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# 新疆维汉民族多囊卵巢综合征患者 CYP17 基因多态性及与发病机制的关系 *

吴苗敏 芦艳丽 韩 璐△ 刘 娜 万 莉

（新疆维吾尔自治区中医药研究院 新疆 乌鲁木齐 830000）

**摘要 目的：**探讨细胞色素 P450 酶 17(CYP17)基因多态性及其与多囊卵巢综合征(PCOS)发病机制的关系。**方法：**选择 2015 年 1 月 ~2017 年 2 月我院收治的新疆维汉民族 PCOS 患者 260 例为 PCOS 组，另选取同期在我院门诊检查的健康育龄妇女 237 例为对照组，采用限制性片段长度多态性聚合酶链反应(PCR-RFLP)技术检测两组受试者的 CYP17 基因多态性，比较两组等位基因及基因频率的分布，结合其临床资料分析 CYP17 基因多态性与 PCOS 发病机制的关系。**结果：**PCOS 组体质量指数(BMI)、卵泡刺激素(FSH)水平低于对照组，黄体生成激素(LH)、睾酮(TES)及黄体生成激素与卵泡刺激素的比值(LH/FSH)高于对照组，差异有统计学意义(P＜0.05)。PCOS 组 CYP17 基因 A1A1、A1A2、A2A2 型频率分别为 34.62%、41.92%、23.46%，与对照组的 34.18%、43.88%、21.94%比较差异无统计学意义(P＞0.05)；PCOS 组等位基因 A1、A2 频率为 55.58%、44.42%，与对照组的 56.12%、43.88%比较差异无统计学意义 (P＞0.05)；PCOS 组不同 CYP17 基因型者的 FSH、LH 及 LH/FSH 水平整体比较差异无统计学意义 (P＞0.05)；PCOS 组 BMI 水平 A2A2＞A1A2＞A1A1，TES 水平 A2A2＜A1A1＜A1A2，差异均有统计学意义 (均 P＜0.05)；对照组不同 CYP17 基因型者的 BMI、FSH、LH、TES 及 LH/FSH 水平整体比较差异均无统计学意义(P＞0.05)。**结论：**CYP17 基因 -34bp 处 T/C 单核苷酸多态性是人群中一种常见的碱基置换，与 PCOS 的发病机制无明显的相关性。

**关键词：**多囊卵巢综合征；CYP17 基因；基因多态性；发病机制

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# Uyhan and Han Nationality Patients with Polycystic Ovary Syndrome in Xinjiang: Polymorphism of CYP17 Gene and Its Relationship with Pathogenesis*

*WU Miao-min, LU Yan-li, HAN Lu△, LIU Na, WAN Li*

*(Chinese Medicine Research Institute of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang, 830000, China)*

**ABSTRACT Objective:** To explore the genetic polymorphism of cytochrome P450 enzyme 17(CYP17) and its relationship with the pathogenesis of polycystic ovary syndrome(PCOS). **Methods:** A total of 260 patients with PCOS of uyhan and han nationality in Xinjiang, who were admitted to Chinese Medicine Research Institute of Xinjiang Uygur Autonomous Region from January 2015 to February 2017, were chosen as PCOS group; the other 237 healthy fertile women, who were examined in the outpatient department during the same period, were chosen as control group. The CYP17 gene polymorphism in the two groups of subjects was detected by the restriction fragment length polymorphism polymerase chain reaction (PCR-RFLP) technique; the distribution of alleles and gene frequencies was compared between the two groups; combining with its clinical data, the relationship between CYP17 gene polymorphism and the pathogenesis of PCOS was analyzed. **Results:** Body Mass Index(BMI) and Follicle-stimulating hormone(FSH) levels in the PCOS group were lower than those in the control group; Luteotropic hormone(LH), Testosterone(TES) and LH/FSH levels in the PCOS group were higher than those in the control group, and the differences were statistically significant (P<0.05). The frequencies of A1A1, A1A2, and A2A2 of CYP17 gene in the PCOS group were 34.62%, 41.92%, 23.46%, respectively, compared with 34.18%, 43.88%, 21.94% in the control group, the difference was not statistically significant (P>0.05). The allele frequency of A1 and A2 in the PCOS group were 55.58%, and 44.42% respectively, compared with 56.12% and 43.88% in the control group, the difference was not statistically significant (P>0.05). There was not statistical significance in FSH, LH and LH/FSH levels of different CYP17 genotypes in the PCOS group (P>0.05). There was statistical significance in BMI level A2A2>A1A2>A1A1 and TES level A2A2<A1A1<A1A2 in the PCOS group (all P<0.05). The BMI, FSH, LH, TES and LH/FSH levels of different CYP17 genotypes in the control group were not statistically significant (P>0.05). **Conclusion:** CYP17 gene -34bp T/C nucleotide polymorphisms is a common base replacement in the population, which is not significantly related to the pathogenesis of PCOS.

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作者简介：吴苗敏(1973-)，女，本科，副主任医师，研究方向：中西医结合妇产科临床及中医证型现代化，E-mail：quysyb@163.com

△ 通讯作者：韩璐(1973-)，女，本科，主任医师，研究方向：中西医结合妇产科临床及中医证型现代化，E-mail：dsgohn@163.com

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## 前言

多囊卵巢综合征(Polycystic ovary syndrome，PCOS)是一种生殖功能障碍与糖代谢异常并存的内分泌功能紊乱综合征[1,2]，以 20~40 岁妇女为易发群体，是育龄妇女常见病之一，发病率约 5%~10%，并存在种族差异[3,4]。PCOS 的确切发病原因迄今尚不十分清楚，多认为是遗传因素与环境因素共同作用的结果，可能是多种基因参与调控的遗传代谢性疾病[5,6]。

细胞色素 P450 酶 17(Cytochrome P45017，CYP17)基因处于 10 号染色体 24.3 区，在其翻译位点上游 -34bp 处存在一个 T/C 碱基置换形成多态位点，具有 17α- 羟化酶和 17、20 裂解酶的双重活性。目前，学界对 CYP17 基因多态性与 PCOS 发病机制的关系的认知尚不统一，甚至得出截然相反的观点。有学者认为 CYP17 基因是 PCOS 的致病基因之一[7,8]，而另有学者的研究显示 CYP17 基因与 PCOS 发病无明显相关[9,10]。本研究通过分析新疆维汉民族 PCOS 患者与非 PCOS 已婚妇女的 CYP17 基因多态性差异，探讨其与 PCOS 发病机制的关系，以期为该病的临床诊治提供参考。

## 1 资料和方法

### 1.1 一般资料

选择 2015 年 1 月 ~2017 年 2 月我院收治的新疆维汉民族 PCOS 患者 260 例(PCOS 组)和同期在我院门诊检查的健康育龄妇女 237 例(对照组)为研究对象。PCOS 组：纳入标准；符合全国卫生产业企业管理协会妇幼健康产业分会生殖内分泌组发布的 PCOS 诊断标准[11]；排除标准：高泌乳素血症、先天性肾上腺皮质增生、甲状腺疾病、皮质醇增多症、羟化酶缺乏非典型肾上腺皮质增生及应用外源性雄激素者；PCOS 组年龄 20~43 岁，平均(28.46± 5.37)岁；所有患者均有月经不调史，存在闭经、月经量少(月经＜6 次 / 年)或月经频发(月经周期＜20d)，均无排卵性不孕，伴生化及内分泌异常，B 超检查显示卵巢基础卵泡＞10 个，同时伴有 PCOS 家族史及糖尿病家族史。对照组：纳入标准；同期在我院门诊检查确定为健康的育龄妇女，月经周期正常，基础内分泌正常，经阴道 B 超检查证实子宫及卵巢无器质性病变及无多囊样表现；排除标准：近 3 个月使用过激素类药物、有内分泌疾病、高血压疾病者；对照组年龄 21~45 岁，平均(29.71± 5.49)岁；至少有 1 次妊娠史。两组一般临床资料比较差异均无统计学意义(P＞0.05)，具有可比性。

### 1.2 方法

**1.2.1 标本采集** 两组患者均空腹采集外周静脉血 4 mL，PCOS 组因月经不规律，于任意时间采血，对照组月经规律，于月经第 2~4 d 采血，取血清采用化学发光法测定血清卵泡刺激素(Follicle-stimulating hormone，FSH)、黄体生成激素(Luteotropic hormone，LH)，采用酶联免疫吸附法测定睾酮(Testosterone，TES)水平。FSH、LH 及 TES 试剂盒均购于上海盈公生物技术有限公司，严格按照试剂盒说明进行操作。血样本采用乙二胺四乙酸(Ethylene diamine tetraacetic acid，EDTA)抗凝，于 -20℃冰箱保存备用。

**1.2.2 主要试剂与仪器** 基因组 DNA 提取试剂盒购于 Qiagen 公司，Taq DNA 聚合酶及 500 bp DNA Marker 购于宝生物工程有限公司，限制性内切酶 MspA1 购于 NEB 公司，引物 Invitrogen 公司合成，梯度 PCR 仪为 BIORAD 公司生产。

**1.2.3 PCR 扩增** 取保存好的 300 μL 全血抗凝，根据试剂盒说明操作提取 DNA，贮存于 -80℃冰箱备用。引物 F：5'-ttcgcactctggagtcattsa-3'；R：5'-agtcttggtgcccatacgac-3'；PCR 退火温度 64℃，产物长度 536bp，反应 ongoing 体系 20 μL，内含引物、样本 DNA、4 种脱氧核糖三磷酸、Taq DNA 聚合酶、氯化镁；扩增条件为在 96℃温度下预变 2 min，94-96 ℃ 30 s，64℃ 30 s，72℃ 30 s，经历 40 个循环，最后 72℃延伸 7 min。

**1.2.4 CYP17 基因多态性检测** 限制性内切酶 *MspA*1 的酶切总体系 20 μL，包括缓冲液、PCR 扩增产物、*MspA*1 省时内切酶、乙酰基和超纯水等，混匀后在 37 ℃恒温水浴槽孵育 2 h，取酶切产物于含有溴化乙锭和 20 g/L 琼脂糖凝胶中电泳，电压 100 V，电流 70 mA，电泳 20 min 后将胶块放在紫外投影仪下摄像并保存。基因型频率 = 该基因型频数 / 总病例数，等位基因频率 = 每种等位基因出现的频数 / 总等位基因数[12]。

### 1.3 观察指标

(1) 一般情况：比较 PCOS 组与对照组体质量指数(Body Mass Index，BMI)、FSH、LH、TES 及 LH/FSH。(2)CYP17 基因多态性检测结果：比较 PCOS 组与对照组 CYP17 各基因型[正常无碱基置换者(A1A1)、杂合子(A1A2)及突变纯合子(A2A2)]频率和等位基因(A1 及 A2)频率。(3)两组不同基因型与临床资料的关系：比较两组 CYP17 各基因型与 BMI、FSH、LH、TES 及 LH/FSH 的关系。

### 1.4 统计学方法

本研究中所有数据均采用 SPSS18.0 进行统计学分析，BMI、FSH、LH、TES 及 LH/FSH 等计量资料用均数± 标准差($\bar{x}$± s)描述，两组比较行 t 检验，多组比较行方差分析 F 检验；各型基因频率、等位基因频率等计数资料用率(%)描述，组间比较采用 $x^2$ 检验或 fisher 确切概率法分析；以 P＜0.05 为差异有统计学意义。

## 2 结果

### 2.1 两组一般情况的比较

PCOS 组 BMI、FSH 水平低于对照组，PCOS 组 LH、TES 及 LH/FSH 水平高于对照组，差异有统计学意义(P＜0.05)。见表1。

### 2.2 两组 CYP17 基因多态性检测结果比较

PCOS 组 CYP17 基因型 A1A1、A1A2、A2A2 频率分布及等位基因 A1、A2 频率分布与对照组比较差异均无统计学意义(P＞0.05)，见表 2。

表 1 两组 BMI、FSH、LH、TES 及 LH/FSH 水平比较($\bar{x}\pm s$)

Table 1 Comparison of BMI, FSH, LH, TES and LH/FSH levels between two groups($\bar{x}\pm s$)

| Groups | n | BMI(kg/m²) | FSH(IU/L) | LH(IU/L) | TES(mmol/L) | LH/FSH |
|---|---|---|---|---|---|---|
| PCOS group | 260 | 22.13± 2.78 | 4.33± 1.54 | 7.43± 2.51 | 2.88± 1.17 | 1.78± 1.01 |
| Control group | 237 | 23.97± 1.55 | 5.06± 1.82 | 5.24± 1.96 | 2.57± 1.04 | 1.39± 0.98 |
| P | | 0.000 | 0.000 | 0.001 | 0.004 | 0.000 |

表 2 两组 CYP17 各基因型频率及等位基因频率比较[例(%)]

Table 2 Comparison of CYP17 genotype frequency and Allele frequency between two groups[n(%)]

| Groups | n | Genotype | | | Allele | |
|---|---|---|---|---|---|---|
| | | A1A1 | A1A2 | A2A2 | A1 | A2 |
| PCOS group | 260 | 90(34.62) | 109(41.92) | 61(23.46) | 289(55.58) | 231(44.42) |
| Control group | 237 | 81(34.18) | 104(43.88) | 52(21.94) | 266(56.12) | 208(43.88) |
| P | | | 0.843 | | 0.931 | |

### 2.3 两组不同 CYP17 基因型与临床特征的关系

PCOS 组:不同 CYP17 基因型者的 FSH、LH 及 LH/FSH 水平整体比较,差异无统计学意义(P＞0.05);不同 CYP17 基因型者的 BMI、TES 水平整体比较,差异有统计学意义(P＜0.05),两两比较结果显示,BMI 水平 A2A2＞A1A2＞A1A1,差异有统计学意义(P＜0.05);TES 水平 A2A2＜A1A1＜A1A2,差异有统计学意义(P＜0.05)。对照组不同 CYP17 基因型者的 BMI、FSH、LH、TES 及 LH/FSH 水平整体比较,差异均无统计学意义(P＞0.05)。见表 3。

表 3 两组不同 CYP17 基因型者的临床资料比较($\bar{x}\pm s$)

Table 3 Comparison of clinical data of different CYP17 genotypes between two groups ($\bar{x}\pm s$)

| Groups | n | BMI(kg/m²) | FSH(IU/L) | LH(IU/L) | TES(mmol/L) | LH/FSH |
|---|---|---|---|---|---|---|
| PCOS A1A1 group | 90 | 21.24± 2.43 | 4.59± 1.90 | 6.83± 2.54 | 2.98± 1.32 | 1.63± 0.94 |
| PCOS A1A2 group | 109 | 21.97± 2.56▲ | 4.43± 1.21 | 8.55± 3.18 | 3.26± 1.31▲ | 1.91± 1.02 |
| PCOS A2A2 group | 61 | 23.73± 2.18▲■ | 3.85± 1.55 | 6.37± 2.13 | 2.04± 0.85▲■ | 1.79± 0.95 |
| P | | 0.036 | 0.412 | 0.387 | 0.021 | 0.674 |
| Control A1A1 group | 81 | 24.08± 1.44 | 5.27± 1.75 | 4.93± 2.89 | 2.74± 1.27 | 0.96± 0.45 |
| Control A1A2 group | 104 | 23.73± 1.59 | 5.13± 1.62 | 3.59± 1.33 | 2.49± 0.99 | 1.34± 0.82 |
| Control A2A2 group | 52 | 24.36± 1.56 | 4.79± 1.71 | 7.84± 3.91 | 2.36± 1.01 | 3.14± 1.12 |
| P | | 0.531 | 0.557 | 0.156 | 0.678 | 0.212 |

Note: Compared with the PCOS A1A1 group, ▲P＜0.05; Compared with the PCOS A1A2, ■P＜0.05.

## 3 讨论

PCOS 是一种最为常见的女性内分泌疾病,以排卵功能紊乱或丧失、高雄性激素血症为主要特征,临床上主要表现为月经失调、不孕、多毛和 / 或痤疮等,其临床表现的多样性提示可能有多种基因参与了其发病过程[13,14]。PCOS 病因遗传学理论根据该病呈家族群居现象,认为其存在遗传基础,高雄激素血症可能是 PCOS 家族患病共同的遗传特征,受遗传因素或遗传易感性影响[15]。细胞遗传学研究显示 PCOS 的遗传方式可能为常染色体显性遗传或多基因遗传,如雄激素合成的调节基因、与胰岛素合成相关的基因、促性腺激素功能及调节的候选基因、胰岛素合成相关基因等是与 PCOS 相关的遗传基因[16]。然而,目前 PCOS 的病因学研究尚没能证实其是由某个基因位点或突变所引起的,通常认为 PCOS 的发病可能与某一些基因在特定环境下发生作用有关。

CYP17 基因是机体重要基因,由于其表达水平一定程度上决定了机体性激素水平,因而被列为与 PCOS 发病机制有关的基因之一[17,18]。CYP17 基因 5' 端 -34bp 处出现 T/C 单核苷酸多态位点 (包括 4 个 CCACC Sp1 识别位点),而其在 -34bp 处的 T/C 碱基置换则产生新的 Sp1 识别组间(CCACT-CCACC)使得 CYP17 基因转录活性增加、表达上调,从而引起高雄性激素血症 [19-21]。关于 CYP17 基因多态性与 PCOS 发病机制的关系问题,目前学界尚存在较大的争议,甚至出现截然相反的观点。有学者的研究[22,23]认为 CYP17 基因多态性与 PCOS 易感染性和表型变化有密切的关系,而另有学者的研究[24,25]则显示 CYP17 基因多态性与 PCOS 发病没有显著的相关性。

本研究中,PCOS 组 BMI、FSH 水平明显低于对照组,PCOS 组 LH、TES 及 LH/FSH 水平显著高于对照组,提示 PCOS 发病与患者身体状况(BMI)和性激素水平(FSH、LH、TES 及 LH/FSH)改变有关[26,27]。本研究中,CYP17 基因多态性检测结果表明 CYP17 基因型 A1A1、A1A2、A2A2 频率分布及等位基因 A1、A2 频率分布情况,PCOS 组与对照组比较差异无统计学意义,提示 CYP17 基因 -34bp 处 T/C 单核苷酸多态性是人群中一种常见的碱基置换,并不是 PCOS 患者独有的表现,这与

多数学者的研究 [28] 一致，说明 CYP17 基因多态性可能不是 PCOS 表型的主要遗传学因素。PCOS 组不同 CYP17 基因型者的 FSH、LH 及 LH/FSH 水平比较差异无统计学意义，说明性激素 FSH、LH 水平不明显受 CYP17 基因型的影响。BMI 水平 A2A2＞A1A2＞A1A1，三组间比较差异有统计学意义，其原因可能是 A2 影响了脂类代谢，进而使得携带 A2 者 BMI 水平较高。而有研究 [29] 显示 A1A2 型者的 BMI 水平高于 A1A1 和 A2A2，与本研究不一致，产生这种差异的原因可能与样本含量和种族差异有关。本研究表明 TES 水平 A2A2＜A1A1＜A1A2，三组间比较差异有统计学意义。有研究[30]表明睾酮水平 A2A2 型显著高于 A1A1 和 A1A2 型，与本研究不一致，产生这种差异的原因仍考虑为样本含量和种族差异。

综上所述，CYP17 基因 -34bp 处 T/C 单核苷酸多态性是人群中一种常见的碱基置换，与 PCOS 的发病机制无明显的相关性。基于 PCOS 临床表现的多样性，其发病机制可能与少数几个关键基因和微效基因共同作用有关，而不同种族的 PCOS 患者其发病关键基因可能存在差异。

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