

## WT1 基因变异与 Denys-Drash 综合征和 Frasier 综合征的 基因型-表型关联性分析

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**【摘要】目的** 探讨 *WT1* 不同基因型与 Denys-Drash 综合征 (DDS) 和 Frasier 综合征 (FS) 不同表型之间的关联。**方法** 检索和归纳 1991 年 1 月 1 日至 2023 年 10 月 31 日期间 NCBI PubMed 和 CNKI 数据库收录的 *WT1* 基因变异患者信息, 分析变异类型、发生位置和进展性肾功能损伤、泌尿生殖系统发育不全、肾母细胞瘤、性腺肿瘤等表型的关联性。**结果** 本研究纳入 128 篇文献, 包含 304 例研究对象, 检出 86 种 *WT1* 致病性变异。这些变异的位置分布特点为: 最常见发生于外显子 9 (24/86, 27.9%) 和外显子 8 (23/86, 26.7%); 变异类型特点为: 错义变异 (51/86, 59.3%) 最常见, 次常见为剪接位点变异 (13/86, 15.1%)。 *WT1* 基因变异导致的疾病种类特点为: DDS 病例数最多 (174/304, 57.2%), 其次为 FS (83/304, 27.3%); DDS 主要由外显子 9 和外显子 8 上的错义变异 (143/174, 82.2%) 导致, 而 FS 主要由内含子 9 上的剪接位点变异 (76/83, 91.6%) 导致。**结论** *WT1* 基因上外显子 9 和外显子 8 的错义变异主要导致 DDS, 而内含子 9 的剪接变异主要导致 FS。对进展性肾损伤的婴幼儿及儿童应进行泌尿生殖系统的全面评估, 早期明确基因诊断, 以改善预后。

**【关键词】** *WT1* 基因; Denys-Drash 综合征; Frasier 综合征; 46,XY 性发育障碍; 孤立性肾病综合征; 肾母细胞瘤

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## Genotype-Phenotype Correlation Analysis of *WT1* Gene Variants in Denys-Drash Syndrome and Frasier Syndrome

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**【Abstract】 Objective** This study aims to explore the association between different genotypes of *WT1* gene variations and the phenotypes of Denys-Drash syndrome (DDS) and Frasier syndrome (FS). **Methods** Through searching and summarizing the case information of *WT1* gene variations recorded in NCBI PubMed and CNKI databases from January 1, 1991 to October 31, 2023, we analyzed the association between variation types, occurrence locations, and phenotypes such as progressive renal function impairment,

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genitourinary developmental abnormalities, nephroblastoma, and gonadal tumors between DDS and FS. **Results** A total of 128 articles, including 304 subjects, were included in this study, and 86 pathogenic variations of the *WT1* gene were detected. The distribution characteristics of these variations were as follows: the most common occurrence was in exon 9 (24/86, 27.9%) and exon 8 (23/86, 26.7%); the most common variation type was missense mutation (51/86, 59.3%), followed by splice site mutation (13/86, 15.1%). The disease types caused by *WT1* gene variations were as follows: DDS had the highest number of cases (174/304, 57.2%), followed by FS (83/304, 27.3%); DDS was mainly caused by missense mutations on exon 9 and exon 8 (143/174, 82.2%), while FS was mainly caused by splice site mutations on intron 9 (76/83, 91.6%). **Conclusions** The missense variants in exon 9 and exon 8 on the *WT1* gene mainly resulted in DDS, while the splice variants in intron 9 mainly resulted in FS. Infants and children with progressive renal injury should undergo a comprehensive evaluation of the genitourinary system, and early genetic diagnosis should be established to improve prognosis.

**【Key words】** *WT1* gene; Denys-Drash syndrome; Frasier syndrome; 46,XY disorders of sex development; isolated nephrotic syndrome; Wilms tumor

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Wilms 瘤基因 1 (Wilms Tumour gene 1, *WT1*) 编码一种锌指样结构的转录因子, 在肾脏和性腺的发育中起着非常重要的作用<sup>[1-2]</sup>。*WT1* 基因位于染色体 11p13, 由 10 个外显子组成<sup>[3]</sup>。该基因的外显子 1~6 编码 WT1 蛋白 N 端富含脯氨酸/谷氨酰胺转录调控区, 包括二聚体结构域、转录抑制结构域和转录激活结构域; 外显子 7~10 则分别编码 WT1 蛋白 C 端与 DNA 或 RNA 结合的 4 个锌指结构域<sup>[4]</sup>。此外, *WT1* 基因存在两个可变剪接位点。可变剪接位点 1 位于第 5 外显子, 不同的剪接方式产生插入或缺失 17 个氨基酸的两种蛋白亚型。可变剪接位点 2 位于外显子 9 末端, 使第 3 和第 4 个锌指之间插入或缺失赖氨酸、苏氨酸和丝氨酸 (KTS) 3 个氨基酸, 产生 (-KTS) 和 (+KTS) 两个蛋白亚型<sup>[5]</sup> (图 1)。不同的亚型可以调节不同细胞的分化过程, 肾脏和性腺的正常发育有赖于二者正常的比例关系。

*WT1* 基因胚系变异以常染色体显性遗传方式导致多种疾病, 包括肾母细胞瘤 (Wilms tumor, WT)<sup>[6]</sup>、孤立性肾病综合征 (isolated nephrotic syndrome, INS)、Frasier 综合征 (Frasier syndrome, FS)、Denys-Drash 综合征 (Denys-Drash syndrome, DDS)、WAGR 综合征和 Meacham 综合征等<sup>[7]</sup>。其中 FS 和 DDS 是发病率较高的、同时包含泌尿系统和生殖系统异常的疾病。FS (OMIM #136680) 主要表现为 46,XY 性发育障碍 (disorders of sex development, DSD), 2~6 岁时出现

进展性肾功能损伤, 以局灶节段性肾小球硬化 (focal segmental glomerulosclerosis, FSGS) 为主要病理特征<sup>[8]</sup>。DDS (OMIM #194080) 主要表现为泌尿生殖系统发育不全和/或 WT, 婴幼儿期出现进展性肾功能损伤, 以弥漫性系膜硬化为主要病理特征<sup>[9]</sup>。

*WT1* 基因变异类型和发生位置是否与 FS 和 DDS 的表型关联, 尚缺乏大样本系统分析研究。本研究拟全面检索 NCBI PubMed 和 CNKI 数据库, 纳入诊断明确的患者, 对其 *WT1* 基因型和对应表型进行关联性分析, 旨在更好地理解 FS 和 DDS 患者的 *WT1* 致病变异的特点, 为早期诊断和有针对性的治疗提供依据, 并为遗传病的精准诊疗提供重要的参考。

## 1 对象与方法

### 1.1 文献检索方法

通过对 NCBI PubMed 和 CNKI 数据库进行全面文献检索, 建立一个 *WT1* 基因变异患者的临床信息数据库。检索的时间范围限定为 1991 年 1 月 1 日至 2023 年 10 月 31 日。在 NCBI PubMed 数据库以 “(Denys Drash syndrome) OR (Frasier syndrome) AND (*WT1*)” 为检索公式, 检索得到 279 篇文献。在 CNKI 数据库以 “(*WT1*) 和 (突变)” 进行检索, 得到 50 篇文献。

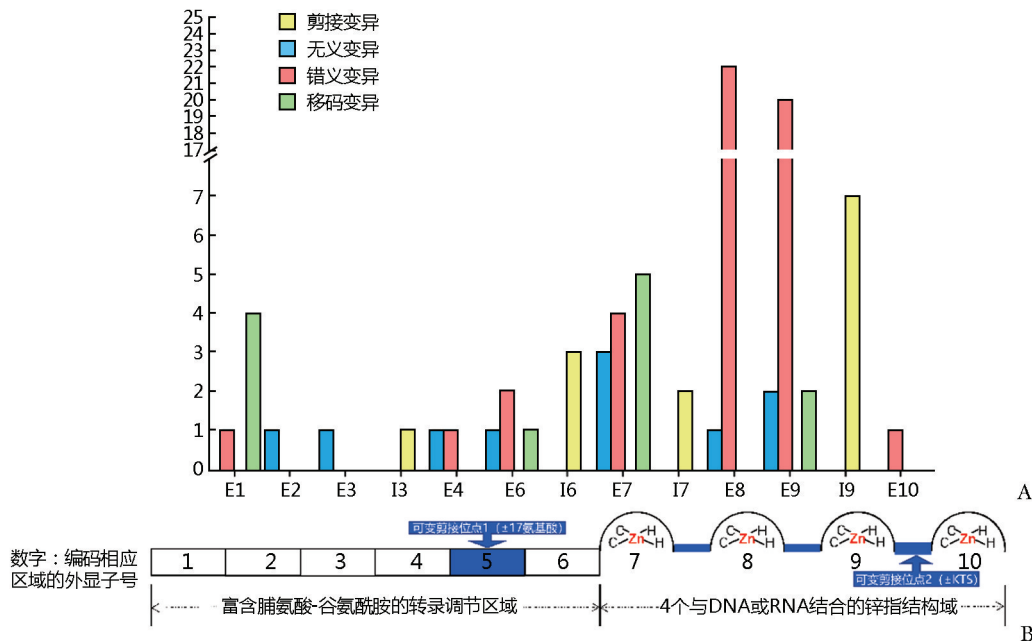


图 1 86 种致病变异位置分布及其对应结构域情况

Fig. 1 Distribution of 86 pathogenic variants and their corresponding structural domains

A. 86 种变异位置分布情况; B. 不同外显子对应的结构域

在 329 篇检索结果中, 通过阅读摘要, 排除动植物实验研究文献 22 篇、与本研究目标无关的文献 61 篇, 其中包括研究 WT1 蛋白分子结构与功能的文献 9 篇、WT1 基因结构与相关调控机制的文献 24 篇, 以及与泌尿生殖系统异常无关的文献 18 篇和细胞实验研究文献 10 篇。此外, 还排除综述 42 篇、书籍和文件 1 篇, 以及无法获取全文的文献 26 篇和以非英文和中文文字发表的文献 7 篇。进一步阅读全文后, 剔除缺乏明确 WT1 基因变异位点和相关临床症状等重要信息的文献 26 篇, 以及变异位点与参考基因组位点不匹配的文献 16 篇。最终纳入文献共 128 篇<sup>[7-134]</sup> (图 2)。

## 1.2 研究对象与数据提取

共纳入 304 例研究对象的基因诊断信息和临床数据。在基因诊断信息中, 均按人类基因组变异学会 (Human Genome Variation Society, HGVS) 命名规则, 以 NM\_024426.6 为参考转录序列, NP\_077744.4 为参考氨基酸序列, 对变异进行表述, 包括变异发生位置、变异造成的核苷酸改变和氨基酸改变; 临床数据包括患者的诊断、年龄、社会性别、核型、肾脏和性腺活检病理结果, 以及是否发生进展性肾功能损伤、终末期肾衰、泌尿生殖系统发育不全及其他系统发育不全、WT 和性腺肿瘤等临床特征。

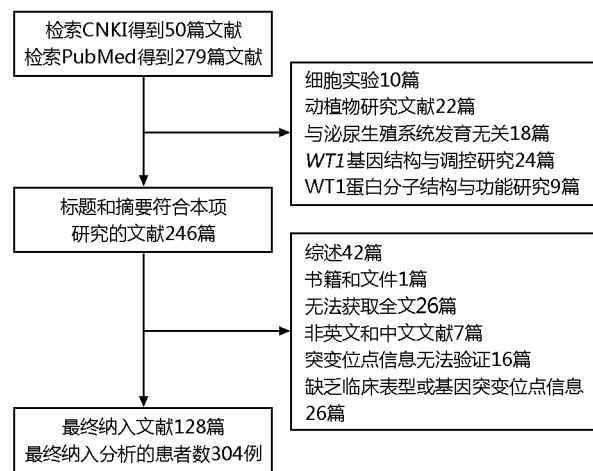


图 2 文献检索流程图

Fig. 2 Flowchart of literature retrieval

由于部分患者处于疾病早期阶段或做预防性肾脏和性腺切除等, 表型可能未能完整描述, 这些患者仅有 INS 和 WT 描述, 也纳入统计分析, 因此, 诊断分组为 WT、INS、FS 和 DDS 四组。对于文献缺乏明确疾病种类诊断的患者, 根据报道表型予以补充。其中, 1 例诊断为 DDS 患者携带 c.1124G>T (p. R375L) 和 c.1114-1G>T 两个未明确顺反排列关系的致病变异, 该例患者以两个变异均导致 DDS 纳

入统计。此外,FS和DDS的表型被总结为进展性肾功能损伤、泌尿生殖系统发育不全、WT和性腺肿瘤四组,以分析变异位置和类型与不同表型组之间的联系。

*WT1* 变异位置分组主要参考 *WT1* 功能结构域位置。*WT1* 基因外显子 1~6 编码二聚体结构域、转录抑制结构域和转录激活结构域(图 1B),且变异较少,将发生于该区域的变异归为“调控域”组,而 *WT1* 外显子 7~10 各自编码 1 个锌指 DNA 结合结构域,是致病变异发生的热点区域,发生于外显子 7~10 及其相应内含子的变异单独成组,分别为 E7、I7、E8、I8、E9、I9 和 E10 组。

### 1.3 统计学分析

符合正态分布的数值变量用均数±标准差表示,不符合正态分布的数值变量采用中位数和四分位间距描述。百分比用于描述分类变量。采用 $\chi^2$ 检验或 Fisher's 精确检验对分类变量进行组间比较,采用秩和检验对非正态分布的定量变量进行组间比较。当 $P<0.05$ (双尾)时,差异有统计学意义。使用 GraphPad Prism v9.0.0 软件进行数据统计和图表制作。

## 2 结果

### 2.1 *WT1* 基因变异的分布特征

共纳入已明确诊断的 302 例 *WT1* 基因变异患者和 2 名文献内表型正常同时携带致病变异的患者的亲属。这些研究对象共检出 86 种致病变异,主要分布在 9 个外显子和 4 个内含子上,其中 51 个错义变异、13 个剪接变异、12 个移码变异和 10 个无义变异

(图 3A)。变异核苷酸在基因分布的位置特征为(图 1A):外显子 9 上的变异数目最多(24/86, 27.9%),其次是外显子 8(23/86, 26.7%)。其余 8 个外显子共检测出 26 个变异。错义变异(42/47, 89.4%)主要发生于外显子 8 和 9,而移码变异和无义变异(17/26, 65.4%)更多见于其余外显子。剪接变异主要发生在内含子 9(7/13, 53.8%)上,其次发生在内含子 6(3/13, 23.1%)、内含子 7(2/13, 15.4%)和内含子 3(1/13, 7.7%)上。

304 例研究对象共检出 *WT1* 基因的 305 个变异,除 1 例研究对象检出 2 个 *WT1* 基因变异外,其余研究对象均检出 1 个 *WT1* 基因变异。176 例研究对象中检出错义变异,为数量最多的变异类型,在 94 例研究对象中检出剪接变异(图 3B),为次多见的致病变异类型。分别有 37.2%(113/304)、28.9%(88/304)和 20.4%(62/304)患者检出外显子 9、内含子 9 和外显子 8 上的变异。研究对象中检出次数最多的 5 个热点变异分别为 c.1399C>T(54, 17.7%, E9), c.1447+4C>T(42, 13.7%, I9), c.1447+5G>A(39, 12.7%, I9), c.1316G>A(19, 6.2%, E8)和 c.1405G>A(17, 5.5%, E9)。

### 2.2 携带 *WT1* 变异患者的临床特征

患者的中位诊断年龄为 3(1, 8.2)岁。74.3%(226/304)的患者社会性别为女性,52.3%(159/304)的患者染色体核型是 46,XY。最常见的临床表现是进展性肾功能损伤,患病率达 85.9%(261/304),其次是泌尿生殖系统发育不全为 62.5%(190/304),WT 为 32.6%(99/304),性腺肿瘤为 8.6%(26/304)。个别患者发生髋关节发育不良、并趾、卵圆孔

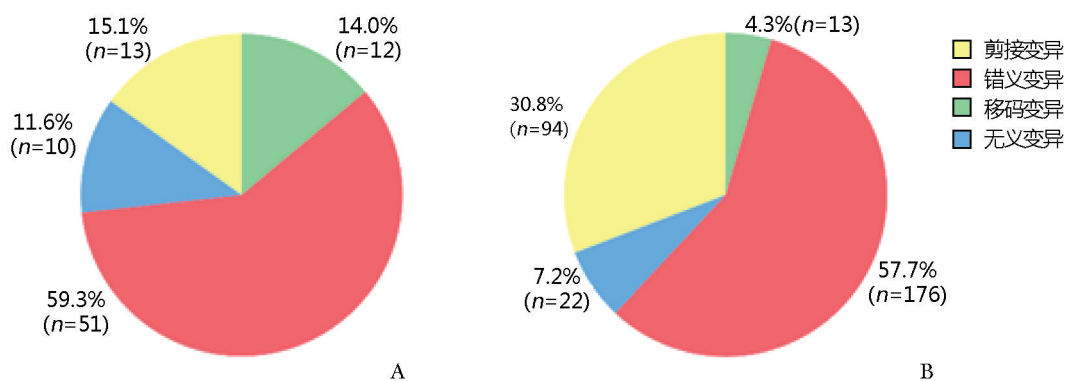


图 3 *WT1* 基因变异总体分布

Fig. 3 Overall distribution of *WT1* gene variants

A. *WT1* 基因 86 种变异类型分布; B. 305 个检出变异的类型分布



未闭、心间隔缺损、左心肥大、心肌肥大、肛门闭锁、膈疝、肌纤维母细胞瘤、血栓性微血管病、神经运动迟缓、肝脏多发结节、非典型溶血性尿毒症等罕见表型。49.7% (151/304) 的患者已发展至终末期肾衰, 年龄范围为 1 d 至 59 岁。138 例肾脏活检结果中, 47.8% 为弥漫性系膜硬化性肾小球病 (diffuse mesangial sclerosis glomerulopathy, DMS), 54.3% 为 FSGS。泌尿生殖系统发育不全主要表现为性腺发育不全 (189/190, 99.5%), 患者可同时合并输尿管畸形、肾盂畸形、马蹄肾、多囊肾等表型。性腺发育不全以 46,XY DSD 为主, 在明确核型为 46,XY 或 47,XXY 的 160 例患者中, 91.9% (147/160) 的患者均为 46,XY DSD。核型为 46,XX 的患者外生殖器正常, 但可出现条索状性腺、卵巢萎缩等性腺发育不全的症状。性腺肿瘤以性腺母细胞瘤为主 (23/26, 88.5%), 此外, 还可发生性腺恶性无性细胞瘤、支持细胞瘤 (表 1)。

表 1 304 例携带 WT1 变异患者的总体临床特征

Tab. 1 Overall clinical characteristics of the 304 patients carrying the WT1 variant

临床特征	数值
检出变异次数	305
社会性别 [% (n/N)]	
女	74.3 (226/304)
男	23.0 (70/304)
未知	2.6 (8/304)
核型 [% (n/N)]	
XY	52.3 (159/304)
XX	18.8 (57/304)
XXY	0.3 (1/304)
未知	28.6 (87/304)
诊断年龄中位数 (IQR, 岁)	3 (1, 8.2)
临床特征 [% (n/N)]	
进展性肾功能损伤	85.9 (261/304)
终末期肾衰	49.7 (151/304)
肾脏活检 DMS	47.8 (66/138)
肾脏活检 FSGS	54.3 (75/138)
泌尿生殖系统发育不全	62.5 (190/304)
46,XY 性发育障碍	91.9 (147/160)
肾母细胞瘤	32.6 (99/304)
性腺肿瘤	8.6 (26/304)

DMS: 弥漫性系膜硬化性肾小球病; FSGS: 局灶节段性肾小球硬化

302 例患者中, 173 例为 DDS、83 例为 FS、36 例为 INS 和 10 例 WT。DDS 和 FS 患者的临床信息见表 2。DDS 患者的中位数诊断年龄为 1.5 (0.6, 4.0) 岁, 而 FS 的中位诊断年龄较大, 为 9 (4, 17) 岁。DDS 与 FS 在发生进展性肾功能损伤 ( $P=0.097$ ) 和肾病进展至终末期肾衰 ( $P=0.759$ ) 的比例上无明显差异。DDS 的肾小球病变主要为弥漫性系膜硬化, 而 FS 的肾脏病理类型通常为 FSGS, 两者比较差异有统计学意义 ( $P<0.001$ )。此外, FS 较 DDS 更易发生泌尿生殖系统发育不全、46,XY DSD 和性腺肿瘤具有显著性差异 ( $P$  分别  $<0.001$ 、 $0.043$ 、 $<0.001$ )。DDS 比 FS 更易发生肾母细胞瘤 ( $P<0.001$ )。值得注意的是, 1 例诊断为 DDS 患者同时有 WT 和性腺母细胞瘤。3 例患者肾脏病理类型为 DMS 和 FSGS 混合, 其中 2 例诊断为 DDS, 1 例诊断为 FS。

### 2.3 WT1 变异的基因型和表型关联分析

首先根据不同疾病类型分析不同变异类型分布情况, 结果表明, 79.3% 的 DDS 和 83.3% 的 INS 由错义变异所致, 91.6% 的 FS 由剪接变异引起, 而 60.0% 的 WT 由无义变异所致 (图 4)。

其次对 WT1 变异发生位置及变异类型与疾病类型的联系进行分析 (图 5)。结果表明, DDS 主要由外显子 9 和 8 上的错义变异导致 (143/174, 82.2%), 热点变异位点为: c.1399C>T (49, 28.1%, E9), c.1405G>A (15, 8.6%, E9), c.1316G>A (14, 8.0%, E8)。除内含子 8 尚未报道任何变异外, 其余组别 (调控域组、E7-E10、I7、I9) 均有报道导致 DDS 的变异。FS 的致病变异主要为内含子 9 上的剪接位点变异 (76/83, 91.6%), 其次为外显子 9 上的错义变异和无义变异 (6/83, 7.2%), 其余位置上的变异罕有报道。FS 的热点变异均分布在内含子 9 上, 主要为: c.1447+4C>T (40, 48.1%), c.1447+5G>A (29, 34.9%) 这两个变异。INS 致病变异的分布特点与 DDS 相似, 热点变异为: c.1316G>A (5, 13.8%, E8) 和 c.1399C>T (5, 13.8%, E9), 也是 DDS 的热点变异。单独导致 WT 的变异主要为外显子 7 上的无义变异 (5/10, 50%), 其余分布在内含子 6 和 7、外显子 1 和 2 上。因病例数量较少, 尚未发现引起 WT 的热点变异。

此外, 对 WT1 变异发生位置与四种 WT1 变异相关常见表型进行分析 (图 6), 结果表明, 进展性肾功能损伤是发生频次最多的表型, 导致其发生的

表 2 Denys-Drash 综合征 (DDS) 和 Frasier 综合征 (FS) 患者的临床特征

Tab. 2 Clinical characteristics of patients with Denys-Drash syndrome (DDS) and Frasier syndrome (FS)

临床特征	DDS	FS	P 值
患者例数	173	83	—
检出变异次数	174	83	—
社会性别 [% (n/N)]			0.004
女	69.4 (120/173)	86.7 (72/83)	—
男	26.6 (46/173)	13.3 (11/83)	—
未知	4.0 (7/173)	0	—
核型 [% (n/N)]			<0.001
XY	50.3 (87/173)	83.1 (69/83)	—
XX	20.8 (36/173)	8.4 (7/83)	—
XXY	0.6 (1/173)	0	—
未知	28.3 (49/173)	8.4 (7/83)	—
诊断年龄中位数 (IQR, 岁)	1.5 (0.6, 4.0)	9 (4, 17)	<0.001
临床特征 [% (n/N)]			
进展性肾功能损伤	85.5 (148/173)	92.8 (77/83)	0.097
终末期肾衰	48.6 (84/173)	50.6 (42/83)	0.759
肾脏活检 DMS	73.1 (49/67)	8.3 (4/48)	<0.001
肾脏活检 FSGS	29.9 (20/67)	93.8 (45/48)	<0.001
泌尿生殖系统发育不全	66.5 (115/173)	90.4 (75/83)	<0.001
46,XY 性发育障碍	89.8 (79/88)	98.6 (68/69)	0.043
肾母细胞瘤	50.9 (88/173)	1.2 (1/83)	<0.001
性腺肿瘤	2.3 (4/173)	26.5 (22/83)	<0.001

DDS: Denys-Drash 综合征; FS: Frasier 综合征; —为未记录

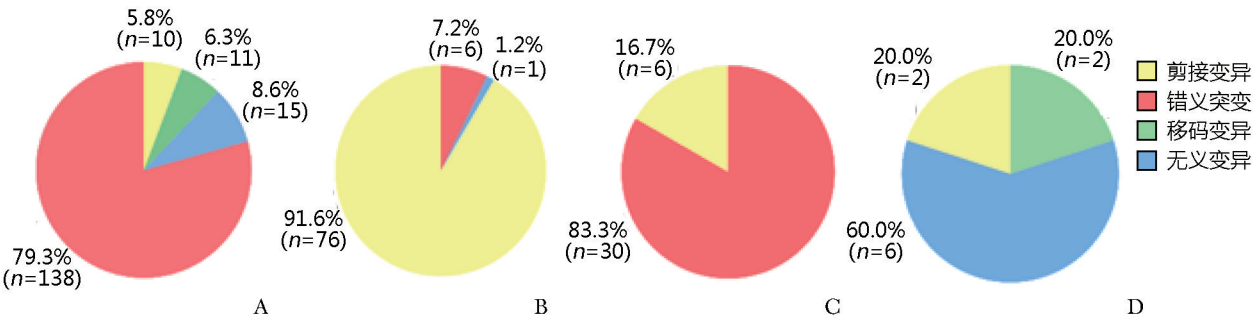


图 4 不同疾病变异类型分布

Fig. 4 Distribution of variant types for different diseases

A. 173 例 DDS 检出 174 个变异的类型分布; B. 83 例 FS 的变异类型分布; C. 36 例孤立性肾病综合征的变异类型分布; D. 10 例肾母细胞瘤的变异类型分布

*WT1* 基因变异在外显子 9 上最多见, 其次是内含子 9、外显子 8, 其热点变异为: c. 1399C>T (50, 19.1%)、c. 1447+5G>A (39, 14.9%)、c. 1447+4C>T (38, 14.5%) 和 c. 1316G>A (17, 6.5%)。泌尿生殖系统发育不全表型所关联的 *WT1* 基因变异在内含子 9 上最常见, 其次是外显子 9 和外显子 8, 热

点变异为: c. 1447+4C>T (37, 19.3%)、c. 1447+5G>A (30, 15.7%)、c. 1399C>T (27, 14.1%) 和 c. 1316G>A (12, 6.2%)。值得注意的是, 6 例 46,XX DSD 均为外显子 9 的错义变异, 分别为: c. 1382G>A (1 例)、c. 1399C>T (3 例)、c. 1405G>A (1 例)、c. 1434T>A (1 例)。WT 相关的 *WT1* 基因变异主要发

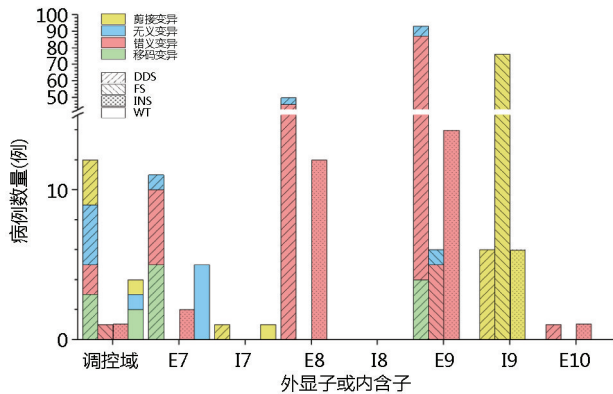


图5 不同外显子和内含子上的疾病类型和变异类型分布情况

Fig. 5 Distribution of disease types and variant types on different exons and introns

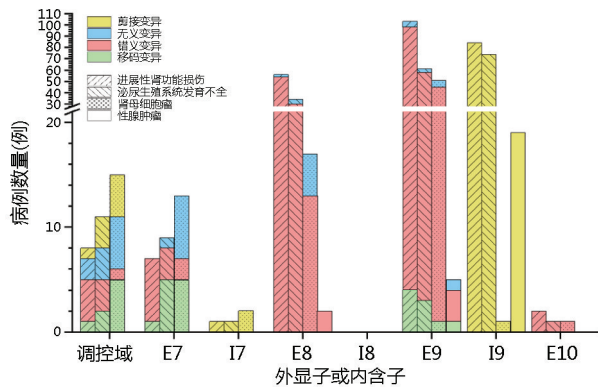


图6 不同外显子和内含子上的表型发生情况

Fig. 6 Phenotypic occurrence on different exons and introns

生于外显子9 (51/56, 91.1%) 和外显子8 (17/19, 89.5%), 除内含子8尚未报道任何变异外, 其余组别均已报道导致WT表型的变异; 变异类型主要为错义变异和无义变异; 热点变异为: c.1399C>T (24, 24%)、c.1405G>A (9, 9%) 和 c.1387C>T (5, 5%)。而更易导致性腺肿瘤 (19/20, 95.0%) 相关的WT1基因变异是主要发生于内含子9上的剪接变异, 热点变异为: c.1447+4C>T (12, 46.1%) 和 c.1447+5G>A (7, 26.9%); 迄今为止, 性腺肿瘤仅与WT1基因内含子9、外显子9和外显子8上的变异有关。

### 3 讨论

WT1基因致病变异主要分布在外显子8、外显子9和内含子9上, 以错义变异和剪接变异为主, 这可

能与下述致病机制有关。外显子8和外显子9分别编码WT1重要功能结构域锌指2和锌指3<sup>[135]</sup>。锌指是一个独立折叠为球状的结构域, 包含X<sub>3</sub>-Cys-X<sub>2,4</sub>-Cys-X<sub>12</sub>-His-X<sub>3,4</sub>-His-X<sub>4</sub>形式的序列基序, 其中X可以是任何氨基酸, 两个半胱氨酸和两个组氨酸形成配体结合锌原子<sup>[130]</sup>。该结构基序常见于真核生物中蛋白质与核酸的相互作用。WT1的锌指结构具有与DNA和RNA结合的功能, 通过转录调控、RNA代谢调控等方式<sup>[4]</sup>, 直接或间接调节不同组织和不同类型细胞的正常分化。研究发现, 敲除WT1基因的小鼠会出现肾脏和性腺缺失等症状, 表明WT1基因在肾脏和性腺的形成和维持中发挥重要作用<sup>[136]</sup>。发生于外显子7~10上的变异易破坏锌指结构, 严重影响WT1蛋白正常功能。此外, 内含子9剪接变异主要发生于与外显子9的3'端相接的5'端, 此处的可变剪接位点2受到影响, 使得WT1(+KTS)亚型产生减少, 进而导致蛋白亚型(+KTS)/(-KTS)比例失衡<sup>[5]</sup>。由于不同蛋白亚型功能有所差异, 不同亚型比例失调最终导致相关组织器官发育异常。

WT1基因相关表型的临床异质性大, 发生率由高到低分别为进展性肾功能损伤、泌尿生殖系统发育不全、WT和性腺肿瘤, 个别患者表现出先天性心脏病、肛门闭锁、膈疝、髋关节发育不良、并趾等罕见表型。此外, 存在同一家系的患者携带同一变异而表型轻重差异较大的情况, 表现为进展至肾功能衰竭的年龄差异较大、性腺发育完全正常至性别完全逆转情况均存在等。可能是由于WT1编码的转录因子具有超过30种的mRNA转录本, 编码33~56 kDa的多种蛋白质亚型<sup>[3,137]</sup>, 不同组织表达不同转录本, 不同变异并不出现在所有转录本中。

基于不同表型的组合, WT1基因变异导致的疾病可分为罕见的遗传综合征DDS、FS, 以及单纯的INS和WT。在本研究中, 患病率由高到低分别为57.2% (173/304) 的DDS、27.3% (83/304) 的FS、11.8% (36/304) 的INS和3.3% (10/304) 的单纯WT。DDS的致病变异主要集中在外显子9和外显子8上, 多为错义变异, 最常见的热点变异为c.1399C>T (49, 28.1%, E9), 与既往报道一致<sup>[4]</sup>。WT1蛋白通过其N-端同源二聚化结构域形成同源二聚体。这种同源二聚体能够与基因启动子中的同源识别基序结合, 以调节靶基因转录。然而, 在外显子9和8上的错义变异会导致对应的锌指3和2结构域发生改变, 导致同源二聚体成为对靶基因亲和力降低

的异二聚体。同时,异二聚体还会干扰来自野生型等位基因的同源二聚体功能,通过显性负效应的机制将正常 WT1 降至 50% 以下,影响发育过程中肾脏及性腺支持类细胞的存活及分化<sup>[4]</sup>,导致肾小球和性腺发育不良,临床上表现为快速进展的肾功能损伤、WT 终身患病率高、46,XY DSD 发生率高,以及小部分发生条索状性腺、性腺缺失或萎缩的 46,XX DSD<sup>[131]</sup>。FS 的致病变异主要为内含子 9 上的剪接变异,热点变异为: c. 1447 + 4C > T (40, 48.1%), c. 1447 + 5G > A (29, 34.9%), 与先前报道相符<sup>[5]</sup>。Tsuji 等<sup>[5]</sup>报道内含子 9 发生剪接变异的等位基因仅允许 WT1 (-KTS) 亚型的表达,使得 WT1 (+KTS) 与 WT1 (-KTS) 亚型的比例从 1:1 转变为 1:3.2~1:3.5。WT1 (-KTS) 亚型可以强烈抑制男性支持细胞中苗勒管抑制物质的表达,并抑制雄激素受体启动子,但 WT1 (+KTS) 没有该功能<sup>[138-139]</sup>。因此 (+KTS) / (-KTS) 比例失衡可以致性腺发育异常,主要是核型为 46,XY 患者出现完全女性外阴、外生殖器模糊、尿道下裂和隐睾等 DSD 表现。内含子 9 的剪接变异容易导致缓慢进展的肾病,这可能与不同蛋白亚型调节功能的差异有关。目前研究发现,激活 nephrin 蛋白所必需的是 (-KTS) 亚型<sup>[140]</sup>,而其他亚型在肾脏发育过程中的功能尚待进一步研究。INS 患者较少,且致病变异的分布特点与 DDS 相似。这种疾病可能只是 DDS 和 FS 的早期状态<sup>[4]</sup>,可随年龄增长发展为伴随 WT 或性腺肿瘤的综合征。Ruf 等<sup>[141]</sup>注意到在患有类固醇抵抗性肾病综合征的 46,XY 男性中有 5% 的 *WT1* 变异,在 46,XX 女性中有 9% 的 *WT1* 变异。其中,5 例核型为 46,XX 的患者中有 1 例发展为 WT,3 例核型为 46,XY 的患者中有 1 例发展为性腺母细胞瘤。此外,核型为 46,XX 的青春期前期患者缺乏明显的外生殖器发育不全,不易被发现内生殖器发育异常和内分泌异常,易被诊断为 INS。部分患者在明确基因诊断后预防性切除发育不良的肾脏,也可避免病情进一步发展为综合征。单独 WT 病例数量最少,*WT1* 基因变异导致 WT 的机制目前尚未明确。

值得注意的是,变异位点可能存在完全不外显的情况。Zirn 等<sup>[132]</sup>报道携带 c. 1569A>G 变异的母亲在 46 岁时进展至终末期肾病,携带同样变异的女儿却发生 WT 和输尿管肾盂发育不全,并在 22 岁时进展至终末期肾病,而携带同样变异的儿子在 17 岁时尚无肾功能异常。Zhu 等<sup>[133]</sup>和 Coppes 等<sup>[142]</sup>报道携带

c. 1399C>T 的父亲表型正常,但携带同样变异位点的儿子和女儿在 4 岁前肾功能异常,且儿子具有性腺发育异常。此外,c. 1316G>C 位点<sup>[134]</sup>也报道过目前在 41 岁时仍然表型正常的父亲,而他的两个双胞胎后代在 2 岁内死亡。由于缺乏长期随访结果,尚未表现出疾病的亲代后续是否发生肾脏疾病无法得知,*WT1* 基因可能存在完全不外显的情况需要进一步研究结果的支持。

本研究也存在一定的局限性。由于检索的文献出版时间跨度较大,不同文献作者对疾病的诊断存在一定差异,有些研究对患者的表型描述欠详尽,可能对统计结果造成一定偏倚,本文结果有待大样本长期随访队列研究进行验证。

DDS 主要由外显子 9 和外显子 8 上的错义变异所导致,而 FS 则主要由内含子 9 上的剪接变异所致。*WT1* 基因变异可以导致一系列表型谱,也存在不完全外显情况。对于出现进展性肾损伤的婴幼儿及儿童,应进行详尽的泌尿生殖系统临床评估,并尽早进行基因诊断,以便为患儿提供精准的病情管理和预防性治疗,从而降低恶性肿瘤的发生率。

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**利益冲突:** 所有作者均声明不存在利益冲突。

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## 中国罕见病联盟简介

中国罕见病联盟 (China Alliance for Rare Diseases, CHARD) 是经国家卫生健康委员会医政医管局批准, 由北京协和医院、中国医药创新促进会、中国医院协会、中国研究型医院学会联合牵头发起, 具有罕见病相关专科的医疗机构、高等院校、科研院所和企业等自发组成的全国非营利性合作交流平台, 于2018年10月24日在北京正式成立。联盟发展宗旨是以推进健康中国建设为奋斗目标, 坚持以人民为中心的发展理念, 充分发挥成员主体作用, 多方通力合作, 整合优质资源, 加强对罕见病临床和相关政策研究, 完善罕见病标准化诊治体系, 推动罕见病相关生物医药产业发展, 普及患者和医务人员健康教育, 努力提升罕见病临床诊治和保障水平, 提高罕见病患者生命质量。

联盟成立以来, 始终坚持以患者为中心的理念, 在国家卫生健康委员会的指导下, 科学准确把握罕见病防治工作所处的历史阶段和面临的主要问题, 积极探索符合中国国情的罕见病防治和保障道路, 在推动全国罕见病诊疗协作网医院建立、促进罕见病信息系统建设、加强多学科交流协作、改善罕见病药物可及性、开展科普知识宣传等方面都做了大量工作, 已取得可喜成绩。

“健康中国, 一个都不能少”。联盟将连接社会各方, 凝聚共识, 在为罕见病防治和促进健康中国建设中做出不懈努力。