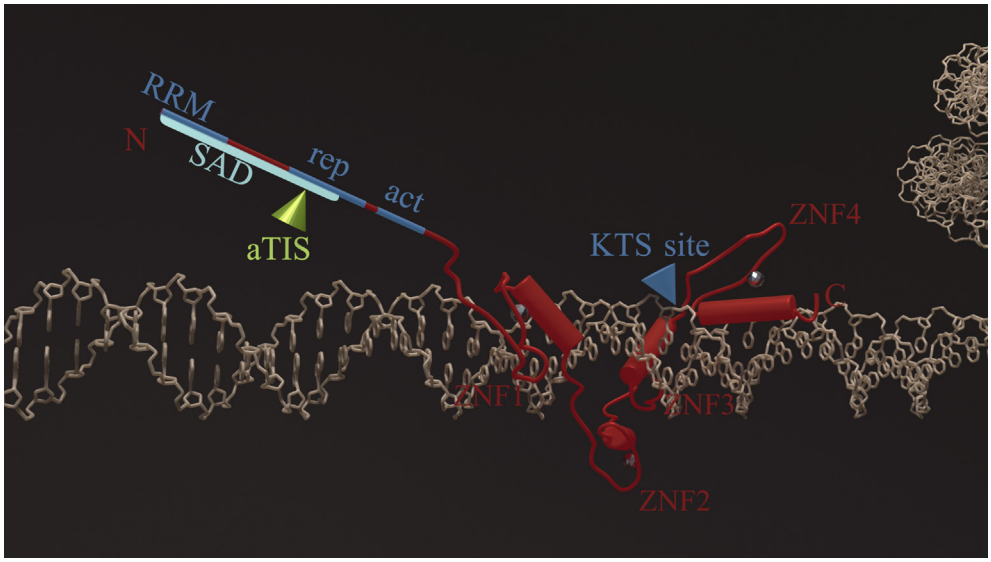

Fig. 1 The proposed structure of the WT1 protein and its association with DNA. RRM, putative RNA binding domain;[31] ZNF, zinc fingers;[30] act, activator domain;[31] rep, repressor domain;[31] SAD, self-association domain;[31] KTS site, tripeptide present or absent due to alternative splicing at exon 9, determining the main isoforms;[17] aTIS, alternative translation initiation site determining a minor isoprotein[35] (near rs2234583, see Section 4.1). Note: 3-dimensional structure of the N-terminal region is unknown.

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