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5α还原酶缺乏症的诊断治疗及研究

国家医学中心

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国家儿童医学中心 National Center for Children's Health, China
北京儿童医院 BEIJING CHILDREN'S HOSPITAL

内容

- 发现及命名
- 病因及病理机制
- 发病率及临床表现
- 诊断及鉴别
- 治疗及随访
- 相关单中心及多中心研究

国家儿童医学中心 National Center for Children's Health, China
北京儿童医院 BEIJING CHILDREN'S HOSPITAL

首次研究报告

Steroid 5α-Reductase Deficiency in Man: An Inherited Form of Male Pseudohermaphroditism

Abstract. *In male pseudohermaphrodites born with ambiguity of the external genitalia but with marked virilization at puberty, biochemical evaluation reveals a marked decrease in plasma dihydrotestosterone secondary to a decrease in steroid 5α-reductase activity. In utero the decrease in dihydrotestosterone results in incomplete masculinization of the external genitalia. Inheritance is autosomal recessive.*

27 DECEMBER 1974

SCIENCE, VOL. 186

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TEOFILO GAUTIER. Universidad Nacional Pedro Henriquez Urena, Department of Pediatrics

1951年，LO Hernandex报道多米尼加Salinas村的13个家庭24例男假2性患者

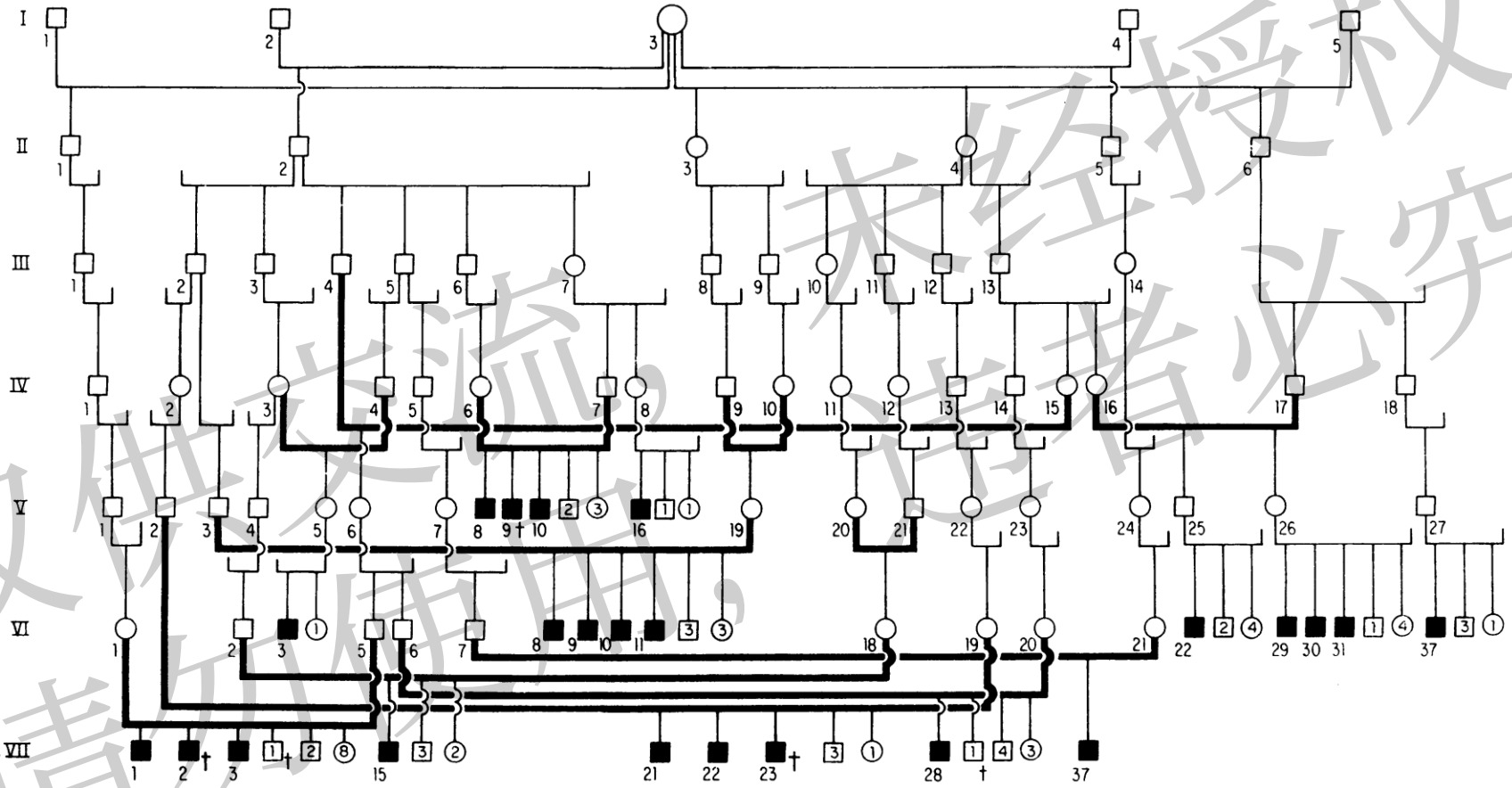

Fig. 4. Pedigree illustrating common ancestry in 12 of the 13 families, and transmission of the defect for male pseudohermaphroditism through seven generations.

特点

L. 0. Hernandex, S. Inchatistegli, C. N. Argtuello, J. Dominicant Med. 6 (2), 114 (1951).

- 46 XY；出生时显著的外生殖器男性分化不完全，模糊，以女性养育。尿生殖窦盲端阴道,阴茎如阴蒂。无苗氏管结构 。
- 内生殖器正常：双侧睾丸在腹股沟或者阴唇包块,或阴唇样的阴囊。
- 睾丸活检：有完整的生精正常的Ledig细胞，正常的副睾和输精管
- 青春期
  - 第二性征：初现声音低沉并出现典型的男性特征：肌肉增无乳房阴茎体增大为有功能的阴茎。（这种变化令人震惊，12岁时被镇上人 称“guevedoces“ 阴茎）
  - 阴囊及睾丸：阴囊变得 褶皱并色素沉着。睾丸降到腹股沟管并且有射精。
  - 前列腺：依然小。胡子,稀少太阳穴的头发无发际线的后退，无痤疮。
  - 心理取向：unequivocally男性。

病因及病理机制

- 疾病影响了外观，并没有影响T的合成，也不是T的作用障碍。
- 提出： 最有可能是睾酮在靶组织的代谢缺陷5a-DHT酶A4-类固醇5a-reductase
  - 确定5a-reductase 的活性缺陷，用双异构体来源的技术测定4例男性T/DHT
  - T/DHT=40~80。T to DHT转换率为0.48~0.75.正常男性为3.5~7。即为正常的1/6.

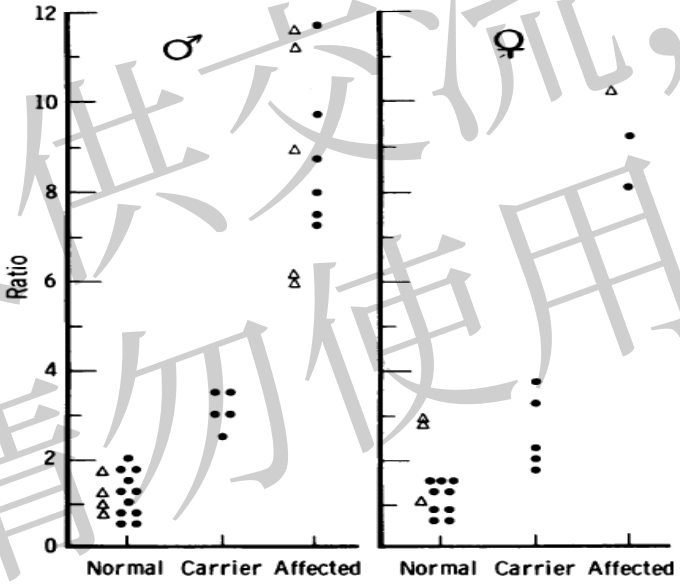

Fig. 1. Ratio of endogenous urinary 3α, 5β-etiocholanolone to 3α,5α-androsterone (●) and 3α,5β-etiocholanediol to 3α,5α-androstanediol (△) in males and females —that is, normals, carriers, and affected.

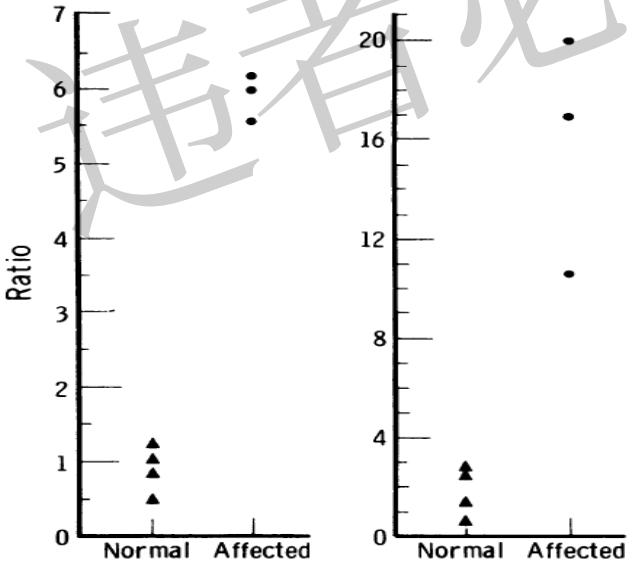

Fig. 2. Ratio of radioactive urinary (left) 3α,5β-etiocholanolone to 3α,5α-androsterone and (right) 3α,5β-etiocholanediol to 3α,5α-androstanediol after [³H]testosterone infusion in normal (▲) and affected (●) males.

5α还原酶有不同的型

- 最早发现不同组织的成纤维细胞，还原酶活性不同。发现了同形异构酶
  - 在**pH 5-5.5最佳活性者，仅来源于生殖器皮肤的成纤维细胞**。其他广泛来源的成纤维细胞则当pH 6-8时活性强。46 XY患者在pH 9 时没见改变。提示人体存在酶的同性异构体。
- 该同型异构酶基因家族包括SRD5A1 and SRD5A2。二者同源50%，都有5个外显子和4个内含子。SRD5A1位于5p15而SRD5A2位于2p23。
- 后续又确认了该家族的其他成员,属于不同的亚家族。SRD5A3位于4q12没有5-α-Reductase的活性;近期发现主要功能是蛋白N端的糖基化
  - 第三亚家族有2基因: GPSN2 和GPSN2-like分别位于19和4号染色体,均参与新生脂肪酸合成
- 尽管每个亚家族酶的底物不同，保守的双键还原特性是共同的生化特点.

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5α还原酶缺乏症的发病率

- 未检索到5αRD的发病率。有DSD发病率及5ARD占DSD的比例。
  - 据初步统计，世界范围内DSD患病率约为1/5500-1/1500[1-2]。5α还原酶缺乏症的患者占DSD患者的4.5％[3]。估计世界范围内5α还原酶2缺乏症发病率为8-30/100万（1：125，000 -1：33,000）。
- **其他类型DSD发病率**
  - CAH世界范围内发病率估计1：15，000；
  - 混合性腺发育不全可能在DSD中排第二位，发病率为1：10,000。
  - CAIS的发病率估计在1：60,000和1：99,000之间，PAIS更常见。
  - 17β-HSD的发生率要低得多，可能为1：150,000，
  - 5α-还原酶（5α-RD）缺乏症可能更不常见[4]。

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3. Bertelloni S, Baldinotti F, Russo G, et al. 5alpha-Reductase-2 Deficiency: Clinical Findings, Endocrine Pitfalls, and Genetic Features in a Large Italian Cohort[J]. Sex Dev, 2016,10(1):28-36.
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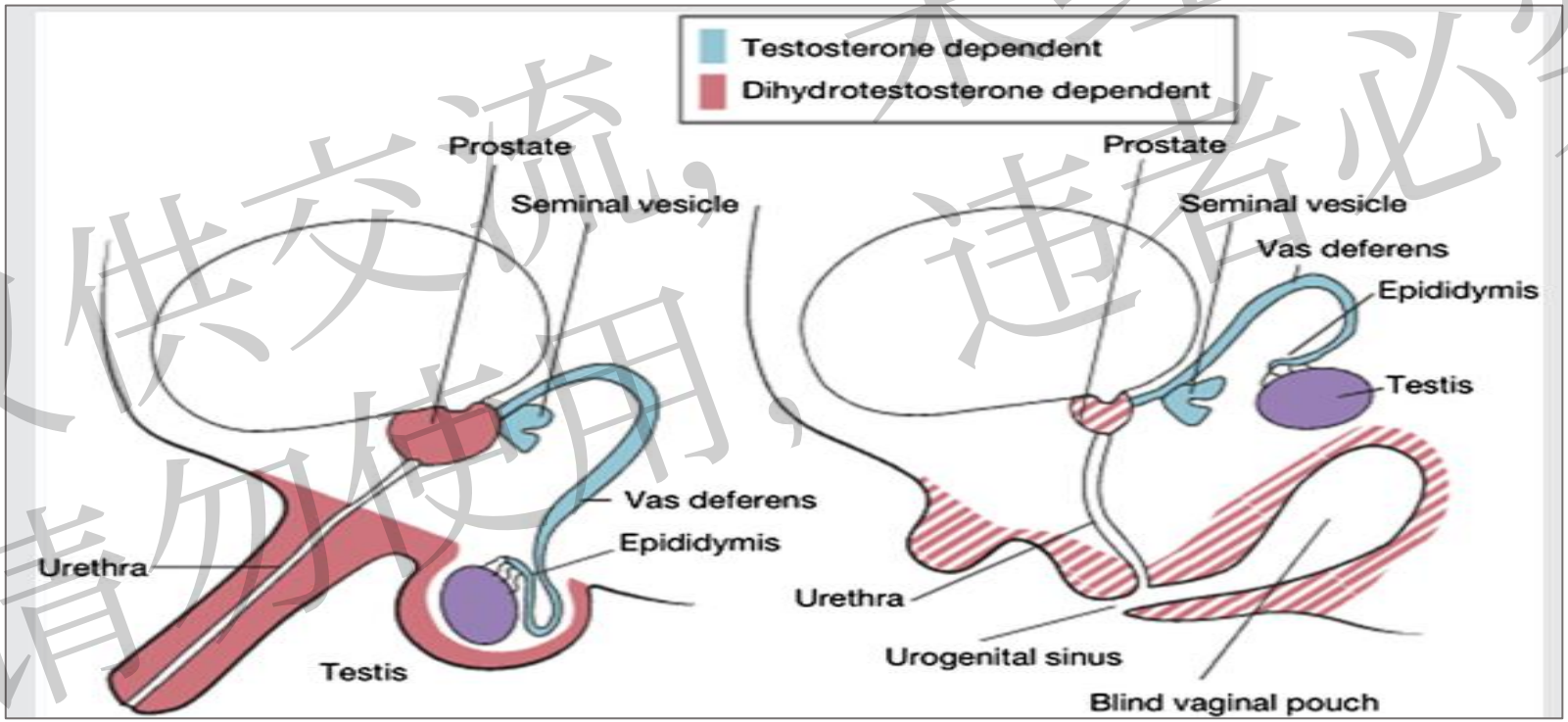
病因及病理机理

- 病因——5α还原酶缺陷
- 病理机理



病理机理

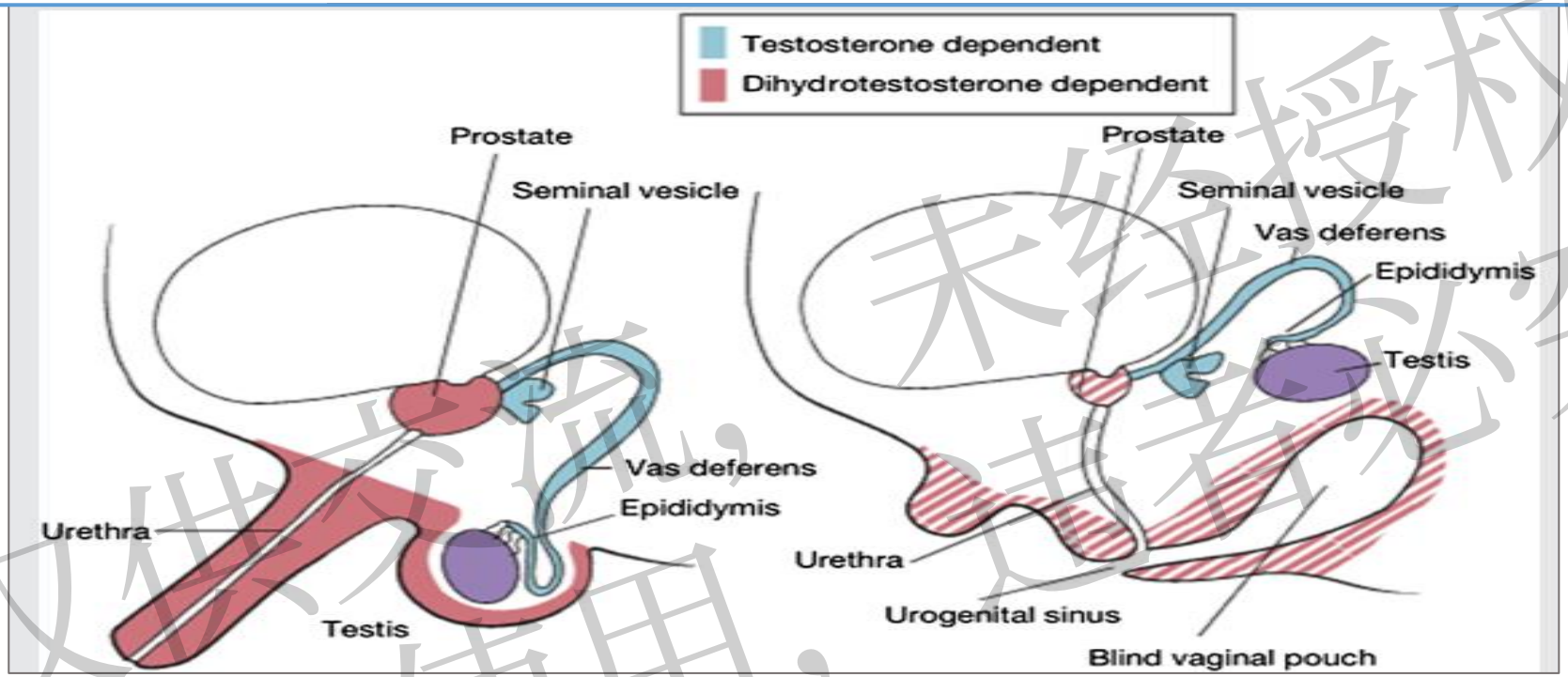


Fig. 3. Illustration of the hypothesis for the role of testosterone and dihydrotestosterone in male sexual differentiation in uitero　睾酮直接作用于胚胎的吴氏管，分化输精管vas deferens, 附睾，储精囊; 而在尿生殖窦和尿生殖结节,睾酮只是前激素，转化为DHT才致外生殖器和前列腺分化

5α -还原酶缺乏症发病机制

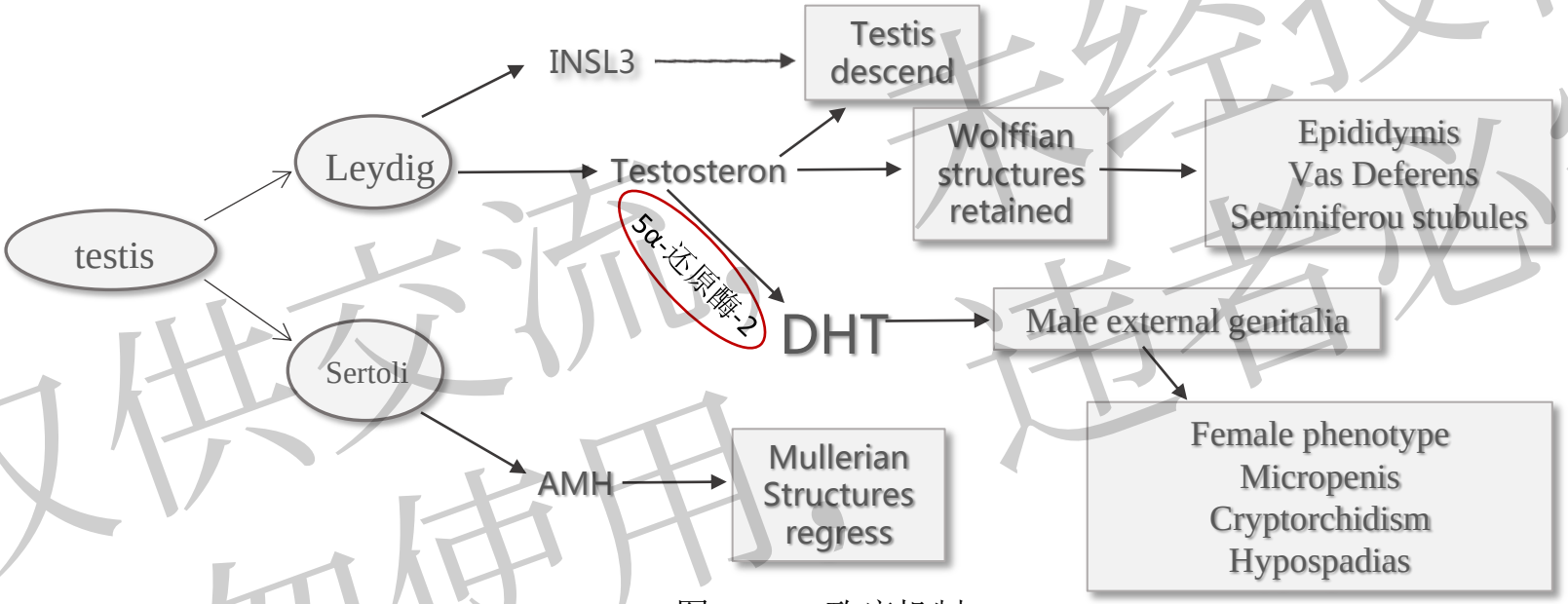


图1 5α-RD致病机制

5α -还原酶缺乏症于1974年在多米尼加共和国被发现，24个病人来自13个不同家系，患者血清睾酮升高，而DHT降低，故考虑5α 还原酶缺陷所致，主要指 II 型5α 还原酶。

临床表现

- 外生殖器畸形
  - 完全女性外观
  - 性别模糊
  - 偏向男性
  - 尿道下裂
  - 孤立小阴茎
  - 正常男性不孕症

基因研究

- 目前报道的SRD5A2基因突变有102种，其中导致5αRD的有77种，可能导致5αRD的有8种。突变类型分为错义突变、无义突变、小片段的缺失或插入、剪接突变等，其中大部分为错义或无义突变，所有的外显子均有突变报道（HGMD 人类基因突变数据库，www.hgmd.cf.ac.uk）。

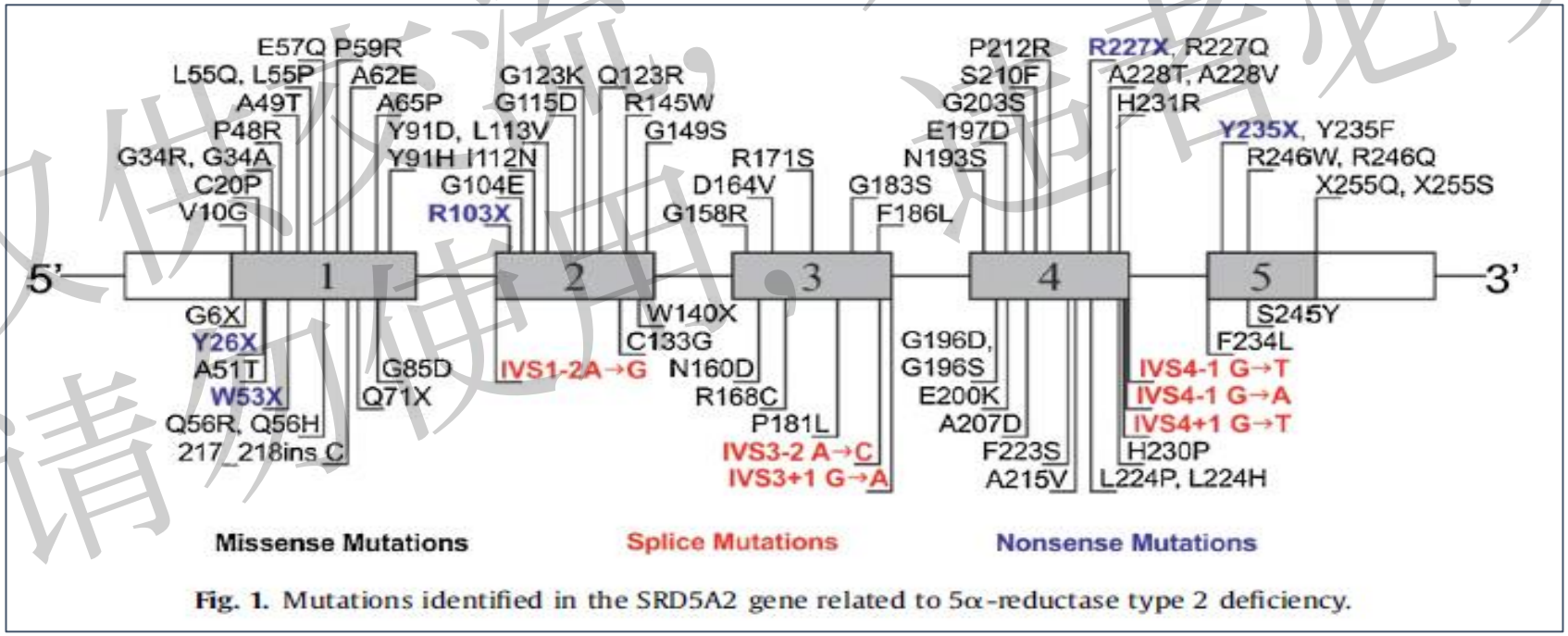


Fig. 1. Mutations identified in the SRD5A2 gene related to 5α-reductase type 2 deficiency.

Mendonca BB et al. J Steroid Biochem Mol Biol,2016,163:206-211.

●突变热点

SRD5A2基因的突变多集中在1 号外显子和4 号外显子上，外显子3相对保守。

●奠基者效应

墨西哥人和埃及人的p.P212R和p.G34R突变；

亚洲人中p.Q6*和 p.R227Q突变；

地中海人的p.R171S ；

巴西及葡萄牙人中 p.Q126R 突变；

p.R246W多米尼加共和国及巴西白人中常见

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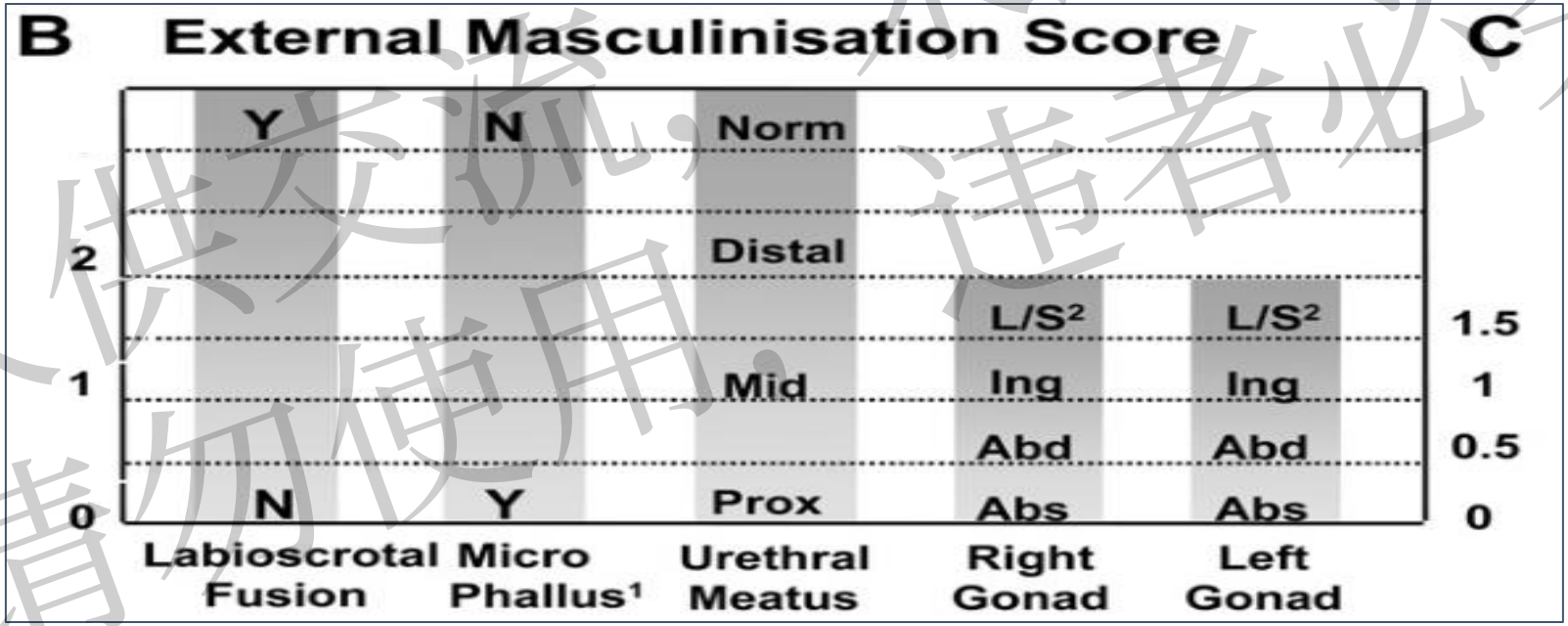
表型-基因型

- 5-α-Reductase type 2 deficiency (OMIM 264600) is infrequent。
- 大多研究显示：突变与表型的关系尚未发现，虽然蛋白的改变会影响表型的严重性。但是相同的突变表型变异大，说明有其他异常因素影响
- 由于临床的差异大，精确诊断和恰当治疗都非常困难
- 过去20年关于SRD5A2 deficiency,认为没有基因表型的关联

表型-基因型

- 自1992至今，方法学评价使用的是EMS, first proposed by Ahmed et al。他构建了很好的有效的临床方法。分值基本在 0 to 12分。完全男性化得分为12分，分值越低男性化程度越低。EMS评分表如下图。



Andrea Avendaño et.al. Hormones (2018) 17:197–204
Ahmed SF et.al.Best Pract Res Clin Endocrinol Metab,2010,24(2):197-218

表型-基因型

Hormones (2018) 17:197–204
https://doi.org/10.1007/s42000-018-0013-9

REVIEW ARTICLE

5-α-Reductase type 2 deficiency: is there a genotype-phenotype correlation? A review

Andrea Avendaño[1] · Irene Paradisi[2] · Francisco Cammarata-Scalisi[1] · Michele Callea[3]

Received: 19 October 2017 / Accepted: 5 February 2018 / Published online: 20 April 2018

表型-基因型

研究方法

■**入组256 例（表型分类）**

- 阴蒂肥大/小阴茎66.1% (169/256);
- 不同程度的尿道下裂 39.84% (102/256)
- 单或双侧隐睾19.92% (51/256)
- 主要为男或为女分别7.03% (18/256)和 3.9% (10/256).

■ **分组（按照SRD5A2基因突变对5αR2的影响将突变分为三组）**

- 影响酶与辅因子NADPH的结合
- 影响酶与T的结合
- 影响酶的活性

■ **方法：**将**5αRD**患者的外生殖器按照external masculinization score (EMS评分)评分，计算同种基因型EMS分值的均数与标准差，并进行比较。

六

- 约60% (150/250)纯合，40% (100/250)复合杂合;比例略低于Maimoun 的报道（即55例患者69.1% 纯合，29.9% 复合杂合，含 V89 L 多态性位点）
- Exons 1 and 4是热点。 SRD5A2基因异常突变导致NADPH，T的Km值升高，（使酶与NADPH，T的亲和力下降）或影响酶活性从而导致T转化为DHT受损。
  - 最多研究的SRD5A2基因多态性V89L, 机会性产生的，Exon 1上G>C 导致V 89L
    - 离体研究显示V89L 约降低酶活性30% .V89L与中国和印度人尿道下裂高危性相关
  - 次之为 A49T; 离体研究显示他产生强的酶活性已经被认为是前列腺癌症高风险, 主要是非裔美国人和拉丁裔的美国人。相反，中度相关的是较轻微的尿道下裂

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基因表型的关联-入组纯合变异分析

Genotype	Number of reported patients	EMS average	Standard deviation	References
p.G34R/p.G34R	12	3.33	2.06	[37, 38]
p.H231R/p.H231R	4	2.00	1.15	[25, 39, 40]
p.G115D/p.G115D	5	2.60	0.55	[22, 39, 41, 42]

表型重

Table 2 External masculinization scores (EMS) for mutations affecting NADPH *Km*

Genotype	Number of reported patients	EMS average	Standard deviation	References
p.P181L/p.181L	2	4.0	2.83	[43]
p.G183S/p.G183S	6	4.17	2.48	[44]
p.G196S/p.G196S	12	3.30	0.95	[38, 42, 44–48]
p.Y235F/p.Y235F	5	4.00	3.46	[22, 37, 43, 45]
p.R246Q/p.R246Q	14	3.68	1.67	[22, 25, 40, 43, 49–53]
p.R246W/p.R246W	6	2.67	1.21	[5, 22, 44, 53]

表型变异小

Table 3 External masculinization scores (EMS) for mutations affecting enzymatic activity

Genotype	Number of reported patients	EMS average	Standard deviation	References
p.L55Q/p.L55Q	8	3.00	3.00	[22, 47, 54]
p.Q126R/p.Q126R	12	4.17	1.47	[22, 40, 47, 55, 56]
p.Y91H/p.Y91H	8	6.12	2.53	[22, 38, 57, 58]
p.N160D/p.N160D	4	4.75	2.98	[8, 37, 39]
p.R227Q/p.R227Q	24	8.00	1.79	[22, 50, 59–61]
IVS1-2A>G/IVS1-2A>G *	4	4.00	1.83	[62, 63]

表型轻微

*Mutation affecting splicing site

R171S多人种(Mexican, Turkish, Spanish, Mediterranean), 少纯合

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诊断

- 有曾误诊为PAIS，最终证实实为SRD5A2基因突变。诊断对处理是非常必须的 。
- 生化诊断是第一步的。HCG后的 血清T / DHT，正常或高

  但是T/DHT 的恰当cutoff value仍有争议。最初定位 20, 又有8.5的建议。
- 近来有建议用 urinary steroid profiling (UPS)和基因。
- 基因小，是的临床应用可行

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诊断研究

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治疗研究

国家儿童医学中心 National Center for Children's Health, China 北京儿童医院 BEIJING CHILDREN'S HOSPITAL

念

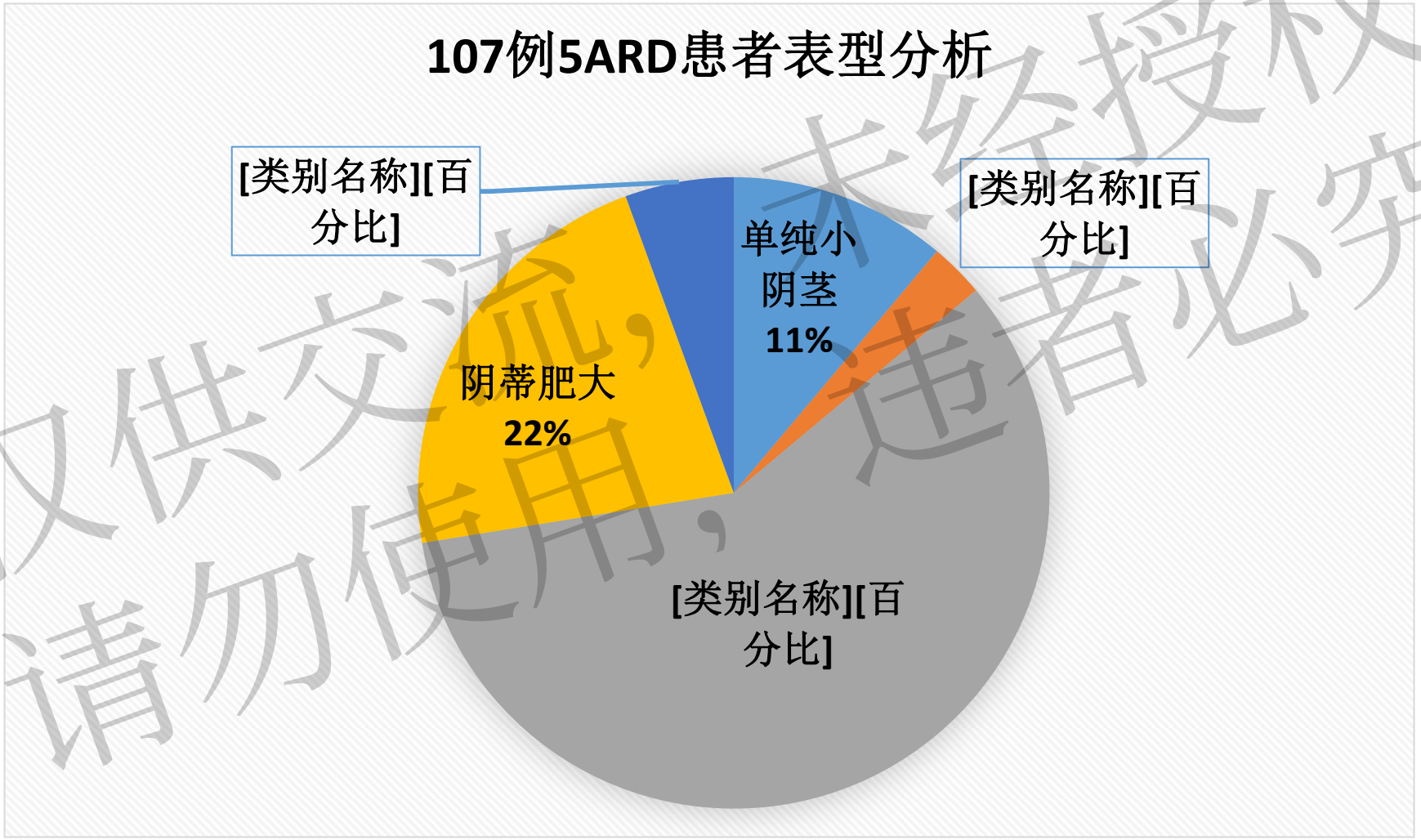
- 理念差别客观存在
  - 医师、患者、家族、各种团体
- 性别选择：
  - 有报道
    - 女性养育者，长大后60%变性，因此要求心理评价需要在27m之前进行，完成后再治疗。
  - 我们的研究
    - 3岁后就诊？
    - 评估以后肯定不变行吗？
    - 我们认为：随时心理评估，不保证不变性

- 替代治疗
  - 男性：青春期后有睾丸功能，不是必须。可改善阴毛和阴茎长度。6月可达到最佳
    - T　　200~500mg im twice a week
    - DHT gel　　5-10mg/day
  - 女性：雌激素替代。综合考虑身高和时机剂量。结合雌激素
    - 低剂量 0.07~0.3mg
    - 正常量：0.625~1.25mg/d
- 手术治疗
  - 并发症：尿瘘，

我们的5α -还原酶缺乏症（5α RD）研究

- 5α RD 诊断研究
- 5α RD 药物治疗
- 生长发育规律研究
- 基因与表型的研究
- 远期随访生活质量研究

我院5ARD患儿表型占比分析



治疗药物研究

1.2 国内外研究现状

- **术前是否激素治疗：**90%以上学者认为尿道下裂术前应用激素治疗有效提高阴茎长度，可减少术后并发症
- **药物种类及给药途径：**口服十一酸睾酮、肌注睾酮、外涂双氢睾酮凝胶
- **用药时机和疗效：**DHT凝胶青春期前给予药效尚可，青春期疗效有待进一步研究。

1.1 研究背景

表1 46，XY DSD雄性激素替代治疗现状

药物种类及方式	剂量及特点
口服	
十一酸睾酮	经肠道淋巴管吸收，不经肝脏
甲二氢睾酮	价格昂贵，药效弱；2~3次/天 口服
氟甲基睾酮/甲基睾酮/达那唑	肝酶升高、紫癜、胆固醇升高
肌注	
睾酮甾醇复合物	100~250mg/次，2~4周1次
庚酸睾酮	100~250mg/次，2~4周1次或50mg/次，每月1次
经皮外用	
睾酮或双氢睾酮凝胶	25~50mg/天
阴囊透皮贴剂	
皮下埋植制剂	缓慢释放睾酮，一般持续4~6个月

2.1 既往研究

既往研究

01 20世纪80年代，青春期前无需药物治疗，待青春期予DHT外涂后行手术治疗

02 部分学者认为性别的再选择需要在27月龄之前完成，利于心理发育

03 2006年芝加哥DSD诊疗会议性腺专家提出一旦确诊尽早治疗

04 5α -还原酶-2型表达的时间性、空间性，部分DHT外涂无效

05 睾酮替代治疗可促进前列腺生长发育，口服相比肌注睾酮阴毛增长情况较少，安全性较高

06 部分轻型5α -RD睾酮替代治疗获得自然生育能力

2.2 我们的研究

- 我们的**前期研究基础**

中国循证儿科杂志 2012 年 5 月第 7 卷第 3 期

·论著·

DOI:10.3969/j.issn.1673-5501.2012.03.002

短期口服小剂量十一酸睾酮治疗青春期前 46，XY 男童阴茎短小自身前后对照研究

陈佳佳　巩纯秀　曹冰燕　吴　迪　李豫川

- **目的：** 5α -还原酶缺乏症口服十一酸睾酮疗效评估

  探讨5α -RD患者最佳用药时机

  研究5α -RD患者应用十一酸睾酮治疗的安全性

3.1研究对象

2009.3~2018.4月北京儿童医院内分泌与遗传代谢中心确诊最终共52例

入组标准

- 5α -还原酶缺乏症患者
- 决定按男性抚养且尚未行尿道下裂手术者
- 术前应用十一酸睾酮口服患者
- 用药前肝肾功能等异常

排除标准

- 非5α -还原酶缺乏症患者
- 女性养育
- 不按照规则服药的
- 肝肾功等异常
- 其他研究者认为不宜

3.1 研究对象--入组流程图

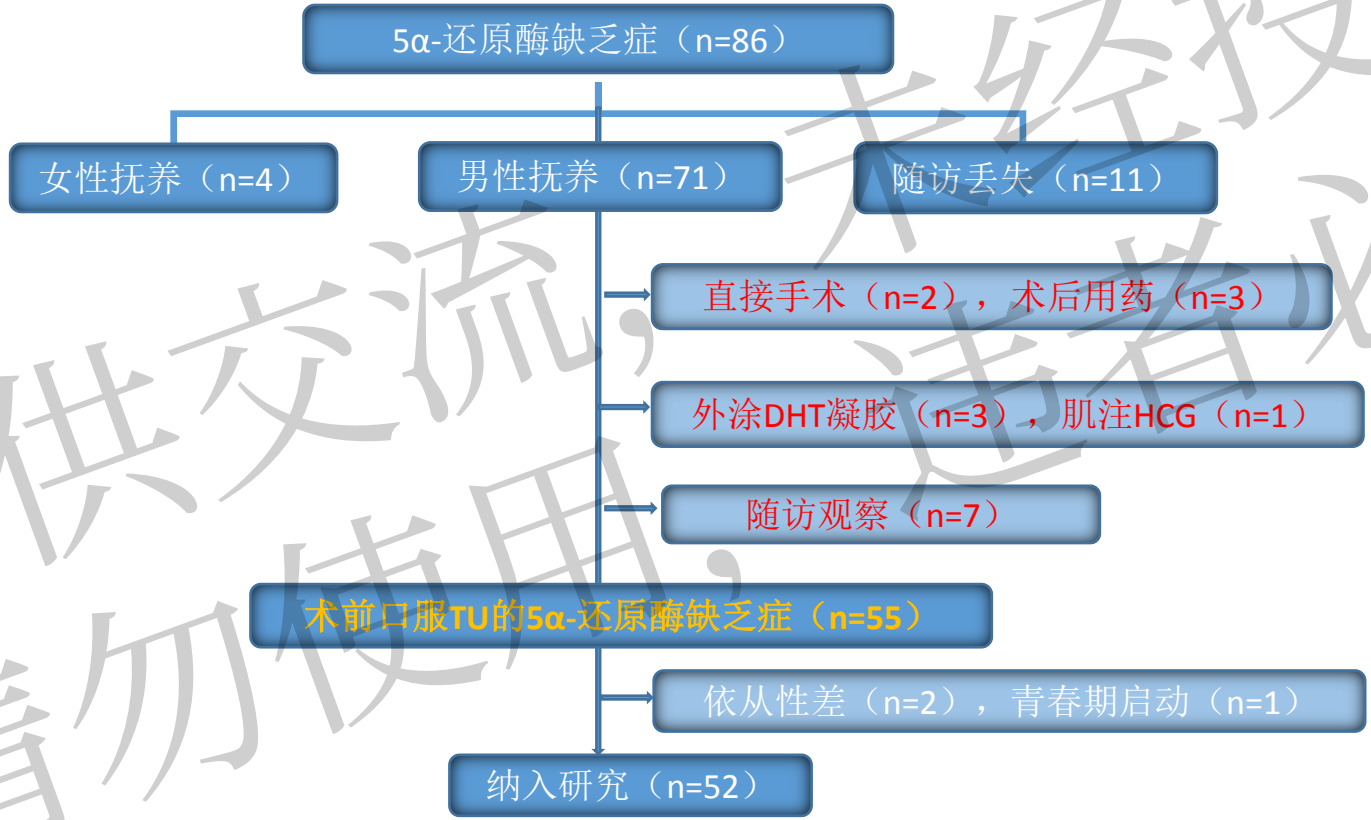


图3 入组流程图

3.2 研究方法

药物剂量	口服十一酸睾酮胶囊，（2~3mg.kg.d，最大120mg）
药物疗程	3个月为一疗程，最长3个疗程
监测指标	阴茎长度、H、W、BA、CBC、肝、肾功等
随访	门诊复诊、电话及问卷调查

3.3 研究方法

- SPSS Statistics-17.0软件和SAS/JMPSW-11软件进行统计分析
- 用 Kolmogorov-Smirnov检验样本正态性，以 $\bar{x} \pm s$表示，非正态分布数据应用百分位法$P_{50}(P_{25}, P_{75})$表示
- 治疗前后自身对照比较，数据符合正态分布者应用配对*t*检验，非正态性数据应用Wilcoxon秩和检验

3.3 研究方法

- 应用JMP软件将第一疗程和达标时的ΔPL、ΔPL%及其对数转换后的数据分别与年龄连续变量进行拟合曲线分析

- 应用SPSS软件one-way ANOVA方法或Kruskal-Wallis方法分析用药效果（包括ΔPL、ΔPL%）和疗程数目与年龄段的关系

4.1 研究结果-- 5α -RD一般情况

86例，就诊年龄：0.25~17岁

Medium 1.875（1.00，3.73）y，

Average （3.32±3.75）

入组52例。就诊年龄：0.25~12岁（2.45±2.21）岁。>5岁共7例，≤5岁者共47例

52例临床表现：Prader3级及4级最多，共占71%。

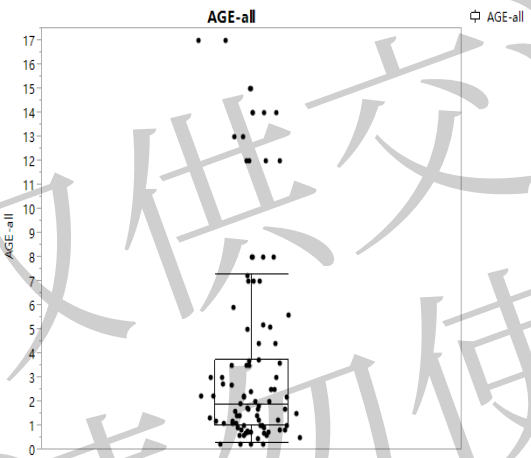


图4 86例5α-RD患者年龄分布图

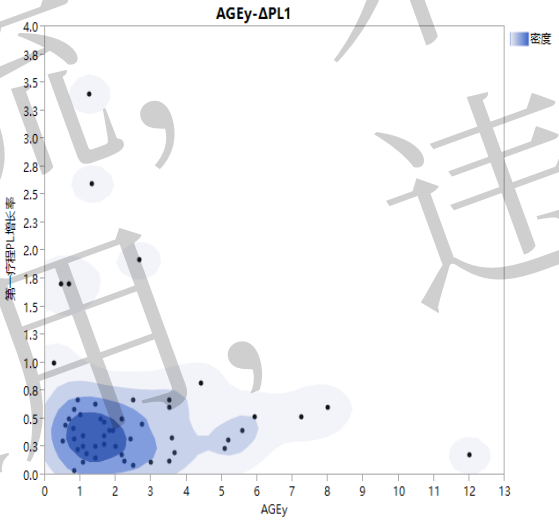


图5 入组52例5α-RD患者不同年龄治疗后阴茎的增长程度（密度图）

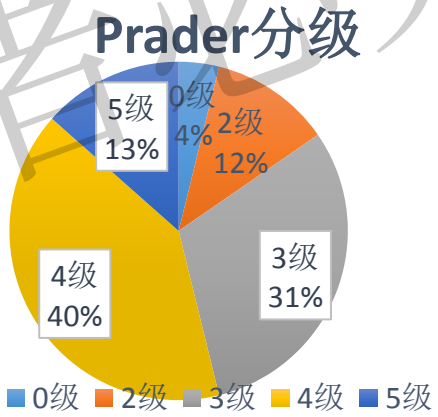


图6 52例5α-RD患者临床表型Prader分级比例

4.2 研究结果—药物疗程

52例患者中，48例口服十一酸睾酮达手术或停药标准，4例随访结束时仍在治疗中。

表2 48例达标患者不同疗程的达标率比较

疗程	First	Second	Third
5α-RD	23	21	4
有效率	47.92%	43.75%	8.33%
合计	47.92%	91.67%	100%

两个疗程有效率91.67%，三个疗程有效率100%。

表3 不同疗程后的阴茎增长比较

	1st course	2nd course	P
ΔPL/cm	0.83±0.47	0.60±0.35	0.038#
PL growth rate/%	0.40 (0.23,0.60)	0.20 (0.148,0.292)	0.002※
PL-Final/cm; SDS	(3.09±0.53) ; (-1.51±1.26)		

两独立样本t检验；※ wilcoxon 秩和检验

第1疗程ΔPL增长长度及增长率均优于第2疗程

第2疗程结束时所达阴茎长度最佳

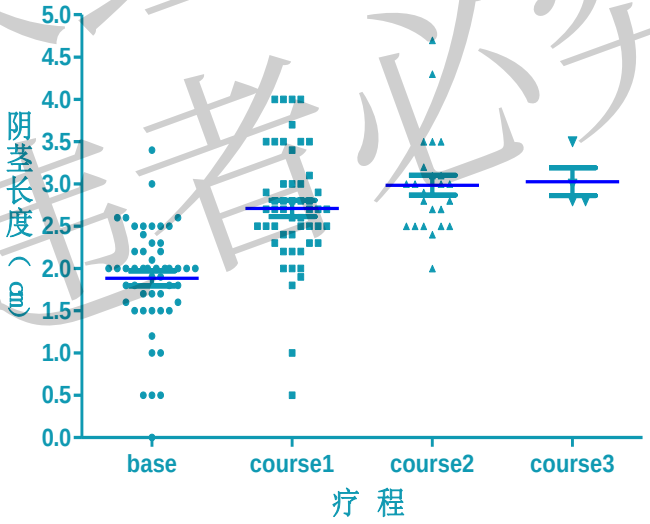


图6 52例5αRD患者各疗程所达阴茎长度比较

4.3 研究结果--药物疗效

表4 第一疗程的人体测量指标、观察指标的变化 及 第1、2疗程比较 配对t检验

	n	base	1st course	t	p	n	1st course	2nd course	t	p
Age/y	52	2.45±2.21				25	1.58±0.93			
Height（cm）	52	88.11±16.67	92.23±16.64	-11.57	0.00	25	87.21±10.62	92.43±10.46	-8.791	0.00
Height-SDS	52	-0.18±1.08	0.31±1.17	-5.862	0.00	25	0.50±0.98	1.17±1.27	-3.908	0.001
Weight（kg）	52	13.50±5.59	15.48±5.91	-13.067	0.00	25	13.80±3.51	15.20±3.35	-6.726	0.00
Weight-SDS	52	0.17±1.34	0.77±1.43	-3.863	0.00	25	1.09±1.06	1.47±1.06	-2.25	0.034
BMI	52	16.95±1.76	17.81±1.70	-4.588	0.00	25	17.93±1.47	17.71±1.81	0.824	0.418
PL（cm）	52	1.89±0.64	2.72±0.69	-12.584	0.00	25	2.38±0.59	2.98±0.59	-8.514	0.00
PL-SDS	52	-4.67±1.37	-2.48±1.39	-12.261	0.00	25	-3.03±1.25	-1.51±1.45	-8.767	0.00
ΔPL（cm）	52	0.83±0.47				25	0.60±0.35			
Pl growth R%	52	0.40(0.23,0.60)				25	0.20(0.148,0.292)			
PW/cm	48	0.88±0.24	1.26±0.28	-11.657	0.00	25	1.18±0.29	.50±0.4	-4.396	0.00

4.4 研究结果—用药时机

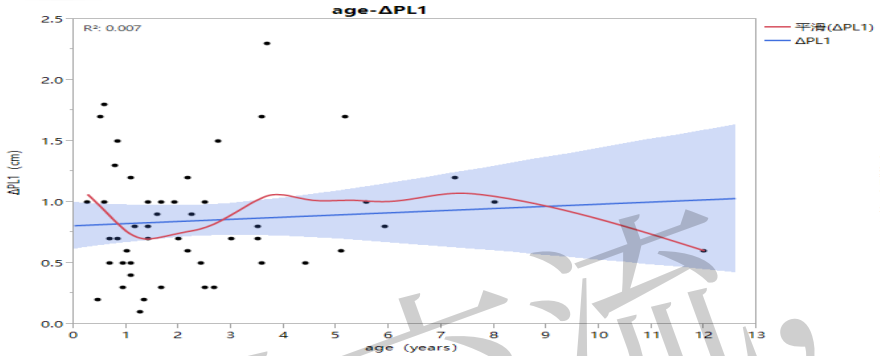


图7a 开始药物治疗的年龄与第1疗程阴茎增长的关系

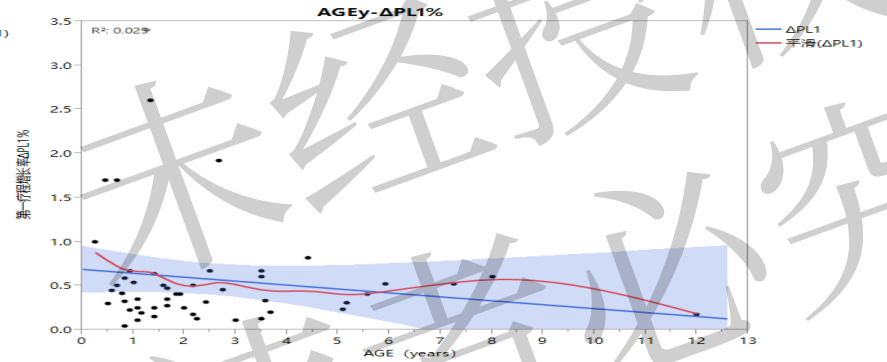


图7b 开始药物治疗的年龄与第1疗程阴茎增长率的关系

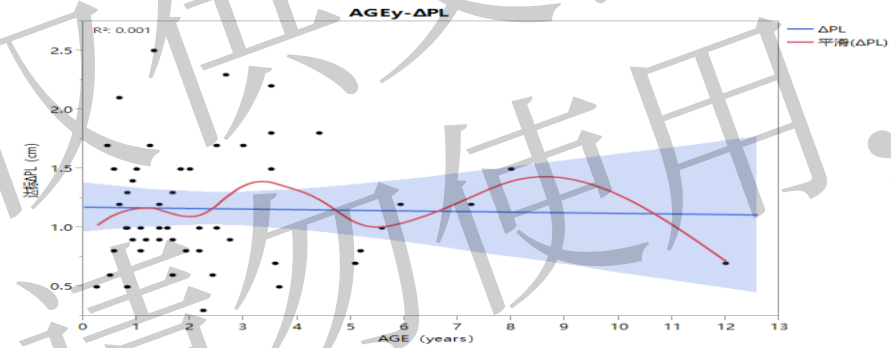


图8a 开始药物治疗的年龄与最终阴茎增长的关系

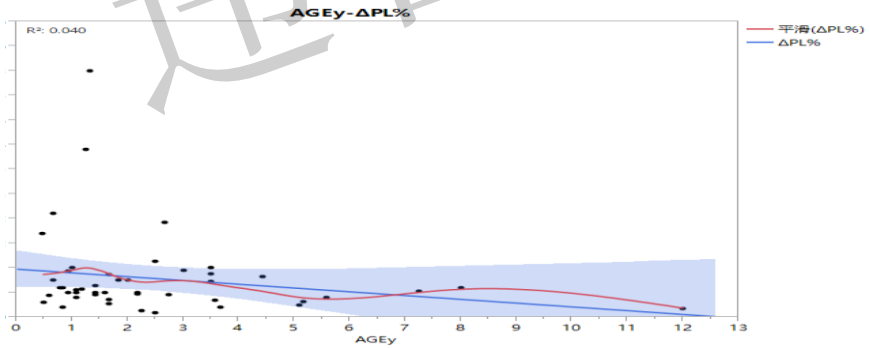


图8b开始药物治疗的年龄与最终阴茎增长率的关系

4.4 研究结果--用药时机

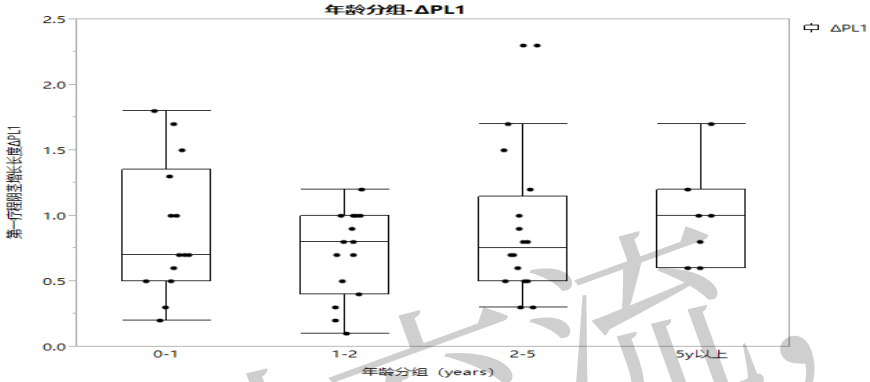


图10a 药物治疗的年龄段与第一疗程阴茎增长的关系

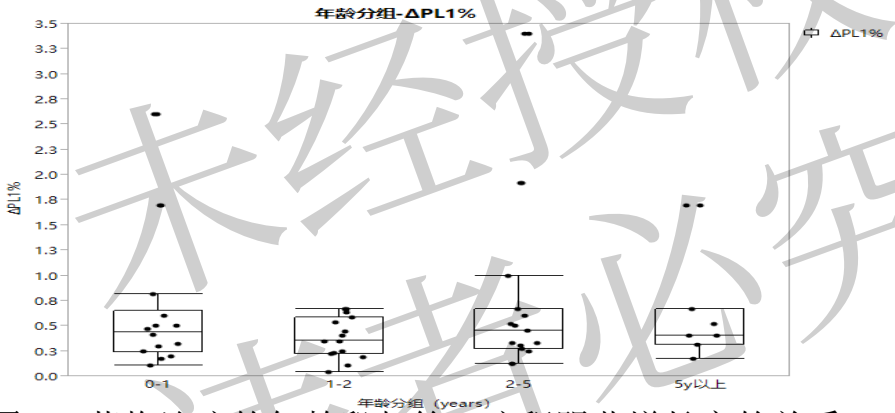


图10b 药物治疗的年龄段与第一疗程阴茎增长率的关系

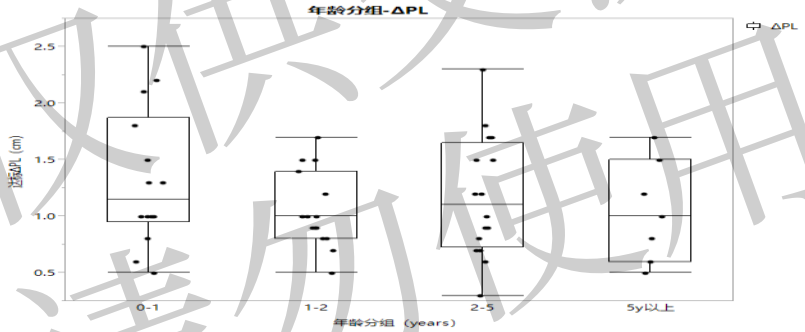


图11a 药物治疗的年龄段与最终阴茎增长的关系

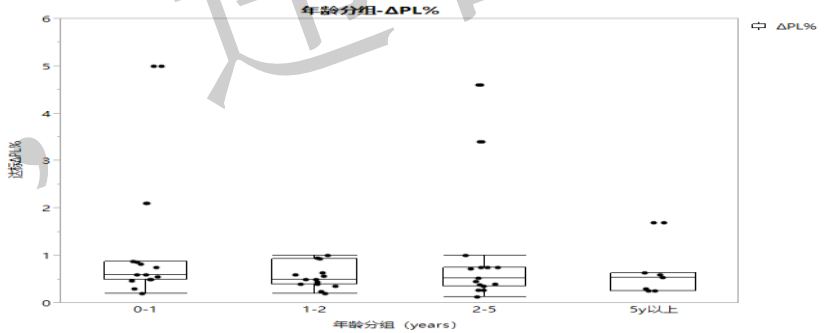


图11b 药物治疗的年龄段与最终阴茎增长率的关系

4.5 研究结果--药物安全性

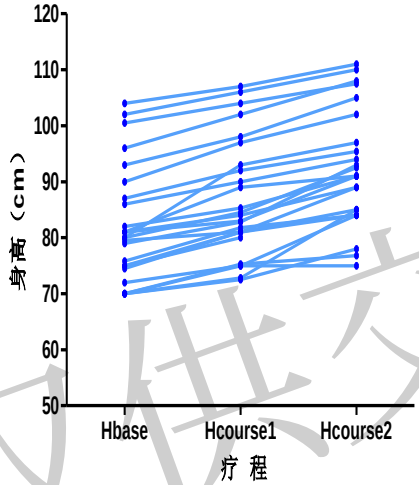


图13a 52例5α -还原酶缺乏症患者的身高随疗程的变化

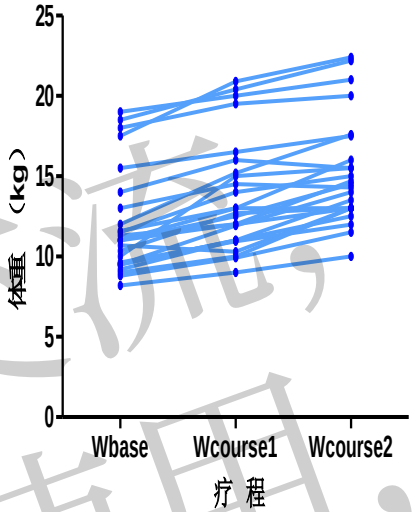


图13b 52例5α -还原酶缺乏症患者的体重随疗程的变化

BA/CA base	0.88±0.27	P=0.498
BA/CA course1	0.93±0.25	
BA/CA course1	0.93±0.25	P=0.909
BA/CA course2	0.92±0.23	

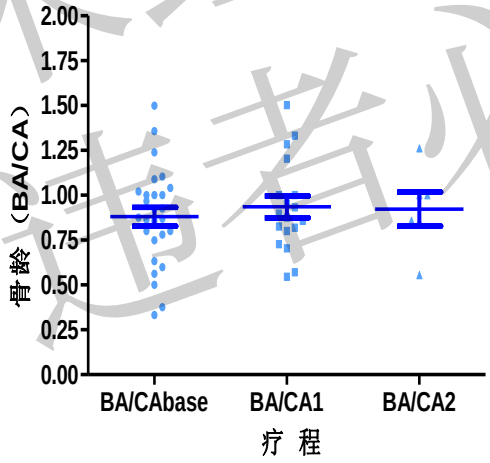


图12 52例5α -还原酶缺乏症患者骨龄与疗程关系

骨龄不随治疗疗程延长而显著增加

4.5 研究结果--药物安全性

表7 52例5α-还原酶缺乏症患者的激素水平与疗程关系

秩和检验

	n	Base	1st course	Z	P
LH mIU.ml	42	0.13(0.10,0.22)	0.10 (0.12,0.14)	-3.084	0.002
FSH mIU.ml	42	0.78(0.56,1.13)	0.43 (0.31,0.91)	-2.178	0.029
T ng.dl	42	20.00(20.00,20.00)	20.00 (20.00,31.90)	-3.010	0.003

n	1st course	2nd course	Z	P
15	0.12 (0.10,0.16)	0.10 (0.10,0.13)	-2.025	0.043
15	0.35 (0.22,1.03)	0.53 (0.30,0.73)	-0.804	0.421
15	20.00 (20.00,23.30)	20.00 (20.00，49.40)	-0.770	0.441

- 定期监测肝肾功能、血常规、胰岛素样生长因子、皮质醇激素以及心电图等检查均无明显异常
- 1例患儿曾诉阴茎勃起痛，减量后好转

4.6 研究结果--随访

- 随访最长年限达8年，平均随访（2.85±2.02）年

- 终身高：2例随访至18周岁
  - 一例预期靶身高为-0.37SD，实际终身高为-0.95SD；
  - 另一例预期靶身高为-0.62SD，实际终身高为-0.55SD

4.7 个例分析

例1

年龄12岁，青春期

社会性别女性

术前，一个疗程

PL由3.4cm增至4.0cm

VS

例2

年龄14岁，青春期

社会性别女性

术后，两个疗程

PL=4cm

有人认为可能与术者操作及手术方式相关，损伤阴茎海绵体，导致激素结合受体减少，从而影响药效。

4.7 个例分析

例2		例3
年龄14岁，青春期		年龄4.17岁，青春期前
社会性别女性	VS	社会性别男性
术后，两个疗程		术后，一个疗程
PL=4.0cm		PL由3.0cm增至4.0cm

青春期启动后睾酮分泌高峰，雄性激素受体结合高饱和，先前占据大部分受体结合位点，即使外界后期干预给予大量睾酮仍无效果。

4.8 结论

结论一

5α -RD患者就诊年龄不同，大多数临床表现为小阴茎合并不同程度尿道下裂

结论二

5α -RD青春期前口服十一酸睾酮半年有效率达91.67%，第一疗程疗效优于第二疗程，半年内达到最佳长度。

结论三

5α -RD患者青春期前药物疗效与年龄及年龄组无关；青春期用药疗效不一。

结论四

52例患者随访年限最长达8年，安全性可靠，家长满意度高

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 30 October 2018
doi: 10.3389/fphar.2018.01224

Phenotype and Molecular Characterizations of 30 Children From China With *NR5A1* Mutations

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Background: Patients harboring *NR5A1* mutations have a wide spectrum of phenotypes.

Objective: To investigate the phenotype of patients with *NR5A1* gene mutations from a 30 Chinese patient cohort.

Methods: We reported the clinical features of children with *NR5A1* gene mutations and compared them between two groups of patients with social genders of male (boys group) and female (girls group).

Results: Thirty patients with *NR5A1* mutations ranging from 2 months to 17 years of age were studied. There were 11 boys and 19 girls who were identified when they visited the hospital. The patients were verified as having testes without a uterus and ovaries by B-mode ultrasound. There was no difference between boys and girls in terms of the Prader stage ($p = 0.086$), but the position of the testes was higher in girls than in boys ($p = 0.013$). The patients' average height is −0.43 SDS according to the normal boys' height with SDS (while their average target height was 0.07 SDS). However, there was no such difference between boys and girls ($p > 0.05$). Although the basal LH and post-hCG testosterone (T) levels were not different ($p > 0.05$), but the basal FSH level, LH/FSH ratio, and INHB level were decreased in girls ($p = 0.002$; $p = 0.001$; $p = 0.006$). All of the mothers of the patients reported to have normal pregnancies. We found 24 patients (80%) with *de novo* mutations in the *NR5A1* gene; 5 patients had inherited mutations from their mothers, and one inherited from the father. Only the mothers of patients 16 and 18 showed premature ovarian failure at the time of reporting. Among 26 disease associated mutations, 14 novel mutations that have been reported the first time and p.R87C is the most common Among the other 12 had had been reported,the p.R313C is the most common.

Conclusion: Patients with 46, XY *NR5A1* mutations presented a wide spectrum of external genitalia characteristics and severe Sertoli cell impairment. The p.R87C and p.R313C mutations appeared to be common (10%) in this group, and 14 new mutations were identified, improving our understanding the genotype phenotype correlations.

New insights into 5α-reductase type 2 deficiency based on a multi-center study: population distribution and genotype-phenotype profiling of *SRD5A2* in 190 Chinese patients

- **Background** The 5α-reductase type 2 (5α-RD2) deficiency caused by the steroid 5α-reductase 2 (*SRD5A2*) gene mutations can generate variable degrees of undervirilization in patients with 46,XY disorders of sex development. **This study aims** to profile phenotypic and genotypic characteristics in a large Chinese 5α-RD2 deficiency cohort through multi-center analysis.
- **Methods：** 190 patients diagnosed with 5α-RD2 deficiency were consecutively enrolled from 8 medical centers in China. Their clinical manifestations and molecular genetic results were analyzed

Fig. 1 Distribution of the enrolled patients with 5α-Reductase-2 deficiency from multiple centers.

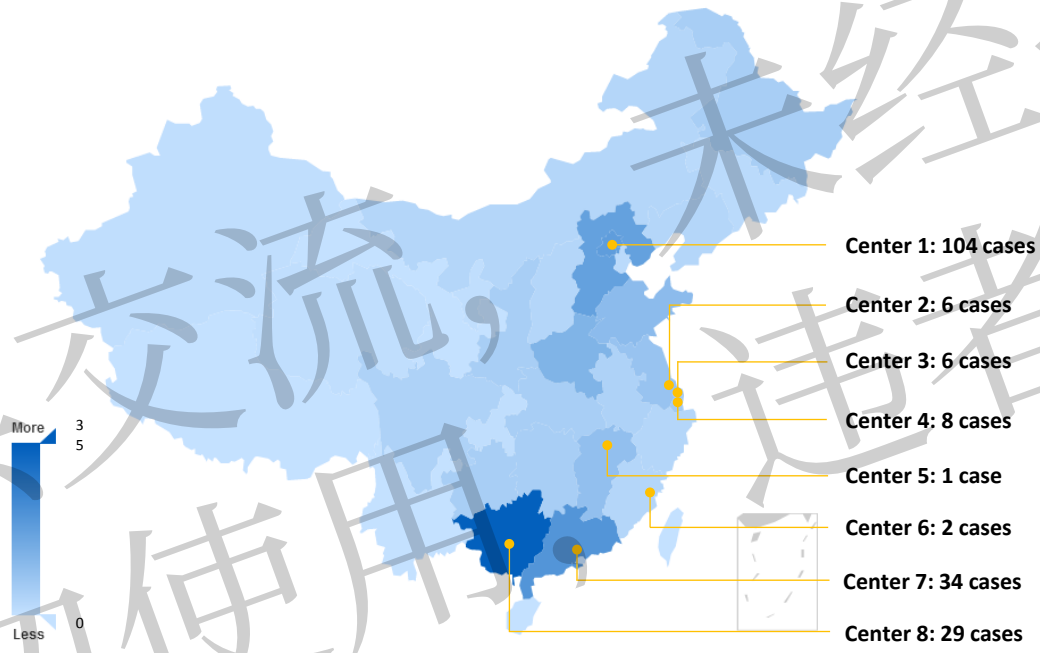


Fig. 2 Clinical manifestations in Chinese patients with 5α-Reductase-2 deficiency.

Hypospadias (isolated or combined with microphallus and/or cryptorchidism) was fairly common in the enrolled subjects (66.32%).

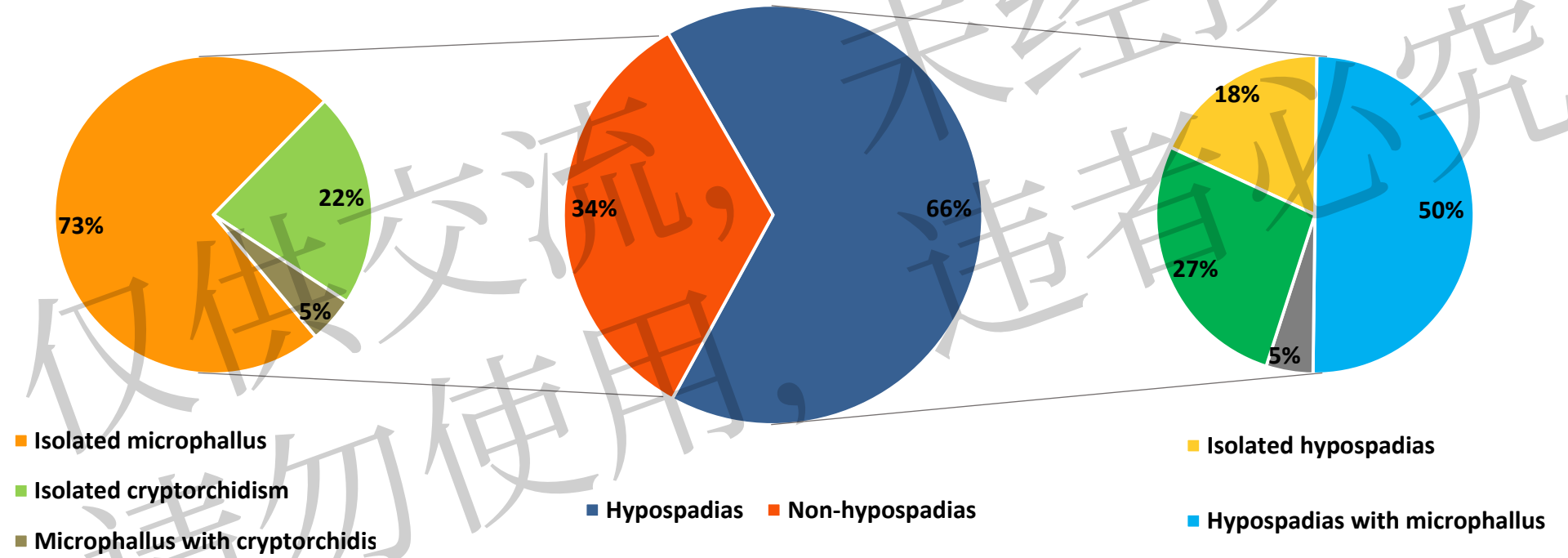
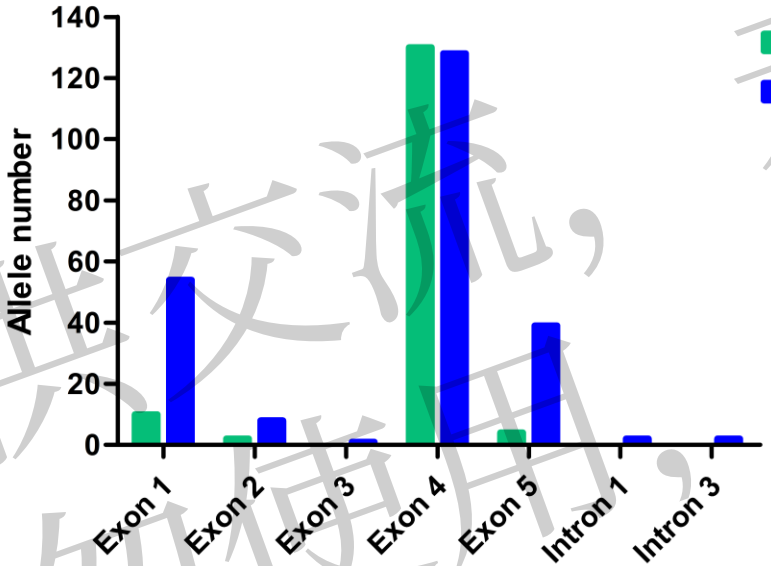


Fig. 3 Distribution of the variants throughout the *SRD5A2* gene region.



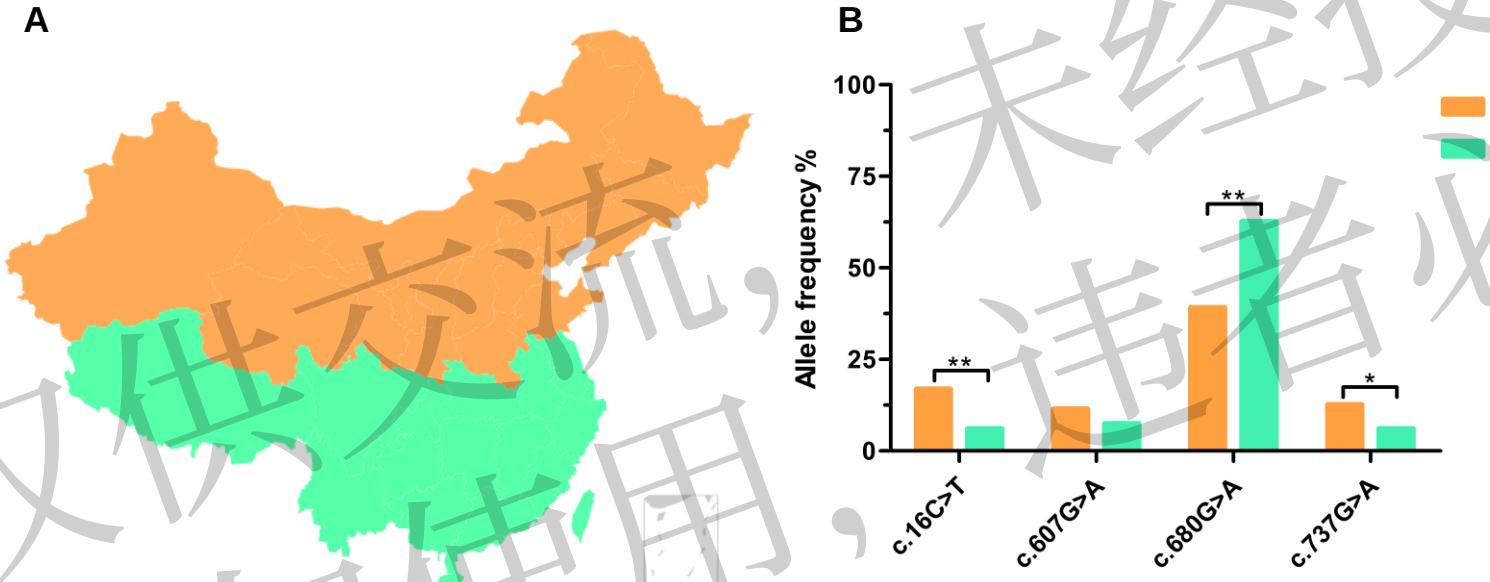
Homozygous

Compound heterozygous

Totally, 42 variants, including 13 novel variants, in *SRD5A2* were identified. Homozygous and compound heterozygous mutations presented in 38.42% and 61.58% of patients, respectively, and predominated in exons 1, 4, and 5.

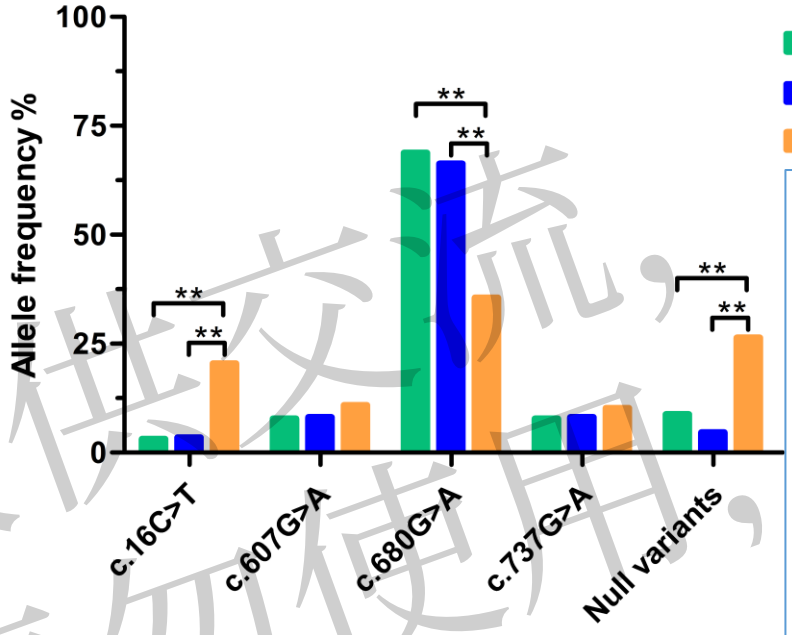
The most prevalent variant was c.680G>A (52.37%), followed by c.16C>T, (10.79%), c.607G>A, (9.21%) and c.737G>A, (8.95%).

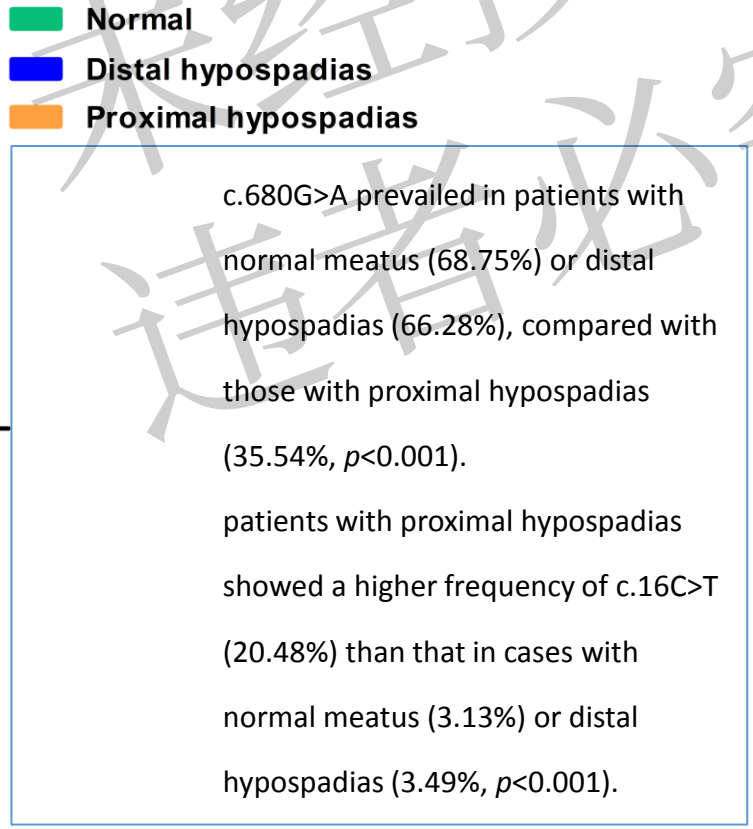
Fig. 4 Territorial distribution of the variants in Chinese population.



c.680G>A was more common in South China than that in North China (62.62% VS 39.16%, $p<0.001$), while c.16C>T was reverse (6.07% VS 16.87%, $p=0.001$).

Fig. 5 Distribution of the variants among groups with different location of urethral meatus.





c.680G>A prevailed in patients with normal meatus (68.75%) or distal hypospadias (66.28%), compared with those with proximal hypospadias (35.54%, $p<0.001$).

patients with proximal hypospadias showed a higher frequency of c.16C>T (20.48%) than that in cases with normal meatus (3.13%) or distal hypospadias (3.49%, $p<0.001$).

- **Conclusions：** The study profiled variable phenotypic and wide mutational spectrum of *SRD5A2* and revealed its distinctive population distribution in Chinese patients with 5α-RD2 deficiency, which further shaped the founder effect and genotype-phenotype correlation of *SRD5A2*.

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家系研究

Background

- Achermann .et.al [1,2] reported initially in 1999 and 2002 that heterozygous mutations of NR5A1 gene could cause adrenal insufficiency and 46,XY severe testicular dysplasia
  - In 46，XY patients
    - Ambiguous genitalia, gonadal dysgenesis without adrenal insufficiency
    - Hypergonadotropic hypogonadism, especially high FSH
    - Low AMH and INHb level
  - In 46，XX patients：POF, sex reverse (testicular DSD or ovotesticular DSD)
- So far, 120 variants of NR5A1 in HGMD database
- The relationship between genotype and phenotype has not been established yet

[2]Achermann et.al.JCEM.2002

Subjects and Methods

- Two probands of 46, XY disorders of sex development and their family members were found in our outpatient Department
- Get two 46,XY DSD probands clinical data
- Genetic detection: test all samples from the 2 families
- Clustal Omega (http:/ / www. ebi. AC. uk/ Tools/ msa/clustalo/) was used to analyze the conservation of the new mutation.

Discussion

Clinical phenotype

- Wide Spectrum of NR5A1-related phenotypes were reported in 46, XY patients
- The two probands' mothers showed premature ovarian failure（POF) or earlier menopause suggested that screening NR5A1 gene is necessary in POF patients
- However, the phenotype of these two families also suggest that some female patients may be easily missed diagnosis because of normal fertility preserved in 46, XX individuals
- We must realized that the negative family history is not reliable
- Also, the unreliable negative family history caused by deliberated by the mother for a protection from family broken.
- Sisters who carried the same should pay attention to the sign of POF because of the mother's example. We suggested them evaluated

有关5ARD生育问题相关研究

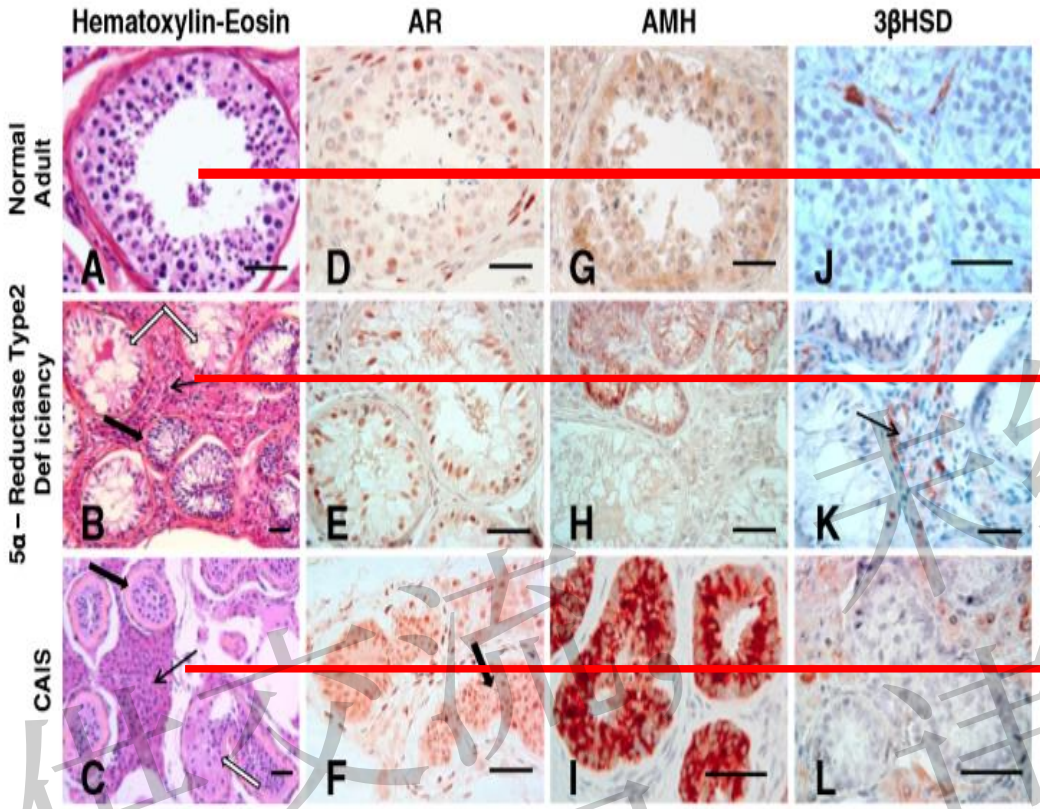
5α RD患者精子质量下降可能由SRD5A2突变直接导致或由突变导致睾丸下降不全间接引起。

- **物理障碍：**小阴茎，尿道下裂
- **前列腺发育不良：**前列腺产生前列腺液及前列腺特异性抗原，防止精液凝固。射精体积小，呈凝胶状，并且不能液化，从而阻碍了精子的运动。
- **精子发生受损？**

Testicular histological and immunohistochemical aspects in a post-pubertal patient with 5 alpha-reductase type 2 deficiency: case report and review of the literature in a perspective of evaluation of potential fertility of these patients

Lavinia Vija[1,2,3,4], Sophie Ferlicot[5], Diana Paun[3], Hélène Bry-Gauillard[6], Gabriela Berdan[7], Issam Abd-Alsamad[8], Marc Lombès[1,2,6] and Jacques Young[1,2,6*]

Lavinia 等人分别对一名青春期5αRD患者（17岁，社会性别女，原发性闭经就诊，阴蒂肥大，双侧隐睾），一名CAIS患者（18岁，社会性别女，原发性闭经就诊，双侧隐睾），一名阻塞性无精子症患者（29岁，精子发生正常）的睾丸组织进行组织学分析与免疫分析，进行比较，并回顾以往报道的5αRD患者睾丸组织学检查，以探求5αRD患者的生育情况。



正常成人睾丸的曲细精管中正常的精子发生

5αRD患者未成熟的曲细精管

AIS患者未成熟的曲细精管

Figure 1 Histological characteristics and immunohistochemical detection for AR, AMH and 3βHSD expression, in testicular paraffin-embedded sections obtained from a 29 year old human adult with normal testicular structures (Figure 1: panels A, D, G, J), a 17 year-old teenager with 5 α-R2 deficiency (Figure 1: panels B, E, H, K) and a 18 year-old CAIS teenager (Figure 1: panels C, F, I, L). Panels **A**, **B**, **C**- histology of testicular samples on haematoxylin-eosin staining. Panel **A** shows complete spermatogenesis in a seminiferous tubule section of the normal adult testis; Panel **B** shows heterogeneous seminiferous tubules (ST), in the 5 α-R2 deficiency, such as tubules presenting large diameters and lumina(white arrows) and other tubules with small diameter lacking lumina (thick black arrow); Panel **C**, shows, in a CAIS patient, used for comparison, a homogeneous pattern, with small diameter, immature STs. In this CAIS patient, STs are delineated by a thickened basal membrane (thick black arrow). In one ST, Sertoli cells with an oncocytic transformation of the cytoplasm are indicated (white arrow).The interstitial compartment contains an area of Leydig cell hyperplasia (thin black arrow). Panels **D**, **E**, **F**- show AR immune detection in testicular sections obtained from the three subjects. AR is immunodetected in Sertoli cells, Leydig cells and peritubular myoid cells. Panel **F** evidentiates positive AR immunostaning in ST of the CAIS patient's testicular sample. Panels **G**, **H**, **I**- show AMH immune detection in STs of the testicular sections obtained from the three subjects. Panels **J**, **K**, **L**- show 3βHSD immune detection in Leydig cells of the testicular sections obtained from the three subjects. Scale bars -50 μm.

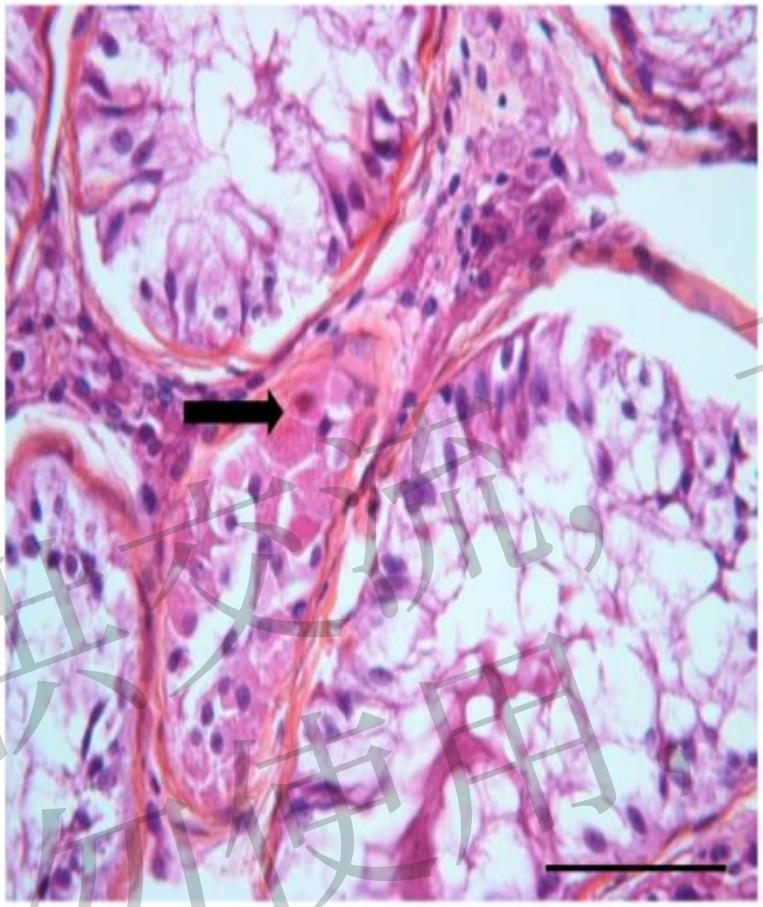


Figure 2 Testicular section magnification, on hematoxylin-eosin staining, of the 17 year-old teenager with 5 α-R2 deficiency. Seminiferous tubules with large diameter and containing only Sertoli cells, surround a flattened section of a tubule, containing Sertoli cells with oncocytic transformation of the cytoplasm (thick black arrow). Scale bar-50 μm.

1. Sertoli细胞胞浆嗜酸性改变

已在不育患者中报道

2.Leydig细胞增生

已在CAIS，Klinefelter综合征及5αRD患者中报道，可能与持续的LH分泌过多有关

Table 1 Phenotypical and histological characteristics in postpubertal patients with 5α-reductase type 2 deficiency

Patient number	Age (years)	Caryotype	Clinical presentation	TV (ml)/TW (g)*	FSH (IU/L)/(xULN)**	T (ng/ml)	T/DHT ratio***	*SRD5A2* sequencing	Histology	Reference (publication year)
1	14	46,XY	Female PA; cryptorchidism	7/NA	20.0/(2.0)	3.6	36	NA	SGA	[22] (1986)
2	16	46,XY	Female PA; PPH; clitoromegaly cryptorchidism§	NA	38.3/(5.0)	NA	NA	NA	PST (1%) SCA (14%) SGA (25%) SCO (60%)	[5] (1999)
3	16	46,XY	Female PA; PPH; 4 cm phallus cryptorchidism§	3/ 15.5	1.0/(0.5)	5.8	29	NA	SCA SGA SCO	[22] (1986)
4	16	46,XY	F emale PA; PPH; 3 cm phallus cryptorchidism	11/ 22	4.5/NA	11.4	34.5	NA	Normal	[22] (1986)
5	16	46,XY	Female PA; cryptorchidism	NA	8.7/(1.0)	9.0	225	NA	SGA	[22] (1986)
6	17	46,XY	Female PA; PPH; 3 cm phallus	3/NA	20/(1.0)	7.2	NA	NA	SCO	[24] (1980)
7	18	46,XY	Female PA; PPH; 3 cm phallus	3/NA	56/(3.1)	6.8	NA	NA	SCO	[24] (1980)
8	18	46,XY	Female PA; PPH; 1.5 cm phallus	15/NA	5.5/(1.1)	10	39	NA	Normal	[19] (1980)
9	18	46,XY	Female PA; PPH; clitoromegaly cryptorchidism§	NA	9.0/(1.3)	NA	NA	NA	PST (10%) SCO (90%)	[5] (1999)
10	18	46,XY	Female PA; PPH; clitoromegaly	NA	13.0/(2.0)	NA	NA	NA	PST (4%) SCO (96%)	[5] (1999)
11	25	46,XY	Female PA; PPH; 3 cm phallus	NA	NA	11	42	NA	Normal	[23] (1979)
12	35	46,XY	Female PA	8/NA	32.0/(3.2)	6.7	33.5	NA	Normal SCO	[22] (1986)
13	45	46,XY	NA	NA	NA	NA	NA	NA	Normal	[25] (1977)
14	65	46,XY	Male perineal hypospadias; 6 cm phallus cryptorchidism	NA	40/(4.0)	5.9	38	NA	SCO (100%)	[21] (1980)
15	NA	46,XY	NA	NA	NA	NA	NA	NA	Normal	[20] (1982)
Our case	17	46,XY	Female PA; PPH; clitoromegaly cryptorchidism	9/ 8	14.5/(2.0)	7.2	45	Gly115Asp	PST (8%) SCO (92%)	present paper

*TV /TW: mean testicular volume in mililiters/ mean testicular weight in grams; **(xULN): ratio between the measured value and the upper limit of normal for the corresponding FSH assay; ***T/DHT ratio: testosterone/dihydrotestosterone ratio; the ratio cutoff for the diagnosis of 5α-reductase type 2 deficiency was set at 10 [3].

PA: primary amenorrhoea; PPH: poseudovaginal perineoscrotal hypospadias; §For these individuals cryptochidism was not specified in the references, but it was suspected, given the female phenotype; NA: not available.

SGA: spermatogenic arrest at the level of spermatogonia; PST: prepubertal seminiferous tubules; SCA: spermatogenic arrest at the level of spermatocytes; SCO: Sertoli cell only; Normal: normal spermatogenesis.

结果：

- 该文5αRD患者的睾丸样品组织学分析示未成熟的曲细精管，部分生精小管中的支持细胞细胞质嗜酸性变，同时也观察到Leydig细胞增生。
- 5αRD青春期后患者的睾丸组织学特征具有异质性，从正常的精子发生到完全缺乏精子发生均可出现。
- 隐睾的5αRD患者显示出高比率的生精障碍（7/8，87％），组织学精子发生受损患者与精子发生正常患者相比血清DHT水平明显降低。

结论：

隐睾本身可能对精子发生有害；5α-RD2患者精子发生受损的程度与5α-R2活性损害程度有关。持久的LH分泌过多，可能导致Leydig细胞增生。

- 对于大多数5α-RD2患者来说，自发性生育不太可能，但辅助生殖技术已经显示出较好的效果。
- 目前有9例5α-RD2患者精液中检测到精子的报道，1例患者妻子通过宫腔内人工授精成功受孕，2名患者通过卵泡浆内单精子注射（Intracytoplasmic sperm injection, ICSI）体外受精生育的报道。
- 早期纠正隐睾症和尿道下裂对于防治生精小管损伤和保存精子发生及未来生育能力至关重要。

Guercio G et al. Endocr Dev, 2014,27:87-98
Katz MD et al. N Engl J Med, 1997,336(14):994-997.
Kang HJ et al. Fertil Steril, 2011,95(6):2125.

存在的问题：

- 以往报道的5αRD患者生育问题部分患者未做基因测序。
- 目前关于5αRD患者生育情况仅为案例报道，尚无大规模研究。
- 5αRD患者精子发生是否受损及机制有待进一步研究。

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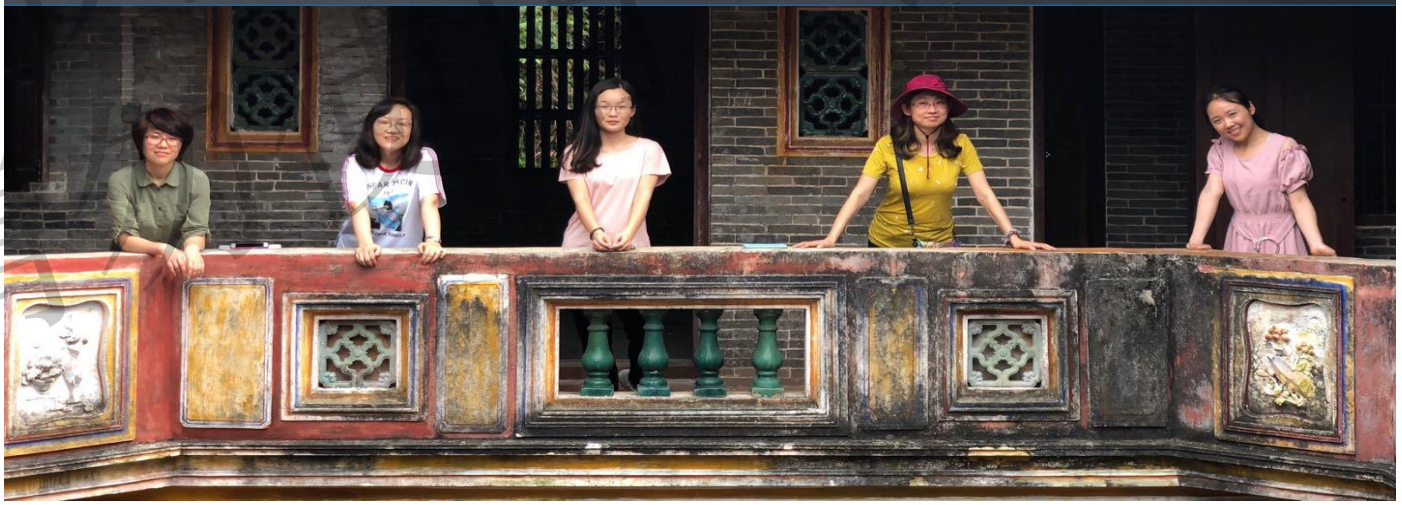

5α -RD诊断研究

5α-还原酶缺乏症中T/DHT截点值的研究

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1 研究背景

2 研究目的

3 研究方法

4 结　果

5 结　论

研究背景

Best Practice & Research Clinical Endocrinology & Metabolism
Vol. 22, No. 1, pp. 119–134, 2008
doi:10.1016/j.beem.2007.11.001
available online at http://www.sciencedirect.com

ELSEVIER

BEST PRACTICE & RESEARCH

8

Disorders of sex development: a new definition and classification

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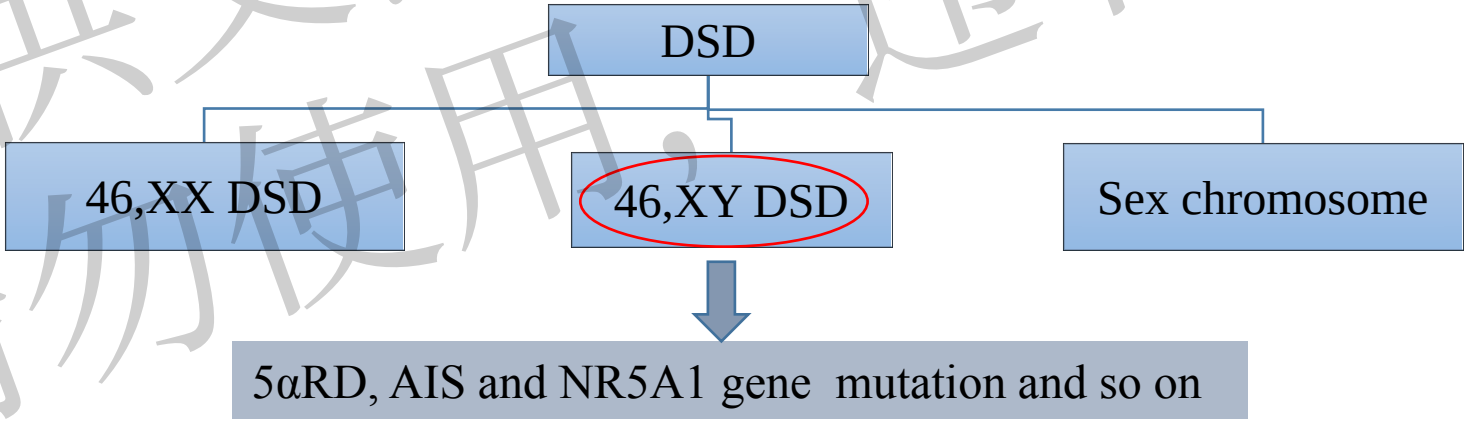
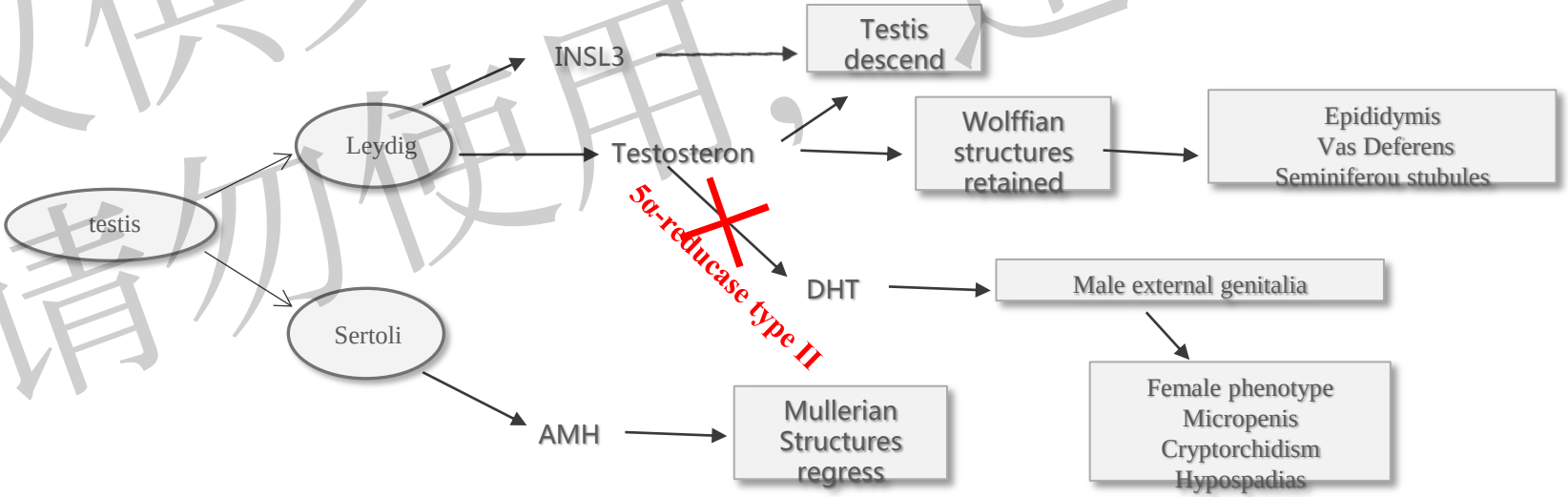


研究背景

- 不同病因引起的DSD 之间会有许多重叠的临床表现，同时同一种病因引起的DSD有时也会有不同的表型
- 但大多46，XY DSD缺乏明确的生物学标志，使46，XY DSD的诊断及鉴别诊断具有挑战性

T/DHT升高是5αRD的重要生物学指标，5αRD最初是由Imperato-McGinley等人在1974年报道的。



研究背景

- T/DHT截点值有争议
  - 最早由McGinley[1]在1974年对4例成年5αRD患者使用放射免疫法检测T/DHT比值均约为40，但是在正常男性中该比值约为14.
  - McGinley[等[2]对5例青春前期5α缺乏症患儿行HCG激发试验发现进行T/DHT均大于20
  - Maimoun等[3]用同样的方法对55例5αRD患儿分析发现，64.7%的患儿在HCG激发试验后T/DHT>10，但是并非所有的患儿均有SRD5A2基因的突变
  - Walter则建议由于在新生儿期，SRD5A1基因有瞬时表达作用，在新生儿期可以将该比值降低到8.5

  以上几项研究中T和DHT均采用放射免疫法检测

- 放射免疫法的缺点

  放射性对酶有损害

  假阳性率高

[1] Imperato.et.al.1974

[2] Imperato.et.al. 1978

[3] Maimoun.et.al.2011

研究背景

新的检测方法的发现势必让我们重新制定T/DHT的比值

本研究首次使用化学发光法测T和液相色谱-质谱法测DHT相结合的方法来研究已基因确诊的5αRD中T/DHT的值。

国家儿童医学中心 National Center for Children's Health, China
北京儿童医院 BEIJING CHILDREN'S HOSPITAL

研究目的

建立5αRD诊断的T/DHT最优Cut-off值

研究方法

从2007年9月至2017年12月在北京儿童医院内分泌遗传代谢科就诊，并且基因确诊的46，XY DSD患儿

- 入组标准

I) 染色体核型为46，XY

II) 患儿有不同程度的尿道下裂

III) 非小青春期患儿hCG标准激发试验后T>100ng/dl或青春期患儿T>100ng/dl；有DHT检测结果

IV) ACTH正常

- 排除标准

I) 非46，XY核型

II) 无尿道下裂；

III) hCG标准试T<100ng/dl，激素资料不完整，无T/DHT

IV) ACTH异常

研究方法

1、临床表现

- 外生殖器表型采用Prader分级，prader分级越小，表型越重
- 睾丸位置：腹腔=1，腹股沟=2，阴囊或阴唇上级=3，阴囊或阴唇内=4，位置越高，表型越重

2、T/DHT

- 激发后T/DHT比值（hCG试验，T采用化学发光法检测，DHT使用质谱法检测）

3、统计方法

- ROC曲线：以5αRD为阳性组，其他疾病为阴性对照组
- SPSS17.0和SAS

结果

——病人

我们选择了115例有基因结果的46，XY DSD患儿

- 组1: 5αRD 62 例
- 组2 (对照组53例)
  - 22 例AIS
    - 14 例NR5A1 基因突变
    - 17 例其他基因突变

结果

——临床诊断

表1 115例患儿的临床表型比较

	Group	N(115)	Prader0-1（%）	Prader 2（%）	Prader 3（%）	Prader 4（%）	Prader 5（%）
组1	5αRD	62	3.2	4.8	37.1	45.2	9.7
组2（对照组）	AIS	22	22.7	18.2	31.8	27.3	0
	NR5A1	14	0	28.6	42.9	21.4	7.1
	Other 46，XY DSD	17	5.9	11.8	29.4	41.1	11.8
	X^2		6.13	20.94	0.023	2.21	0.36
	P		0.12	0.051	0.849	0.249	0.469

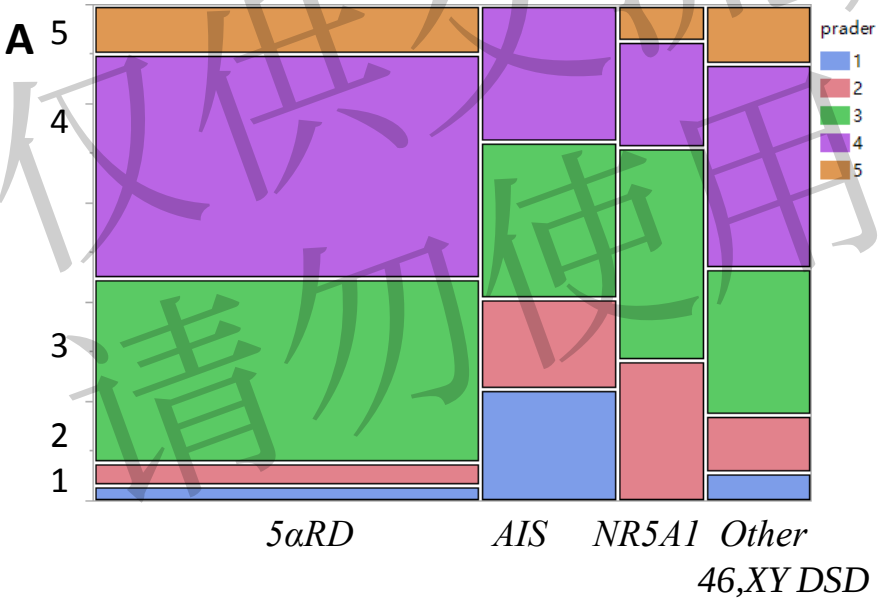


Fig1A 外生殖器Prader分级

- 5αRD多位于Prader3-4级
- AIS相对于其他疾病来说，prader0-1级所占的比例最大
- 各疾病间临床表型重叠较多

结果

——临床诊断

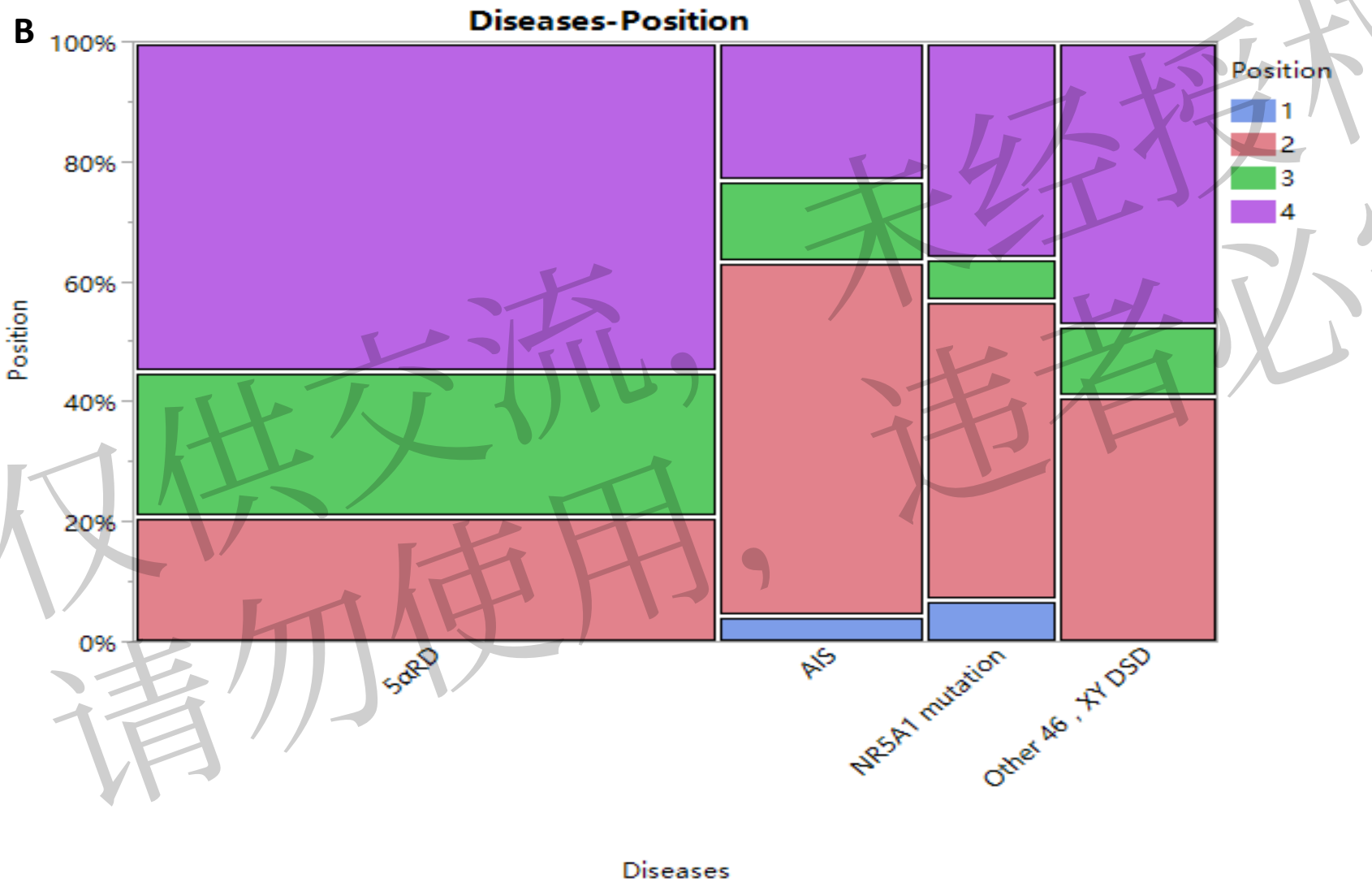


Fig1B 睾丸位置

结果

——T/DHT截点值

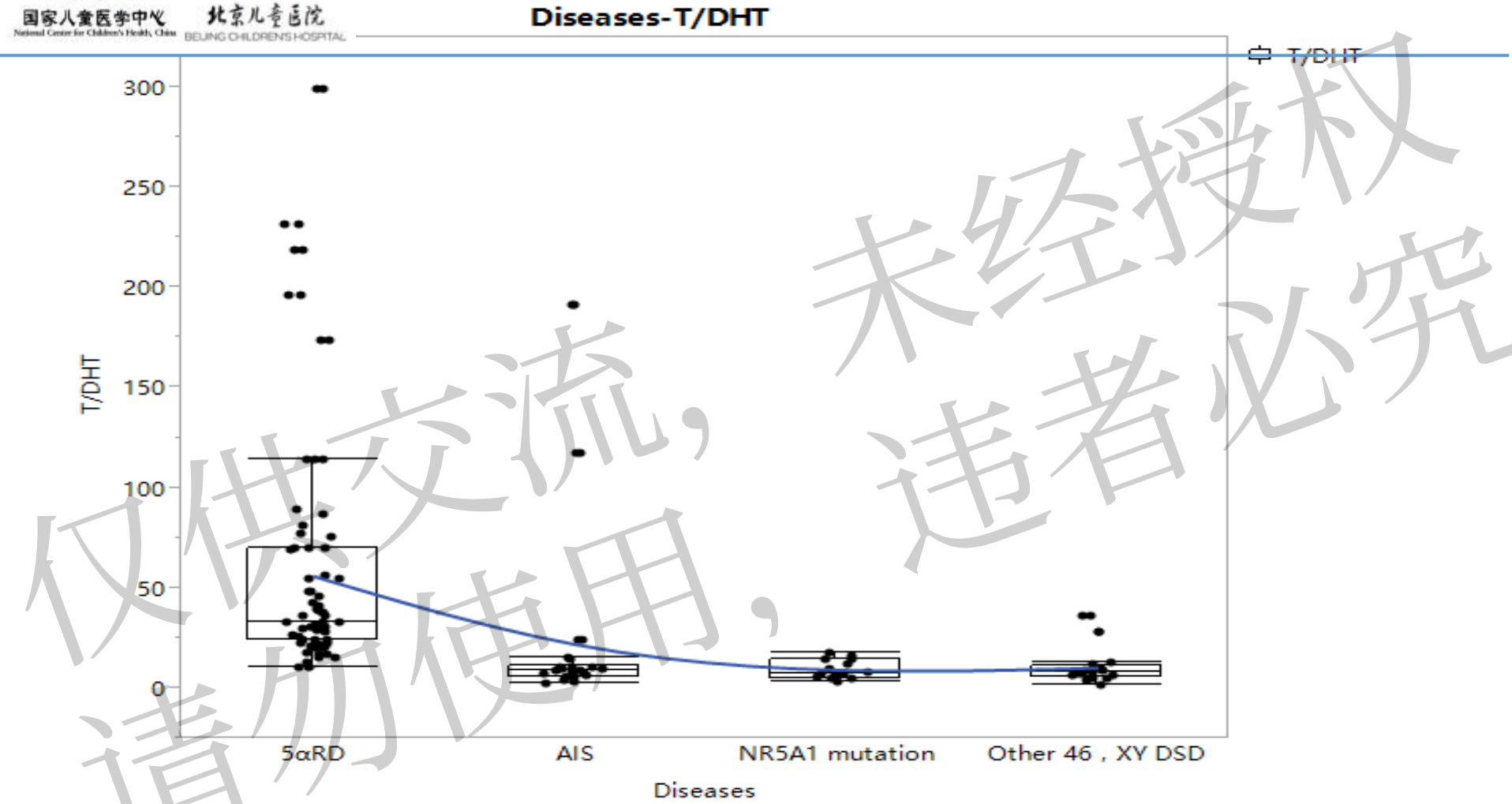
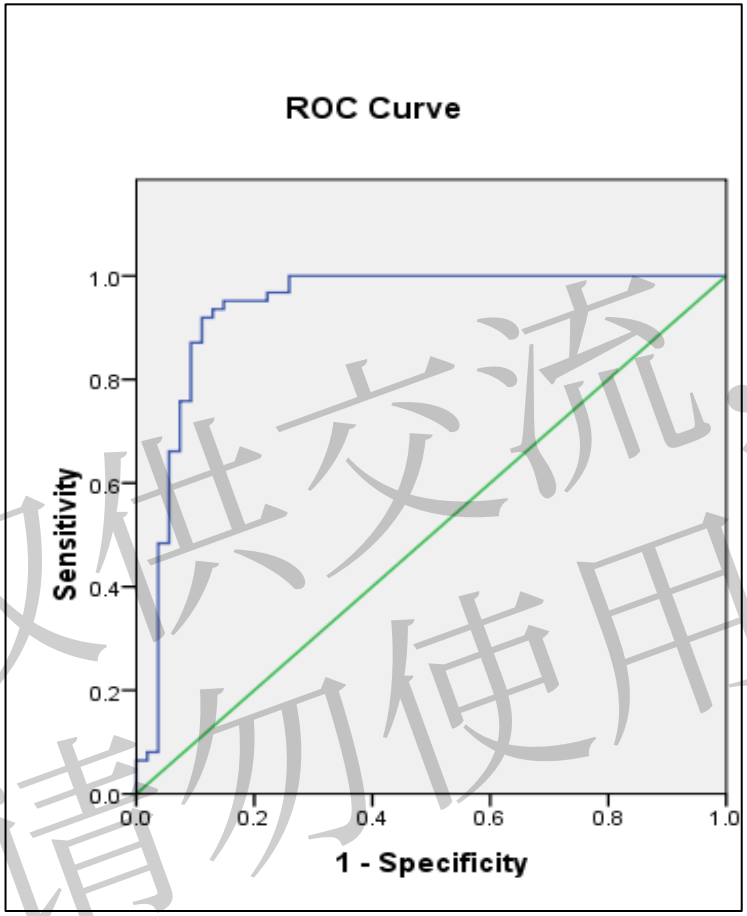


Fig 2　5αRD与其他疾病间T/DHT的比较

- 四组间有明显差异（p=0.000）
- 5αRD中T/DHT要明显高于其他三种疾病,5αRD ，而其他三种疾病（AIS，NR5A1突变与病因不明46，XY DSD）间T/DHT无明显差异

结果

——T/DHT的ROC曲线



Area Under the Curve

Test Result Variable(s):V

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.935	.027	.000	.883	.988

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

曲线的坐标

检验结果变量：

大于或等于此值时为正[a]	敏感度	1 - 特异性	
14.9085	0.937	0.148	0.788359788
15.0756	0.921	0.148	0.772486772
15.2539	0.921	0.130	0.791005291
15.7313	0.905	0.130	0.775132275

* 当灵敏度和特异度都达到最大时，T/DHT比值为15.25，此时灵敏度为92.1%，特异度为87%，Youden指数为0.79

图3 5α RD中T/DHT的ROC研究

Results

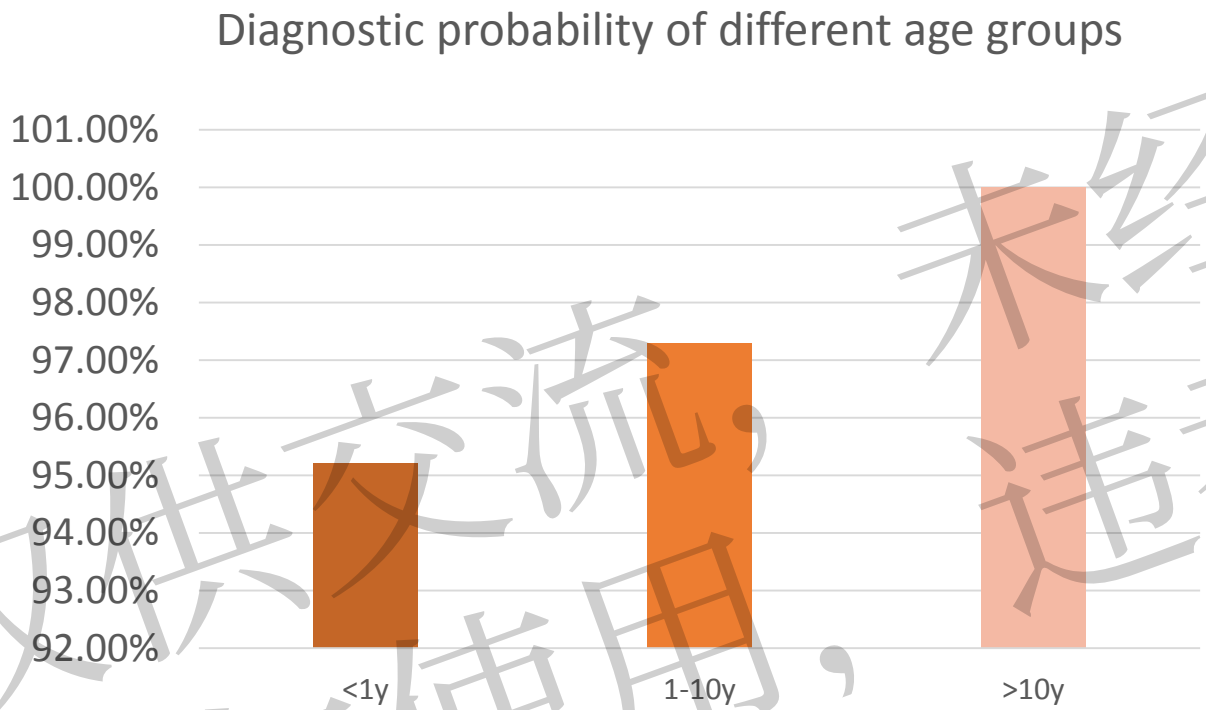
——T/DHT>15.25 在不同疾病中的验证

表 2 T/DHT>15.25 在不同疾病中的验证

T/DHT（115）	Group 1		Control group		
	5αRD	5αRD	AIS	NR5A1 mutation	Other 46,XY DSD
Rate (%)	Diagnosis (%)	Missed-diagnosis (%)	Misdiagnosis (%)	Misdiagnosis (%)	Misdiagnosis (%)
>15.25	90.6（58/64）	4.8（4/62）	4.7（3/64）	1.6（1/64）	3.1（2/64）
>20	91.4 (53/58)	14.5(9/62)	5.2(3/58)	0	3.4(2/58)
>30	90.6（29/32）	53.2(33/62)	6.3（2/32）	0	3.1(1/32)
P	0.988	0	0.948	0.493	0.994

Results

——Age specificity of T/DHT in 5αRD



we considered it's not necessary to do genetic testing for older children based on T/DHT>15.25 , but for younger children, it is best to use genetic to recheck

Fig 4 The diagnosed rate in different age of 5αRD when T/DHT at 15.25

- When T/DHT>15.25, the diagnostic rate was 95.2% (20/21) in <1 years old children
- 97.3% (36/37) in 1-10 year old children
- while the rate of >10 years old children was 100% (4/4)

结果

——诊断建议

通过以上描述

- ***对于>的5αRD患儿来说，如果T/DHT>15.25，可以不做基因直接诊断***
- ***但是对于小年龄患儿，当T/DHT>15.25时，最好再用基因复核是否为SRD5A2基因突变***

结论

- 我们制定了5αRD中T/DHT的截点值
- 当 T/DHT>15.25 , 5αDR的诊断率最高，同时漏诊率最低
- 在5αRD中，T/DHT>15.25 适用于所有年龄段的患儿，尤其对大年龄患儿
- 对于 大年龄段的5αRD 患儿来说，如果T/DHT>15.25，可以不做基因直接诊断，但是对于小年龄患儿，当T/DHT>15.25时， 最好再用基因复核是否为SRD5A2基因突变