

TAB2基因多态性与中国西南汉族人群 隐睾症易感性的相关性研究*

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【摘要】目的 初步探讨TAB2(transforming growth factor-beta activated kinase 1 binding protein 2)基因与中国西南地区汉族人群隐睾症发病的相关性。**方法** 选取西南地区259名隐睾患者和355名成年男性健康对照,采用聚合酶链式反应-限制性片段长度多态性分析方法,对TAB2基因的3个标签单核苷酸多态性位点(tag single nucleotide polymorphism, tag SNP)rs237028、rs521845、rs652921进行基因分型,并采用卡方检验分析3个tag SNP位点与隐睾症发病的关系。**结果** 本实验的3个tag SNP位点基因型频率分布均符合Hardy-Weinberg平衡,限制性酶切实验分型结果与Sanger测序结果一致。TAB2 rs237028位点的G等位基因在隐睾组中的频率高于对照组(30.9% vs. 25.6%, $P=0.04$, $OR=1.31$, 95%CI: 1.01~1.70),在显性遗传模型中AG/GG基因型携带者罹患隐睾症的风险升高($P=0.006$, $OR=1.57$, 95%CI: 1.14~2.17)。在隐睾组中rs652921位点的TC/CC基因型频率高于对照组,差异有统计学意义(75.3% vs. 67.0%, $P=0.03$; $OR=1.50$, 95%CI: 1.05~2.14)。未观察到rs521845与中国人群隐睾遗传易感性的相关性。**结论** TAB2基因rs237028的AG/GG基因型和rs652921的TC/CC基因型可能与中国西南地区汉族人群罹患隐睾症的风险性增加相关。

【关键词】 隐睾症 TAB2基因 单核苷酸多态性 聚合酶链式反应 遗传易感性

Association Between TAB2 Gene Polymorphisms and Susceptibility to Cryptorchidism in Han Chinese Population in Southwest China SU Min, LI Zhi-long, SONG Ya-ping, WANG Yan-yun, ZHOU Bin, LI Qin[△]. Laboratory of Molecular Translational Medicine, Center for Translational Medicine, Key Laboratory of Birth Defects and Related Diseases of Women and Children of the Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu 610041, China

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【Abstract】 Objective To conduct preliminary investigation into the correlation between transforming growth factor beta-activated protein kinase 1-binding protein 2 (TAB2) gene and the incidence of cryptorchidism in Han Chinese population in Southwest China. **Methods** A total of 259 patients with cryptorchidism and 355 healthy controls from Southwest China were enrolled for the study. Polymerase chain reaction-restriction fragment length polymorphism method was used to analyze the genotype of the 3 tag single nucleotide polymorphisms (SNPs) of TAB2 gene, i.e., rs237028, rs521845 and rs652921. The Chi-square test was used to analyze the relationship between the genotype frequency of the three tag SNPs and the incidence of cryptorchidism. **Results** The distribution of the 3 tag SNPs' alleles and genotypes were in agreement with the Hardy-Weinberg equilibrium, and the genotype results of polymerase chain reaction-restriction fragment length polymorphism assay were consistent with those of Sanger sequencing. The frequency of the G allele at TAB 2 rs237028 was significantly higher in the cryptorchidism group than that in the control group (30.9% vs. 25.6%, $P=0.04$, $OR=1.31$, 95% CI: 1.01-1.70). In the dominant model, the risk of cryptorchidism was significantly higher in AG/GG genotype carriers ($P=0.006$, $OR=1.57$, 95% CI: 1.14-2.17). In the cryptorchidism group, the TC/CC genotype frequency of the rs652921 locus were significantly higher than that of the control group (75.3% vs. 67.0%, $P=0.03$, $OR=1.50$, 95% CI: 1.05-2.14). Correlation between rs521845 and susceptibility to cryptorchidism was not observed in the Han Chinese population. **Conclusion** The AG/GG genotype of rs237028 locus and the TC/CC genotype of rs652921 locus of the TAB2 gene may be associated with increased risks of cryptorchidism in Han Chinese population in southwest China.

【Key words】 Cryptorchidism TAB2 gene Single nucleotide polymorphism Polymerase chain reaction Susceptibility

隐睾是新生儿最常见的一种先天性异常^[1-2],足月新生儿患病率约1%~4%,而早产儿约占30%,其不仅造成

生育力降低,也是引起睾丸癌变的潜在风险因素^[3]。研究表明,隐睾属于先天发育异常性疾病,部分患儿伴随其他部位的先天性异常^[4],遗传因素在其发生发展中扮演着重要角色^[5]。

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TAB2(transforming growth factor-beta activated

kinase 1 binding protein 2)基因位于6号染色体6q25.1,其编码蛋白通过磷酸化或泛素化激活核因子 κ B(nuclear factor kappa-B, NF- κ B)和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路,参与了机体先天免疫及相关生命活动的调控^[6-7]。研究表明, *TAB2*单倍体不足与多种发育性疾病相关,并参与了先天性心脏病的发生^[8-9]。此外,含致病性*TAB2*变异的患者约53%的个体表现出发育迟缓的特征^[10]。因此, *TAB2*基因可能与隐睾风险相关,但目前尚未见相关报道。本研究拟初步探讨中国西南地区汉族人群隐睾发病风险与*TAB2*基因3个标签单核苷酸多态性(single nucleotide polymorphisms, SNPs)位点的关联。

1 材料和方法

1.1 研究对象

本研究为病例对照研究,回顾性纳入于2017年2月-2021年9月前往四川大学华西医院、四川大学华西第二医院就诊的259例隐睾症患者。隐睾患者的诊断采用刘毅东等^[11]提出的隐睾诊断专家共识标准。排除标准:存在其他先天性疾病及家族史、或生殖器相关疾病的患者。

截止本研究结束,根据诊断标准共纳入了隐睾患者259例,排除8例临床信息不完整样本(年龄不详)后,具备完整且详细的临床信息记录病例共251例(单侧隐睾170例,双侧隐睾81例),其中患者睾丸位置有46例位于腹股沟、23例位于高位腹腔内、4例位于内环口,睾丸萎缩患者有13例。患者年龄范围6个月~32岁,中位年龄1岁,平均年龄(4.01±5.64)岁。

本实验在筛选对照组时,由于健康男童样本较难获得,因此纳入了自发前往四川大学华西医院、华西第二医院体检的355例年龄22~77岁的健康成年男性对照,中位年龄49岁,平均年龄(49.16±15.75)岁。所有对照组成员均无隐睾或其他生殖器相关疾病,且无先天性疾病病史及家族史。本研究针对研究对象进行基因层面检测分析,且人类遗传信息不会随着年龄的增加而发生变化,即

年龄因素不对组间遗传信息的结果造成影响。

本实验所有研究对象均为来自于中国西南地区的汉族个体。本研究已通过四川大学华西第二医院伦理委员会批准(批准号2020ZYD007),并且所有参与者或其监护人均签署了书面知情同意书。

1.2 DNA提取

所有受试者均抽取2 mL外周静脉血于EDTA抗凝采血管中,并在24 h内处理分装至冻存管,统一于-80 °C超低温冰箱内冷冻保存,分批次进行DNA的提取。所有样本均采用离心柱型全血基因组DNA提取试剂盒(BioTeke, 中国),严格按照说明书提取全基因组DNA。

1.3 SNP的筛选及基因分型

本研究使用在线软件SNPinfo^[12]从HapMap项目(the third phase)的CHB(Han Chinese in Beijing, China)人群数据中筛选SNP位点,得到*TAB2*基因的3个标签SNP(tag SNP)位点:rs237028 (A>G)、rs521845 (T>G)和rs652921 (C>T)。使用在线引物设计软件Primer3(<https://primer3.ut.ee/>)设计引物^[13]。具体引物序列见表1。采用聚合酶链式反应-限制性片段长度多态性(polymerase chain reaction-restriction fragment length polymorphism, PCR-RFLP)分析技术,对纳入样本*TAB2*基因的3个tag SNP位点进行检测分析。

PCR反应体积为10 μ L,其中包含100 ng DNA, 0.3 nmol/L正向和反向引物(擎科生物,北京), 5 μ L 2 \times Taq PCR Master Mix(BioTeke, 中国)及无酶水。PCR条件从95 °C初始变性4 min开始,随后94 °C变性30 s, 60 °C退火30 s, 72 °C延伸30 s,共计33个循环,最后72 °C终延伸10 min。使用限制性内切酶*Hpy*188 I (New England Biolabs, 北京)于37 °C消化rs237028位点扩增产物2 h;使用限制性内切酶*Ac* II (Thermo Fisher Scientific, 上海)于37 °C消化rs521845位点扩增产物2 h;使用限制性内切酶*Bse*J I (Thermo Fisher Scientific, 上海)于60 °C消化rs652921位点扩增产物1 h。取5 μ L酶切产物与2 μ L loading buffer(Biosharp, 中国)进行聚丙烯酰胺凝胶电泳

表1 3个tag SNP位点PCR-RFLP引物序列及反应条件

Table 1 Primer sequences and reaction conditions for genotyping three tag SNPs

SNP	Primer sequence	Wild/mutated allele	Annealing temperature/°C	Restriction enzyme	Product size/bp
rs237028	F: 5'-GCAGACTTGGAAGCAAACA-3'	G/A	60	<i>Hpy</i> 188 I	A (138)
	R: 5'-CCAGCCTGAGCAACAAGAG-3'				G (106+32)
rs652921	F: 5'-CAGTGAACTTTTCCCGATG-3'	C/T	60	<i>Bse</i> J I	T (120)
	R: 5'-TCGCTGTGAACAGTGTGAGA-3'				C (99+21)
rs521845	F: 5'-TAGGGCGGTTGAGAAGTGAA-3'	G/T	60	<i>Ac</i> II	T (120)
	R: 5'-CCTGGGTGACTGAGCTCTTA-3'				G (100+26)

SNP: Single nucleotide polymorphism; F: Forward primer; R: Reverse primer.

和硝酸银染色,最后判定基因型。实验中随机选取10%的样本重复上述步骤,以排除实验操作过程中或基因型判定时出现的人为误差。最后随机选取各基因型样本进行Sanger测序验证分型结果是否与限制性酶切实验结果一致。

1.4 统计学方法

连续变量采用Pearson相关性分析,而分类变量的相关性分析和实验人群的Hardy-Weinberg遗传平衡检验采用卡方检验。样本量的power值($\alpha=0.05$)使用Power and Sample Size Calculator软件计算^[14]。实验组与对照组间的基因型在共显性、显性、隐性和超显性模型中的分布差异,以及连锁不平衡和单倍型分析均采用SNPStats(<https://www.snpstats.net/snpstats/start.htm>)在线评估软件进行计算。实验组和对照组中等位基因与基因型之间的差异分析采用优势比(OR)和95%置信区间(95%CI)进行评估。 $P_{\text{双侧}} < 0.05$ 为差异有统计学意义。

2 结果

2.1 *TAB2*基因rs237028、rs521845和rs652921位点的等位基因频率分布结果分析

本实验的3个tag SNP位点基因型频率分布均符合

Hardy-Weinberg平衡(rs237028: $P=0.490$; rs521845: $P=0.560$; rs652921: $P=0.390$)。研究纳入的所有样本SNP位点均分型成功(图1),且限制性酶切实验分型结果与Sanger测序结果一致。3个tag SNP位点的power值为分别rs237028: 0.857, rs521845: 0.894, rs652921: 0.902,提示本研究的样本量具有一定的代表性。

如表2所示,rs237028位点的等位基因分布频率在病例组和对照组之间存在明显差异,与A等位基因相比,病例组的G等位基因频率高于对照组(30.9% vs. 25.6%, $P=0.04$),G等位基因携带者的隐睾患病风险是未携带者的1.31倍。然而rs521845和rs652921位点的等位基因分布频率在病例组和对照组之间差异无统计学意义($P > 0.05$)。

2.2 *TAB2*基因rs237028位点多态性与隐睾症易感性的分析

表3展示了*TAB2* rs237028位点的基因型在病例组和对照组中的分布情况。结果显示,AA、AG和GG基因型分布频率在病例组中分别为44.8%、48.6%和6.6%,而对照组中则分别为56.1%、36.6%和7.3%。在显性模型中,与AA基因型相比较,病例组中携带AG/GG基因型的患者比例(55.2%)高于对照组中AG/GG基因型携带者

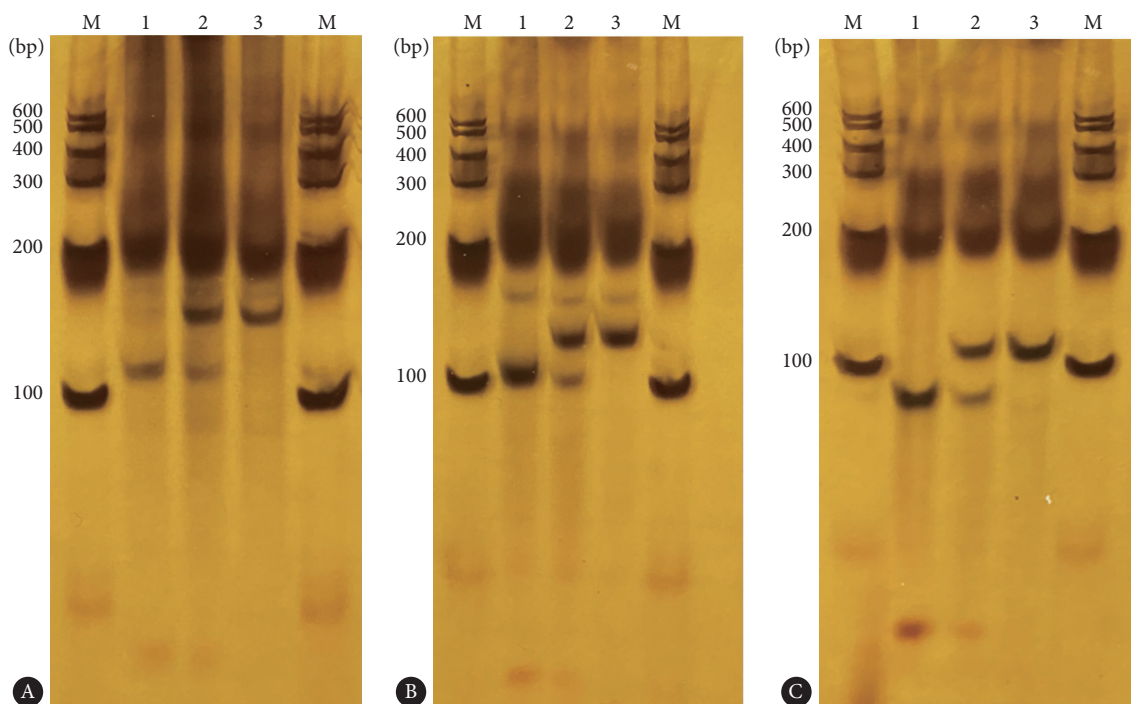


图1 rs237028、rs521845和rs652921位点聚丙烯酰胺凝胶电泳分型图

Fig 1 Genotypes of *TAB2* rs237028, rs521845 and rs652921

A: Genotypes of rs237028 polymorphism (Lane 1: GG genotype; Lane 2: AG genotype; Lane 3: AA genotype); B: Genotypes of rs521845 polymorphism (Lane 1: GG genotype; Lane 2: TG genotype; Lane 3: TT genotype); C: Genotypes of rs652921 polymorphism (Lane 1: CC genotype; Lane 2: TC genotype; Lane 3: TT genotype); M: Marker.

表2 病例组及对照组*TAB2*基因的SNP位点等位基因频率分布Table 2 Allele frequencies of SNPs in *TAB2* gene among patients and controls and their association with risks for cryptorchidism

SNP	Genotype	Control group/case (%)	Patient group/case (%)	OR (95% CI)	P
rs237028	A	528 (74.4)	358 (69.1)	1 (ref)	0.04*
	G	182 (25.6)	160 (30.9)	1.31 (1.01-1.70)*	
rs521845	T	462 (65.1)	317 (61.2)	1 (ref)	0.17
	G	248 (34.9)	201 (38.8)	1.18 (0.93-1.49)	
rs652921	T	400 (56.3)	270 (52.1)	1 (ref)	0.14
	C	310 (43.7)	248 (47.9)	1.19 (0.94-1.49)	

SNP: Single nucleotide polymorphism; OR: Odds ratio; CI: Confidence interval. * indicates a significant difference at the 5% level.

表3 病例组及对照组*TAB2*基因rs237028基因型频率比较Table 3 Genotype frequencies of rs237028 in *TAB2* gene among patients and controls and their association with cryptorchidism

Model	Genotype	Control group/case (%)	Patient group/case (%)	OR (95% CI)	P
Codominant	AA	199 (56.1)	116 (44.8)	1 (ref)	0.01*
	AG	130 (36.6)	126 (48.6)	1.66 (1.19-2.33)*	
	GG	26 (7.3)	17 (6.6)	1.12 (0.58-2.15)	
Dominant	AA	199 (56.1)	116 (44.8)	1 (ref)	0.006*
	AG/GG	156 (43.9)	143 (55.2)	1.57 (1.14-2.17)*	
Recessive	AA/AG	329 (92.7)	242 (93.4)	1 (ref)	0.71
	GG	26 (7.3)	17 (6.6)	0.89 (0.47-1.67)	
Over-dominant	AA/GG	225 (63.4)	133 (51.4)	1 (ref)	0.003*
	AG	130 (36.6)	126 (48.6)	1.64 (1.18-2.27)*	

OR: Odds ratio; CI: Confidence interval. * indicates a significant difference at the 5% level.

(43.9%), 且差异有统计学意义 ($P=0.006$; $OR=1.57$, $95\%CI: 1.14 \sim 2.17$), 表明AG/GG基因型携带者较AA基因型携带者具有更高的罹患隐睾症的风险。在超显性模型中, 与AA/GG纯合子相比较, 病例组中AG杂合子频率高于对照组 (48.6% vs. 36.6%, $P=0.003$; $OR: 1.64$, $95\%CI: 1.18 \sim 2.27$), 提示rs237028位点AG杂合突变增加了隐睾患病风险。

2.3 *TAB2*基因rs521845位点多态性与隐睾症易感性的分析

*TAB2*基因rs521845位点基因多态性分析结果显示, 病例组与对照组的基因型频率分布在共显性、显性、隐性和超显性遗传模型上差异均无统计学意义 ($P>0.05$, 表4)。

2.4 *TAB2*基因rs652921位点多态性与隐睾症易感性的分析

表5呈现了*TAB2* rs652921位点的基因频率分布情况。结果显示病例组中TT、TC和CC基因型分布频率分别为24.7%、54.8%和20.5%, 而对照组中则分别为33.0%、

46.8%和20.3%。显性模型中, 与TT基因型相比较, 病例组携带TC/CC基因型的患者比例高于对照组 (75.3% vs. 67.0%), 且差异有统计学意义 ($P=0.03$; $OR: 1.50$, $95\%CI: 1.05 \sim 2.14$), 表明TC/CC基因型携带者较TT基因型携带者具有更高的罹患隐睾症的风险。在超显性模型中, 与TT/CC纯合子相比较, 病例组中TC杂合子频率高于对照组 (54.8% vs. 46.8%, $P=0.048$; $OR: 1.38$, $95\%CI: 1.00 \sim 1.91$), 提示rs237028位点TC杂合突变提升了隐睾症罹患风险。

2.5 连锁不平衡与单倍型分析

见表6。*TAB2*基因rs237028、rs521845和rs652921位点间存在较低连锁不平衡(rs237028 vs. rs521845, $D' = 0.8219$, $r^2 = 0.6726$; rs237028 vs. rs652921, $D' = 0.9068$, $r^2 = 0.6173$; rs521845 vs. rs652921, $D' = 0.9177$, $r^2 = 0.7634$), 提示3个SNP位点均具有代表性。在单倍型分析中, 实验组与对照组的总体单倍型分析比较有统计学意义 ($P=0.04$), 然而并未发现任何存在显著差异的单一分型。我们发现了一个呈高危趋势的单倍型GGC(rs237028-rs521845-

表 4 病例组及对照组TAB2基因rs521845基因型频率分布

Table 4 Genotype frequencies of rs521845 in TAB2 gene among patients and controls and their association with cryptorchidism

Model	Genotype	Control group/case (%)	Patient group/case (%)	OR (95% CI)	P
Codominant	TT	153 (43.1)	95 (36.7)	1 (ref)	0.28
	TG	156 (43.9)	127 (49.0)	1.31 (0.93-1.86)	
	GG	46 (13.0)	37 (14.3)	1.30 (0.78-2.14)	
Dominant	TT	153 (43.1)	95 (36.7)	1 (ref)	0.11
	TG/GG	202 (56.9)	164 (63.3)	1.31 (0.94-1.82)	
Recessive	TT/TG	309 (87.0)	222 (85.7)	1 (ref)	0.58
	GG	46 (13.0)	37 (14.3)	1.12 (0.70-1.78)	
Over-dominant	TT/GG	199 (56.1)	132 (51.0)	1 (ref)	0.21
	TG	156 (43.9)	127 (49.0)	1.23 (0.89-1.69)	

OR: Odds ratio; CI: Confidence interval.

表 5 病例组及对照组TAB2基因rs652921基因型频率比较

Table 5 Genotype frequencies of rs652921 in TAB2 gene among patients and controls and their association with cryptorchidism

Model	Genotype	Control group/case (%)	Patient group/case (%)	OR (95% CI)	P
Codominant	TT	117 (33.0)	64 (24.7)	1 (ref)	0.07
	TC	116 (46.8)	142 (54.8)	1.56 (1.07-2.28)	
	CC	72 (20.3)	53 (20.5)	1.35 (0.84-2.15)	
Dominant	TT	117 (33.0)	64 (24.7)	1 (ref)	0.03*
	TC/CC	238 (67.0)	195 (75.3)	1.50 (1.05-2.14)*	
Recessive	TT/TC	283 (79.7)	206 (79.5)	1 (ref)	0.96
	CC	72 (20.3)	53 (20.5)	1.01 (0.68-1.50)	
Over-dominant	TT/CC	189 (53.2)	117 (45.2)	1 (ref)	0.048*
	TC	166 (46.8)	142 (54.8)	1.38 (1.00-1.91)*	

OR: Odds ratio; CI: Confidence interval. * indicates a significant difference at the 5% level.

表 6 实验组与对照组的TAB2基因单倍型频率

Table 6 Haplotype frequencies of TAB2 gene in patients and controls

Haplotype	rs237028	rs521845	rs652921	Controls	Patients	OR (95% CI)	P
1	A	T	T	0.5510	0.4811	1 (ref)	-
2	G	G	C	0.2279	0.2572	1.32 (0.99-1.75)	0.06
3	A	G	C	0.1091	0.1092	1.15 (0.77-1.70)	0.50
4	A	T	C	0.0778	0.0868	1.27 (0.81-1.97)	0.30
5	G	T	C	0.0218	0.0257	1.46 (0.65-3.31)	0.36

Global haplotype association $P=0.04$. OR: Odds ratio; CI: Confidence interval.

rs652921), 其可能与隐睾易感性增加相关($P=0.06$, $OR=1.32$, $95\%CI: 0.99 \sim 1.75$), 但需要更大样本量的实验数据加以验证。

3 讨论

隐睾是男性最常见的泌尿系统先天性缺陷, 是男性

不育和睾丸癌的诱发因素之一^[15]。目前临床上对于隐睾患者的治疗大多行手术干预, 且争取在患儿18个月龄前进行睾丸固定术, 以最大限度地保留患儿生育能力, 降低未来罹患睾丸癌的风险^[16]。近年来, 对于隐睾的研究主要集中在致病基因和环境因素等方面, 但其发病机制尚未阐明, 亟需更多的研究和探索。

*TAB2*作为先天免疫信号通路的重要组分,已被证实与多种疾病相关。研究表明*TAB2*介导炎症与雌激素相关通路参与中国汉族女性上皮性卵巢癌的发病^[17],同时乳腺癌的内分泌抵抗相关耐药机制也与*TAB2*调控的信号通路存在一定的联系^[18]。迄今为止,已有研究显示*TAB2*变异与先天性心脏病(congenital heart defect, CHD)相关^[19-20],CHD患者体内检测到的*TAB2*微缺失提示*TAB2*单倍剂量不足可能导致CHD的发生。同时,SHEN等^[21]也证实*TAB2*的突变与中国汉族扩张型心脏病的发病及不良预后相关。人类与斑马鱼体内均存在*TAB2*的表达,有研究指出斑马鱼胚胎敲除*TAB2*导致表皮发育迟缓^[22]。一项对*TAB2*基因变异者的分析报告显示,超过一半的受试者患有综合性CHD或成人型心肌病,且53%(8/15)的受试者表现出发育迟缓^[10]。这提示除心脏之外*TAB2*还可能引起其他系统的先天性疾病^[23]。

我们选择了3个位于*TAB2*基因的Tag SNPs: rs237028(A>G)、rs521845(T>G)和rs652921(C>T),其中rs237028和rs521845位于内含子区域,rs652921位于外显子同义密码子区域。研究结果表明,*TAB2*基因突变可能与隐睾易感风险相关,rs237028位点的G碱基携带者(AG/GG基因型)罹患隐睾的风险性高于AA基因型携带者,rs652921位点的C碱基携带者(TC/CC基因型)较TT基因型携带者具有更高的隐睾患病风险。有研究发现*TAB2*与TAK1和TAB1形成的蛋白酶复合物调节下游信号分子的活化,参与NF- κ B和MAPKs信号通路,从而调节先天免疫过程^[21,24]。结合目前的研究结果,我们推测*TAB2*基因可能通过MAPKs和NF- κ B信号通路影响隐睾的发病^[25],但具体关联性和作用机制尚待更深入的研究。本研究涉及的所有样本均来自中国西南汉族人群,由于中国总体人群具有民族多样性,且汉族人口占绝大多数,因此具有一定的代表性。但本研究依然存在几个局限:首先,本实验纳入的总体样本量偏小,且部分隐睾患者的临床信息不完整,按照患者临床信息分层分组后各组样本量亦偏小,因此未针对患者的临床信息特征进行更深入的统计学分析;其次,rs237028和rs652921在隐睾发生中的具体机制尚未探究清楚。因此多中心、多地区、多民族人群中的更大样本量验证实验是必不可少的,隐睾症发病机制的探讨也是本研究后期需要深入的方向。

综上所述,本研究结果提示,在中国西南汉族人群中*TAB2*的rs237028和rs652921 SNP位点与隐睾患病风险升高相关,*TAB2*基因可能是中国西南汉族人群隐睾症的潜在危险指标。本研究为隐睾的早期筛查提供了一定的理

论基础,然而*TAB2*基因与隐睾症的发病机制还需要更深入的探索。

* * *

利益冲突 所有作者均声明不存在利益冲突

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