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中国浙江省精神疾病患者中FKBP5、ABCB1、MC4R、ANKK1和DRD2基因多态性的分析

杨　倩[1]，周月强[2]，张　骏[1]，冯立锋[1]，徐安宁[3]，金　蓉[3]，张素娟[4]，章健民[5*]

[1]浙江省嘉兴市海宁市第四人民医院精神科，浙江　嘉兴
[2]浙江省嘉兴市海宁市第四人民医院内科，浙江　嘉兴
[3]浙江省舟山市第二人民医院精神科，浙江　舟山
[4]迪安诊断技术集团有限公司，浙江　杭州
[5]浙江省立同德医院(浙江精神卫生中心)精神卫生科，浙江　杭州

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摘　要

目的：探究浙江省患有精神疾病的汉族患者中ABCB1、MC4R、ANKK1、DRD2、FKBP5基因的多态性，以指导药物选择。方法：2023年至2024年期间，从浙江省的三家医院收集了762名患者。通过数字飞行时间质谱法检测了FKBP5 (rs4713916)、ABCB1 (rs1045642)、MC4R (rs489693)、ANKK1 (rs1800497)和DRD2 (rs1799978, rs1799732)的基因多态性。通过性别比较基因型频率，然后与其他汉族人群进行比较。结果：在所有基因型频率方面，男女之间没有统计学上的显著差异。与其他汉族人群相比，FKBP5 rs4713916 (χ^2 =13.000, p = 0.002)、MC4R rs489693 (χ^2 = 17.712, p = 0.000)、DRD2 rs1799978 (χ^2 = 6.620, p = 0.037)和DRD2 rs1799732 (χ^2 = 17.452, p = 0.000)的基因型频率存在显著差异。而在ABCB1 rs1045642 (χ^2 = 1.400, p = 0.506)和ANKK1 rs1800497 (χ^2 = 0.133, p = 0.936)的基因型频率方面未检测到显著差异。结论：本研究尚不清楚为何汉族人群在MC4R rs489693、DRD2 rs1799978和DRD2 rs1799732这些基因多态性方面存在差异。不过，FKBP5、ABCB1、MC4R、ANKK1和DRD2的基因型分布应是药物代谢、反应和毒性选择方面的重要考量因素之一。

关键词

基因型，多态性，等位基因，精神疾病，汉族

Analysis of Gene Polymorphisms of FKBP5, ABCB1, MC4R, ANKK1 and DRD2 in Patients with Psychiatric Disorders in Zhejiang Province, China

*通讯作者。

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Qian Yang[1], Yueqiang Zhou[2], Jun Zhang[1], Lifeng Feng[1], Anning Xu[3], Rong Jin[3], Sujuan Zhang[4], Jianmin Zhang[5*]

[1]Department of Psychiatry, The Fourth People's Hospital of Haining City, Jiaxing City, Zhejiang Province, Jiaxing Zhejiang
[2]Department of Internal Medicine, The Fourth People's Hospital of Haining City, Jiaxing City, Zhejiang Province, Jiaxing Zhejiang
[3]Department of Psychiatry, The Second People's Hospital of Zhoushan City, Zhejiang Province, Zhoushan Zhejiang
[4]Di'an Diagnostic Technology Group Co., Ltd., Hangzhou Zhejiang
[5]Department of Psychiatry, Tongde Hospital of Zhejiang Province (Zhejiang Mental Health Center), Hangzhou Zhejiang

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Abstract

Objective: To investigate the gene polymorphisms of ABCB1, MC4R, ANKK1, DRD2, and FKBP5 in Han Chinese patients with psychiatric disorders in Zhejiang Province to guide drug selection. Methods: From 2023 to 2024, 762 patients were collected from three hospitals in Zhejiang Province. The gene polymorphisms of FKBP5 (rs4713916), ABCB1 (rs1045642), MC4R (rs489693), ANKK1 (rs1800497) and DRD2 (rs1799978, rs1799732) were detected by digital time-of-flight mass spectrometry. The genotype frequencies were compared by gender, and then compared with those of other Han Chinese populations. Results: There were no statistically significant differences in the frequencies of all genotypes between males and females. Compared with other Han Chinese populations, the genotype frequencies of FKBP5 rs4713916 (χ^2 = 13.000, p = 0.002), MC4R rs489693 (χ^2 = 17.712, p = 0.000), DRD2 rs1799978 (χ^2 = 6.620, p = 0.037), and DRD2 rs1799732 (χ^2 = 17.452, p = 0.000) showed significant differences. However, no significant differences were detected in the genotype frequencies of ABCB1 rs1045642 (χ^2 = 1.400, p = 0.506) and ANKK1 rs1800497 (χ^2 = 0.133, p = 0.936). Conclusions: This study does not yet clarify why there are differences in the genetic polymorphisms of MC4R rs489693, DRD2 rs1799978 and DRD2 rs1799732 among the Han Chinese population. However, the genotype distributions of FKBP5, ABCB1, MC4R, ANKK1 and DRD2 should be one of the important considerations in the selection of drug metabolism, response and toxicity.

Keywords

Genotype, Polymorphism, Alleles, Psychiatric Disorders, Han Chinese

1. 引言

遗传因素在精神疾病的发生、发展及治疗过程中起着重要作用。FKBP5、ABCB1、MC4R、ANKK1和DRD2等基因的多态性是当前研究的重点。FKBP5基因位于人类第6号染色体p21.31区域[1]，是与压力相关的精神疾病的重要候选基因[2]，还参与抗抑郁药的代谢[3]。ABCB1基因编码P-糖蛋白(P-GP)，其基因变异会影响P-GP的功能和表达。P-GP活性降低会使抗抑郁药物在大脑中的浓度增加[4]，影响药物的肠道转运，从而影响药代动力学特征[5]-[7]。ABCB1中最常见的研究多态性为1236C>T、2677G>T/A

和 3435C>T，这些多态性与药代动力学和治疗反应有关[8] [9]。黑皮质素 4 受体基因(MC4R)位于人类第 18 号染色体的 q21.3 区域[10]，其主要在下丘脑的副中央核中表达，与食欲调节密切相关，对肥胖的发生起着重要作用[10] [11]，并且是抗精神病药物所致代谢紊乱的候选基因之一[12]-[15]。ANKK1 基因位于第 11 号染色体的 q23.2 区域，与多巴胺受体 D2 (DRD2)基因相邻。ANKK1 的多态性与控制大脑中多巴胺的合成有关，其在 3’末端区域与 DRD2 基因重叠。所有这些都可能通过 ANKK1 基因与多巴胺信号相互作用，并影响信号结果[16]。DRD2 是编码多巴胺-D2 受体的基因，位于第 11 号染色体的 q22~23 区域，由 8 个外显子组成，其遗传变异与多种抗精神病药物的治疗结果相关，包括治疗反应、迟发性运动障碍的发生以及还参与催乳素浓度的调节[17]。在本次研究中，共收集了 762 名患有精神疾病患者的数据，以调查 FKBP5、MC4R、ABCB1、ANKK1 和 DRD2 这些基因的多态性，为药物的精准治疗提供参考依据。

2. 材料与方法

2.1. 研究对象

2023 年至 2024 年期间，从浙江省三个医院收集了 762 名患有精神疾病患者。对 FKBP5 rs4713916、MC4R rs489693、ABCB1 rs1045642、ANKK1 rs1800497、DRD2 rs1799978 和 DRD2 rs1799732 这些基因的多态性进行了检测。由于本文主要研究基因频率，与病程、是否首次发病、用药史无关，故未采集相关临床信息。

2.2. 研究方法

基因多态性测试由迪安诊断技术集团进行。将 2 毫升肘静脉血置于 EDTA 抗凝管中，然后轻轻颠倒并搅拌 5~6 次以避免溶血。从全血样本中提取 DNA 后，应用 DP-TOF 时间飞行质谱检测系统来检测候选基因的多态性位点。

详细步骤如下：(1) 多重 PCR 扩增：设计针对目标位点的特异性多重 PCR 引物。以人类基因组 DNA 为模板，通过多重 PCR 引物扩增包含待检测单核苷酸多态性(SNP)的目标片段；(2) dNTP 反应去除：加入虾碱性磷酸酶(SAP)以去除反应溶液中的 dNTP；(3) 单碱基延伸：向 SNP 位点添加特定的单碱基延伸引物，从而在 PCR 产物中仅形成一个碱基的差异；(4) 共结晶：将单碱基延伸产物转移到模板上，并将其加载到机器中。用树脂进行脱盐处理后，自动将它们点印在芯片矩阵上，形成共晶体；(5) 脱附电离：在质谱仪的真空管中，共晶体被强激光激发，核酸分子被解吸为离子；(6) 质谱飞行：带正电荷的单电荷离子在真空管中朝高灵敏度检测器加速。离子在电场中的飞行时间与其质量成正比。离子的质量越小，到达检测器的速度就越快。因此，不同质量的离子可以通过飞行时间来区分；(7) 数据分析：检测器将信号转换为可见的峰图。每个基因型都有一个独特的质量。软件会自动分析相应的碱基类型，从而获得最终的基因分型结果。

3. 统计分析

(1) 使用 SPSS 26.0 的卡方检验来确定研究样本的基因型频率是否符合哈迪－温伯格平衡(HWE)，其中 p 值大于 0.05 则认为符合 HWE，(2) 性别之间是否存在统计学差异，以及(3) 与之前的相关研究相比是否存在统计学差异。对于(2)和(3)，p 值小于 0.05 则认为具有统计学意义。

4. 结果

本研究纳入了 762 名患者，其中 481 名为女性(63.1%)。患者的平均年龄为 29.6 岁，标准差为 17.8 岁(男性为 29.8 岁，标准差为 17.52 岁，女性为 29.42 岁，标准差为 17.90 岁)，年龄范围在 11 至 89 岁之间。所有测试的基因型均符合哈温平衡(HWE) (表 1)，且性别之间无统计学差异(表 2)。FKBP5 rs4713916、

ABCB1 rs1045642、MC4R rs489693、ANKK1 rs1800497、DRD2 rs1799978、DRD2 rs1799732 的基因型频率如表 2 所示。

本文将所有收集到的数据与其他汉族人群的基因位点进行比较分析。与其他汉族人群相比，FKBP5 rs4713916 (χ^2 =13.000, p = 0.002)、MC4R rs489693 (χ^2 = 17.712, p = 0.000)、DRD2 rs1799978(χ^2 = 6.620, p = 0.037)和 DRD2 rs1799732 (χ^2 = 17.452, p = 0.000)的基因型频率存在显著差异。而在 ABCB1 rs1045642 (χ^2 = 1.400, p = 0.506)和 ANKK1 rs1800497 (χ^2 = 0.133, p = 0.936)的基因型频率方面未检测到显著差异(表 3)。

Table 1. Hardy-Weinberg equilibrium analysis of the genotypes studied in this paper
表 1. 本文所研究基因型的 Hardy-Weinberg 平衡分析

SNP	基因型	人数(%)	χ^2	HWE-P
FKBP5 rs4713916	CC	450 (59.06)	1.566	0.457
	CT	279 (36.61)		
	TT	33 (4.33)		
ABCB1 rs1045642	CC	313 (41.10)	0.331	0.848
	CT	345 (45.30)		
	TT	104 (13.60)		
MC4R rs489693	AA	37 (4.86)	0.484	0.785
	CA	247 (32.41)		
	CC	478 (62.73)		
ANKK1 rs1800497	AA	117 (15.35)	0.000	1.000
	GA	363 (47.64)		
	GG	282 (37.01)		
DRD2 rs1799978	AA	494 (64.83)	1.231	0.540
	GA	233 (30.58)		
	GG	35 (4.59)		
DRD2 rs1799732	CC	593 (77.82)	1.067	0.587
	DEL_C	155 (20.34)		
	DEL_DEL	14 (1.84)		

Table 2. Comparison of genotype frequencies between genders
表 2. 性别间基因型频率的比较

基因	基因型	男性，人数(%)	女性，人数(%)	χ^2	p 值
FKBP5 rs4713916	CC	159 (56.58)	291 (60.50)	1.764	0.414
	CT	107 (38.08)	172 (35.76)		
	TT	15 (5.34)	18 (3.74)		
ABCB1 rs1045642	CC	121 (43.06)	192 (39.92)	0.724	0.696
	CT	123 (43.77)	222 (46.15)		
	TT	37 (13.17)	67 (13.93)		

续表

MC4R rs489693	AA	11 (3.91)	26 (5.41)		
	CA	100 (35.59)	147 (30.56)	2.547	0.280
	CC	170 (60.50)	308 (64.03)		
ANKK1 rs1800497	AA	40 (14.23)	77 (16.01)		
	GA	139 (49.47)	224 (46.57)	0.736	0.692
	GG	102 (36.30)	180 (37.42)		
DRD2 rs1799978	AA	178 (63.35)	316 (65.70)		
	GA	94 (33.45)	139 (28.90)	3.228	0.199
	GG	9 (3.20)	26 (5.40)		
DRD2 rs1799732	CC	218 (77.58)	375 (77.96)		
	DEL_C	58 (20.64)	97 (20.17)	0.031	0.985
	DEL_DEL	5 (1.78)	9 (1.87)		

Table 3. Comparison of the genotype of the current sample with that of similar studies
表 3. 将当前样本的基因型与类似研究进行比较

SNP	基因型	本研究－人数(%)	既往研究－人数(%)	χ^2	p 值
FKBP5 rs4713916	CC	450 (59.06)	489 (51.90) [18]		
	CT	279 (36.61)	381 (40.45)	13.000	0.002
	TT	33 (4.33)	72 (7.64)		
ABCB1 rs1045642	CC	313 (41.10)	189 (37.80) [19]		
	CT	345 (45.30)	240 (48.00)	1.400	0.506
	TT	104 (13.60)	71 (14.20)		
MC4R rs489693	AA	37 (4.86)	35 (10.26) [20]		
	CA	247 (32.41)	130 (38.12)	17.712	0.000
	CC	478 (62.73)	176 (51.61)		
ANKK1 rs1800497	AA	117 (15.35)	14 (14.00) [21]		
	GA	363 (47.64)	48 (48.00)	0.133	0.936
	GG	282 (37.01)	38 (38.00)		
DRD2 rs1799978	AA	494 (64.83)	418 (66.35) [22]		
	GA	233 (30.58)	166 (26.35)	6.620	0.037
	GG	35 (4.59)	46 (7.30)		
DRD2 rs1799732	CC	593 (77.82)	532 (84.44) [22]		
	DEL C	155 (20.34)	78 (12.38)	17.452	0.000
	DEL DEL	14 (1.84)	20 (3.17)		

5. 讨论

FKBP5、ABCB1、MC4R、ANKK1 和 DRD2 这些基因在药物代谢和反应过程中都发挥着重要作用，

对这些基因型频率的分析能够指导准确选择不同的药物。在本研究中，对 762 名精神疾病患者进行了 FKBP5 rs4713916、ABCB1 rs1045642、MC4R rs489693、ANKK1 rs1800497、DRD2 rs1799978 和 DRD2 rs1799732 这些基因型的检测。上述基因型频率在性别方面没有显著差异。

FKBP5 rs4713916 在一些欧洲国家与抑郁症的遗传易感性有关，但在亚洲人群中的突变率较低，因此在亚洲人群中研究较少[23]。本研究与既往汉族相关研究存在统计学差异，可能的原因是研究样本量较小，未来还需增加样本量。FKBP5 rs4713916 多态性与情绪障碍患者治疗反应率之间存在显著的遗传关联，且携带 T 等位基因的患者相比携带 C 等位基因的患者具有更高的治疗反应率[24]。

ABCB1 基因编码 P-GP 效应转运体，参与药物转运。ABCB1 基因 rs1045642 的单核苷酸多态性与药物的反应性和安全性密切相关[25]。研究表明，携带 rs1045642 TT 基因型的患者对抗癫痫药物的反应比其他基因型的患者更好[25]。而抗癫痫药物通常用作情绪稳定剂，因此 TT 基因型患者在使用情绪稳定剂时可能疗效更佳。同时，ABCB1 基因 rs1045642 的多态性会影响抑郁症的反应时间，携带 TT 基因型的个体与携带 CC 或 CT 基因型的个体相比，其反应时间更短[6]。本研究中仅有 13.6%的患者具有 ABCB1 rs1045642 TT 基因型，这与其他中国汉族人群的研究结果无统计学差异，表明汉族人群中的大多数患者使用抗抑郁药时会经历更长的缓解期。因此，我们可以初步判断具有 rs1045642 TT 基因型患者的预后情况。

MC4R (黑皮质素 4 受体)在下丘脑神经细胞中表达，与肥胖、胰岛素抵抗以及抗精神病药物引起的代谢紊乱有关[12] [26]。与 CA 和 CC 基因型相比，携带次要等位基因纯合 AA 基因型的患者在使用第二代抗精神病药物后体重显著增加[27]。在本研究中，AA 基因型的比例为 4.86%。对于 MC4R rs489693 的 AA 基因型患者，医生应选择体重增加较小的药物，以提高患者的用药依从性。关于 MC4R 基因与抗抑郁药导致体重增加相互作用的研究较为少见，未来还需要更多的研究。

ANKK1 基因与多巴胺受体 D2 (DRD2)基因的功能密切相关，并与多种精神疾病的发生有关，如创伤后应激障碍[28]、精神分裂症[29]。来自埃及的一项研究显示，rs1800497 的 G 等位基因影响精神分裂症的风险[30]。它还与不良药物反应有关，如锥体外系反应[31]和体重增加[32]。AA 或 AG 基因型相较于纯合子 GG 基因型的携带者，患代谢综合征的风险更高[16]。对于携带 A 等位基因的个体，我们需要考虑抗精神病药物带来的代谢风险，并告知这些患者他们需要控制饮食并增加运动以降低患代谢综合征的风险。

DRD2 基因与多种精神疾病的发生和发展有关，不同基因位点的单核苷酸多态性与精神疾病之间的关联并不一致。DRD2 rs1799732 和 DRD2 rs1799978 基因型与华北地区的其他汉族人群不同[22]。中国是一个地域辽阔的国家，南北方存在巨大差异，其人口的基因型也可能有所不同。此外，上述研究仅包括对照组和精神分裂症患者，而我们研究中的受试者来自门诊服务，大多数患者可能患有焦虑和抑郁障碍，少数患者可能患有精神分裂症。因此，DRD2 rs1799732 和 DRD2 rs1799978 基因型之间的这些差异可能是由于样本选取、地区差异或不同的疾病诊断所导致的。还需要更多的研究来确认中国北方和南方地区的 DRD2 基因型是否存在差异。研究表明，难治性精神分裂症患者中 DRD2 rs1799978 G 等位基因的频率较低[33]。rs1799978 的单核苷酸多态性与第二代抗精神病药物的疗效和不良反应有关[34]，而利培酮对 A 等位基因携带者更有效[35]。携带 rs1799978 G 等位基因和 rs1799732 缺失基因的使用奥氮平的患者反应较慢、疗效较差、体重增加更多、处方剂量更高且耐受性更强[36]。根据基因监测的结果，临床医生应考虑对 DRD2 rs1799978 A 基因型携带者使用利培酮，但对于 rs1799978 G 基因型携带者和 rs1799732 缺失基因携带者应避免使用奥氮平。

6. 结论

不同的基因多态性对抗精神病药物和抗抑郁药物的使用具有指导作用。在临床工作中，医生可以根据基因检测结果选择疗效更好且副作用更少的药物。然而，单个基因多态性对精神疾病的发生和发展以

及药物代谢的影响有限[37]。除了单个基因多态性外，未来还可以增加更多的单倍型分析，以加深对遗传变异与精神疾病及药物使用之间关系的理解。

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