· 论著 ·

DRD2 基因 rs2587552 多态性对儿童肥胖干预效果的影响:一项前瞻性、平行对照试验

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[摘 要] **目的**:在我国儿童中探索 *DRD2* 基因 rs2587552 多态性与肥胖干预效果的关联,为将来开展基于遗传背景的个性化儿童肥胖干预提供科学依据。**方法**:基于一项儿童肥胖干预研究的多中心整群随机对照试验,纳入北京地区 8 所小学的 382 名儿童作为研究对象,采集唾液,提取 DNA,检测 *DRD2* 基因 rs2587552 多态性,并分析基因与干预措施对儿童肥胖干预效果(包括体质量、体重指数、体重指数 Z 评分、腰围、臀围、腰臀比、腰围身高比和体脂百分比指标)的交互作用。**结果**:干预组中未发现 rs2587552 多态性与儿童臀围和体脂百分比的变化相关($P>0.05$),而在对照组中,携带 rs2587552 位点 A 等位基因的儿童相比于非携带儿童,其臀围和体脂百分比升高更多($P<0.001$)。*DRD2* 基因 rs2587552 多态性与干预措施对儿童臀围和体脂百分比存在交互作用(P 分别为 0.007 和 0.015)。与对照组相比,干预组携带 A 等位基因的儿童相比于非携带儿童,臀围下降(−1.30 cm,95% *CI*:−2.25 ~ −0.35,$P=0.007$),体脂百分比下降(−1.34%,95% *CI*:−2.42 ~ −0.27,$P=0.015$)。显性与加性遗传模型的结果较为一致(臀围下降:−0.66 cm,95% *CI*:−1.28 ~ −0.03,$P=0.041$;体脂百分比下降:−0.69%,95% *CI*:−1.40 ~ 0.02,$P=0.056$)。未发现 rs2587552 多态性与干预措施对其他儿童肥胖相关指标存在交互作用($P>0.05$)。**结论**:在 *DRD2* 基因 rs2587552 位点携带 A 等位基因的儿童对干预措施更加敏感,干预期间在臀围和体脂百分比指标上获得更多改善,提示未来可基于儿童 rs2587552 位点的基因型开展个性化的生活方式干预。

[关键词] 儿童肥胖;多态性,单核苷酸;生活方式;干预效果
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Influence of rs2587552 polymorphism of *DRD2* gene on the effect of a childhood obesity intervention: A prospective, parallel-group controlled trial

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ABSTRACT **Objective**: To explore the association between rs2587552 polymorphism (has a strong linkage disequilibrium with rs1800497 which had been found in many studies to be related to obesity, $r^2=0.85$) of *DRD2* gene and the effect of a childhood obesity intervention in Chinese population, and provide a scientific basis for future personalized childhood obesity intervention based on genetic background. **Methods**: From a multi-center cluster randomized controlled trial studying the effect of a childhood obesity intervention, we enrolled 382 children from 8 primary schools (192 and 190 children from intervention and control groups, respectively) in Beijing as study subjects. Saliva was collected and DNA was extracted to detect the rs2587552 polymorphism of *DRD2* gene, and the interactions between the gene and study arms on childhood obesity indicators [including body weight, body mass index (BMI), BMI Z-score, waist circumference, hip circumference, waist-to-hip ratio, waist-to-height ratio, and body fat percentage] were analyzed. **Results**: No association was found between rs2587552 polymorphism and the changes in hip circumference or body fat percentage in the intervention group ($P>0.05$). However, in the control group, children carrying the A allele at *DRD2* rs2587552 locus showed a greater increase in hip circumference and body fat percentage compared with those not carrying A allele ($P<0.001$). There were interactions between rs2587552 polymorphism of *DRD2* gene and study arms on the changes in hip circumference and body fat percentage ($P=0.007$ and 0.015, respectively). Compared with the control group, children in the intervention group carrying the A allele at *DRD2* rs2587552 locus showed decrease

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in hip circumference by (−1.30 cm, 95% *CI*: −2.25 to −0.35, *P* = 0.007) and decrease in body fat percentage by (−1.34%, 95% *CI*: −2.42 to −0.27, *P* = 0.015) compared with those not carrying A allele. The results were consistent between the dominant model and the additive model (hip circumference: −0.66 cm, 95% *CI*: −1.28 to −0.03, *P* = 0.041; body fat percentage: −0.69%, 95% *CI*: −1.40 to 0.02, *P* = 0.056). No interaction was found between rs2587552 polymorphism and study arms on the changes in other childhood obesity-related indicators (*P* > 0.05). **Conclusion**: Children carrying the A allele at rs2587552 polymorphism of *DRD2* gene are more sensitive to intervention and showed more improvement in hip circumference and body fat percentage after the intervention, suggesting that future personalized childhood obesity lifestyle intervention can be carried out based on the rs2587552 polymorphism of *DRD2* gene.

KEY WORDS Pediatric obesity; Polymorphism, single nucleotide; Life style; Intervention effect

儿童肥胖是严重的公共卫生问题。1975—2016年全球儿童肥胖率增长近8倍[1],我国儿童肥胖率也不断升高[2],近几年新型冠状病毒疫情的流行,进一步加剧了儿童肥胖问题的严峻性[3]。儿童肥胖不仅会引起近期代谢紊乱[4]、抑郁、焦虑[5-6]等身心健康问题,还会增加成年期发生2型糖尿病、冠状动脉疾病等慢性疾病的风险[7]。已有多项研究证实生活方式干预可有效预防和控制肥胖[8-10],但不同个体对同一干预方案的敏感度不同,遗传背景是其影响因素之一[11],因此亟需阐明基因与儿童肥胖干预效果的关联。目前,相关研究多关注脂肪与肥胖相关(fat mass and obesity-associated, *FTO*)基因[12-13]和黑素皮质素受体-4(melanocortin-4 receptor, *MC4R*)基因[14-15]等,较少关注多巴胺受体 D_2(dopamine receptor D_2, *DRD2*)基因。多巴胺信号在与奖赏和中枢饱腹感信号密切相关的纹状体中起着关键作用[16],因此,*DRD2* 基因可能通过影响上述信号作用于儿童肥胖的发生和发展。

前期系统综述报道[17],到目前为止,仅有2篇研究分析了 *DRD2* 基因对儿童肥胖干预效果的影响[18-19]。Roth 等[18]在德国423名超重肥胖儿童中开展了为期1年的生活方式干预,分析了 *DRD2* 基因 rs1800497 多态性(较多研究报道其与肥胖相关[19-20])与干预期间体重指数(body mass index, BMI)Z评分变化的关联。Zhu 等[21]对我国109名肥胖儿童在首次门诊时实施了生活方式干预,并在8年后随访,研究 *DRD2* 基因 rs1076562、rs2075654、rs4586205 多态性与肥胖缓解率的关联。但尚未有研究探索 rs1800497 位点多态性对我国儿童肥胖干预效果的影响。

因此,本研究将基于一项整群随机对照干预试验(randomized controlled trials, RCT),在我国儿童中探讨 *DRD2* 基因 rs2587552(与 rs1800497 位点强连锁不平衡,r^2 = 0.85)多态性与儿童肥胖干预效果的关联,为将来开展基于遗传背景的个性化儿童肥胖干预提供科学依据。

1　资料与方法

1.1　研究对象

研究对象来自一项多中心(北京、山西长治、新疆乌鲁木齐)RCT[22],共纳入24所小学1 392名儿童,先根据地区进行分层,之后在每层将学校按1∶1的比例随机分入干预组与对照组。干预组儿童接受改善饮食和运动行为的综合干预,对照组儿童则保持日常学习和生活状态,不额外接受干预。该试验2018年9月开展基线调查,持续干预一学年(9个月),2019年6月结束干预。本研究选取参加这项干预试验且完成基因检测的北京地区儿童,排除身体测量指标不完整或未通过基因检测质量控制者,最终纳入382名儿童。本研究经北京大学生物医学伦理委员会审查批准(IRB00001052-18021, IRB00001052-20058),已获得儿童和家长的书面知情同意。

1.2　肥胖相关指标的测量与计算

在基线调查和干预结束(基线调查9个月)时测量肥胖相关指标:身高、体质量、腰围、臀围和体脂百分比。除体脂百分比测量1次外,每个指标至少测量2次,且体质量、身高、腰围和臀围的相邻2次测量值差不得超过0.1 kg、0.5 cm和1.0 cm,否则进行第3次测量,最终选取符合上述测量误差要求的相邻2次测量值并取平均值。计算 BMI[体质量(kg)/身高^2(m^2)]、腰臀比(腰围/臀围)以及腰围身高比(腰围/身高);根据世界卫生组织参考值计算 BMI Z评分[23];根据2018年《学龄儿童青少年超重与肥胖筛查》标准[24]判定儿童是否超重或肥胖。

1.3　DNA样本采集和基因多态性检测

随访调查时采集研究对象的唾液,通过口腔拭子基因组 DNA 提取试剂盒(离心柱型)提取口腔上皮细胞中的基因组 DNA,并用专为亚洲人群设计的高通量基因分型芯片(Illumina ASA)检测基因多态性。根据基因检测的质量控制标准[25],排除单核苷酸多态性(single nucleotide polymorphism, SNP)缺失

率 >2%、最小等位基因频率(minor allele frequency, MAF) <5%、Hardy-Weinberg 平衡检验 P 值 $<10^{-6}$、杂合率大于 3 个标准差、有亲属关系的儿童。对通过质量控制的基因数据进行插补[26],并对插补后的基因数据重复上述质量控制过程。数据的质量控制与插补用 PLINK 1.90 和 IMPUTE2 软件进行。本研究分析的 *DRD2* 基因 rs2587552 多态性来自插补后的基因数据,已通过质量控制。

1.4 统计学分析

比较干预组和对照组儿童基线特征有无差异时,对分类变量使用 χ^2 检验,对连续变量使用 t 检验。采用多元线性回归模型分析 rs2587552 多态性与干预效果的关联:用模型①分析基因与基线儿童肥胖相关指标水平的关联;用模型②分别在干预组和对照组中分析基因与肥胖相关指标变化(随访 - 基线)的关联;用模型③分析基因与干预措施对肥胖相关指标变化的交互作用,即检验模型③中的 β_1 系数是否为 0。由于样本量较少,主要结果分析时将 AA/AG 基因型儿童合并为一组,与 GG 基因型儿童进行比较;敏感性分析时,采用加性遗传模型,以验证主要结果的稳健性。用 R 4.1.0 软件进行分析,以双侧检验 $P<0.05$ 为差异具有统计学意义。

分析模型:①基线肥胖相关指标 $=\beta_0+\beta_1\times$ 基因 $+\beta_2\times$ 年龄 $+\beta_3\times$ 性别 $+\varepsilon$;② 9 个月肥胖相关指标 $=\beta_0+\beta_1\times$ 基因 $+\beta_2\times$ 年龄 $+\beta_3\times$ 性别 $+\beta_4\times$ 基线指标水平 $+\varepsilon$;③ 9 个月肥胖相关指标 $=\beta_0+\beta_1\times$(基因 $\times$ 干预措施) $+\beta_2\times$ 基因 $+\beta_3\times$ 干预措施 $+\beta_4\times$ 年龄 $+\beta_5\times$ 性别 $+\beta_6\times$ 基线指标水平 $+\varepsilon$。

2 结果

2.1 研究对象基线特征

干预组和对照组儿童的基线特征相似($P>0.05$,表 1)。382 名儿童中,*DRD2* 基因 rs2587552 位点基因型为 AA、AG、GG 的分别有 77、185、120 名,不同基因型儿童的基线肥胖相关指标差异均无统计学意义($P>0.05$,表 2)。

表 1 研究对象基线调查特征

Table 1 Baseline characteristics of subjects

Characteristics	Intervention group ($n=192$)	Control group ($n=190$)	P
Age/years	9.55 ± 0.29	9.56 ± 0.31	0.596
Female	90 (46.87)	97 (51.05)	0.475
Overweight/Obesity	74 (38.54)	74 (38.95)	1.000
Obesity	48 (25.00)	41 (21.58)	0.503
Weight/kg	36.96 ± 9.35	35.97 ± 8.95	0.287
BMI/(kg/m^2)	18.57 ± 3.71	18.23 ± 3.29	0.333
BMI Z-score	0.72 ± 1.46	0.61 ± 1.40	0.426
Waist circumference/cm	65.00 ± 10.45	64.42 ± 9.92	0.573
Hip circumference/cm	76.45 ± 8.09	76.42 ± 7.84	0.971
Waist-to-hip ratio	0.85 ± 0.06	0.84 ± 0.05	0.232
Waist-to-height ratio	0.46 ± 0.07	0.46 ± 0.06	0.735
Body fat percentage/%	21.16 ± 10.77	20.25 ± 9.43	0.379

Data are expressed as n(%) or $\bar{x}\pm s$. P values were calculated by χ^2 test for categorical variables and t-test for continuous variables.

2.2 *DRD2* 基因 rs2587552 多态性与儿童肥胖干预效果的关联

DRD2 基因 rs2587552 多态性与儿童肥胖干预效果的关联结果见表 3 和图 1。基线至随访调查时,干预组中未发现 rs2587552 多态性与肥胖相关指标的变化相关,而在对照组中携带 rs2587552 位点 A 等位基因的儿童相比于非携带儿童,其体质量、BMI、BMI Z 评分、腰围、臀围以及体脂百分比升高更多,腰围身高比降低更少($P<0.05$)。

基因与干预组别对肥胖相关指标变化的交互作用分析结果显示,与对照组相比,干预组携带 A 等位基因的儿童相比于非携带儿童,臀围下降(−1.30 cm, 95% *CI*: −2.25 ~ −0.35, $P=0.007$),体脂百分比下降(−1.34%, 95% *CI*: −2.42 ~ −0.27, $P=0.015$)。将遗传模型从显性模型转换为加性模型进行敏感性分析,结果较为一致(臀围: −0.66 cm, 95% *CI*: −1.28 ~ −0.03, $P=0.041$;体脂百分比: −0.69%, 95% *CI*: −1.40 ~ 0.02, $P=0.056$)。

表 2　rs2587552 多态性与基线调查肥胖相关指标水平的关联

Table 2　The associations between rs2587552 polymorphism and the level of obesity-related indicators at baseline

Indicators	AA/AC ($n=262$)	GG ($n=120$)	P
Male	134 (51.15)	61 (50.83)	
Overweight/Obesity	95 (36.26)	53 (44.17)	0.136
Obesity	59 (22.52)	30 (25.00)	0.576
Age/years	9.57 ± 0.30	9.52 ± 0.30	
Weight/kg	36.38 ± 9.28	36.65 ± 8.91	0.592
BMI/(kg/m^2)	18.35 ± 3.59	18.51 ± 3.33	0.573
BMI Z-score	0.63 ± 1.46	0.74 ± 1.35	0.440
Waist circumference/cm	64.59 ± 10.41	64.97 ± 9.70	0.592
Hip circumference/cm	76.29 ± 8.06	76.76 ± 7.75	0.425
Waist-to-hip ratio	0.84 ± 0.06	0.84 ± 0.05	0.932
Waist-to-height ratio	0.46 ± 0.06	0.46 ± 0.06	0.604
Body fat percentage/%	20.62 ± 10.39	20.89 ± 9.55	0.733

Data are expressed as $n(\%)$ or $\bar{x} \pm s$. P values were calculated by Logistic regression or multiple linear regression adjusted for age and gender.

表 3　rs2587552 多态性与干预措施对干预后肥胖相关指标变化的交互作用

Table 3　The interactions between rs2587552 polymorphism and study arms on the changes in obesity-related indicators after intervention

Obesity-related indicators	SNP's effects in intervention group			SNP's effects in control group			Interaction (intervention-control)	
	AA/AG ($n=125$)	GG ($n=67$)	P^a	AA/AG ($n=137$)	GG ($n=53$)	P^a	β coefficient (95% CI)[b]	P^b
ΔWeight/kg	2.47 ± 2.03	2.26 ± 2.75	0.372	3.73 ± 3.39	2.63 ± 2.24	0.029	−0.738 (−1.880 to 0.404)	0.205
ΔBMI/(kg/m^2)	−0.05 ± 0.84	−0.15 ± 1.20	0.507	0.50 ± 1.30	−0.01 ± 0.90	0.006	−0.430 (−0.910 to 0.049)	0.078
ΔBMI Z-score	−0.22 ± 0.34	−0.30 ± 0.52	0.268	0.005 ± 0.64	−0.21 ± 0.36	0.008	−0.162 (−0.372 to 0.049)	0.132
ΔWaist circumference/cm	1.20 ± 3.30	0.72 ± 2.94	0.289	1.65 ± 2.84	0.62 ± 3.29	0.014	−0.702 (−2.039 to 0.635)	0.302
ΔHip circumference/cm	2.33 ± 2.20	2.21 ± 2.00	0.734	3.01 ± 2.12	1.62 ± 2.61	<0.001	−1.302 (−2.251 to −0.353)	0.007
ΔWaist-to-hip ratio	−0.01 ± 0.04	−0.01 ± 0.04	0.471	−0.01 ± 0.03	−0.01 ± 0.03	0.826	0.003 (−0.011 to 0.017)	0.671
ΔWaist-to-height ratio	−0.01 ± 0.02	−0.01 ± 0.02	0.348	−0.004 ± 0.02	−0.01 ± 0.02	0.011	−0.006 (−0.015 to 0.004)	0.245
ΔBody fat percentage/%	−1.03 ± 2.79	−1.10 ± 2.01	0.894	0.46 ± 2.30	−0.85 ± 2.99	<0.001	−1.342 (−2.419 to −0.266)	0.015

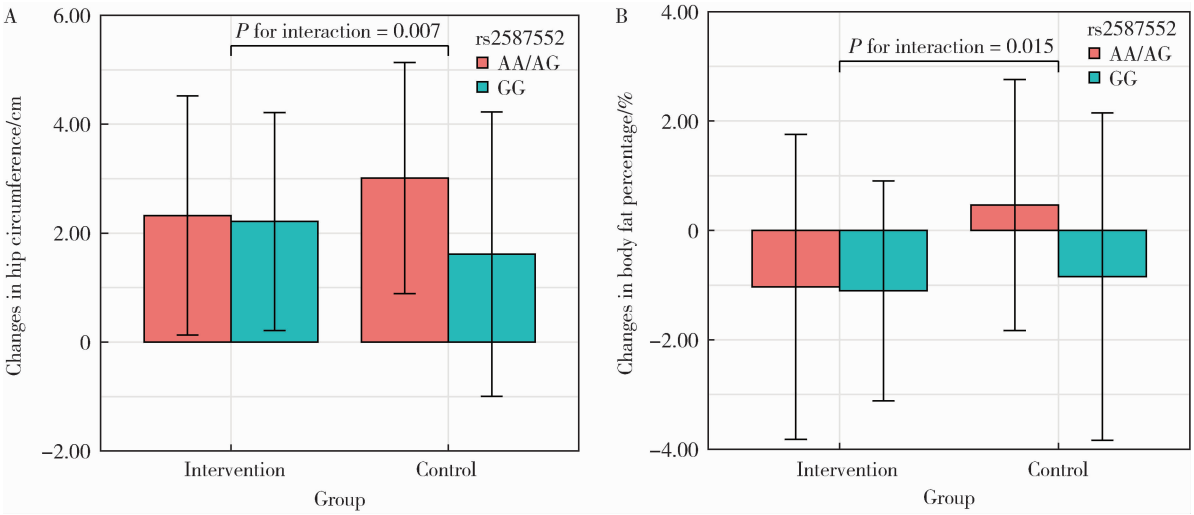
Data are expressed as $\bar{x} \pm s$. Δ = the value of indicators after the intervention − baseline value of indicators. rs2587552 genotypes were assigned by dominant genetic model (AA/AG = 1; GG = 0). a, the correlation P values of gene item were calculated by linear regression model adjusted for age, gender, and baseline value of indicators; b, the correlation P values of interaction item (gene-study arm) were calculated by linear regression model adjusted for age, gender, and baseline value of indicators.

3　讨论

本研究发现 *DRD2* 基因 rs2587552 多态性与儿童肥胖干预效果相关。与对照组相比,干预组携带 rs2587552 位点 A 等位基因的儿童相比于非携带儿童,干预后臀围增加更少,体脂百分比降低更多,这说明 rs2587552 多态性与干预措施对臀围和体脂百分比存在交互作用,即 rs2587552 多态性调节了儿童肥胖干预效果。

针对 *DRD2* 基因 rs1800497(或其强连锁位点)多态性在儿童肥胖干预效果中的作用,Roth 等[18]曾基于单臂干预研究设计(未设立对照组),在 423 名德国超重肥胖儿童中探索该位点与 BMI Z 评分变化的关联,发现 TT 基因型儿童 BMI Z 评分下降较少,即干预效果较差。本研究中干预组携带 rs2587552 位点 A 等位基因(与 rs1800497 位点 T 等位基因对

应)儿童相比于非携带儿童,有 BMI 下降更少的趋势,但结果没有统计学意义。研究结果之间的差异可能与超重肥胖儿童所占比例以及分析遗传模型不同有关。



Data are expressed as $\bar{x} \pm s$. *P* values were tested for the interactions between rs2587552 genotypes and study arms on the changes in hip circumference or body fat percentage.

图 1 干预组和对照组 rs2587552 不同基因型儿童的臀围(A)和体脂百分比(B)变化情况

Figure 1 The changes in hip circumference (A) and body fat percentage (B) of children with different genotypes of rs2587552 in intervention and control groups

本课题组前期系统梳理相关研究后发现,国际上目前开展的基因与儿童肥胖干预效果的关联研究多集中在 *FTO*、*MC4R* 等基因,且仅纳入超重和肥胖儿童,主要关注 BMI 和 BMI Z 评分,未见关注体脂百分比和腰臀比等肥胖相关指标,而且我国相关研究较少[17]。本研究基于整群 RCT 研究设计,分析了 *DRD2* 基因 rs2587552 多态性与干预期间儿童多个肥胖相关指标变化的关联,结果提示未来可基于儿童 rs2587552 位点的基因型开展个性化的生活方式干预,重点关注 rs2587552 位点 AA/AG 基因型的儿童,尽量使不同基因型儿童的干预效果最大化。

Cardel 等[27]发现 rs1800497 位点 TT 基因型儿童相比于 CT/CC 基因型儿童,总能量摄入和来自糖的热量所占百分比更高,这提示 *DRD2* 基因 rs2587552 多态性可能通过影响饮食行为影响肥胖的发生。然而,本研究未发现 *DRD2* 基因 rs2587552 多态性对除儿童臀围和体脂百分比以外的肥胖指标有影响,可能是因为基因影响不同肥胖相关指标的机制有差异[28]。将来需要相关生理学研究深入阐明该位点多态性对儿童肥胖干预效果的作用机制。

本研究的优势在于:首先,RCT 研究设计可较好地控制混杂偏倚,相比于单臂干预试验相关结果中会混杂基因在"自然环境"中的作用,RCT 研究可通过将基因在干预组(干预环境)和对照组(自然环境)中的作用相减的方式,更为精准地回答研究问题;其次,本研究使用多个肥胖相关指标进行分析,可更为综合地体现个体肥胖程度;再次,敏感性分析结果与主要结果基本一致,体现了研究结果的稳健性。然而,本研究样本量较小,可能会导致统计效能不足。

综上所述,儿童肥胖干预效果与 *DRD2* 基因 rs2587552 多态性相关,携带该位点 A 等位基因的儿童对生活方式干预更加敏感,干预期间在臀围和体脂百分比指标上获得更多改善。本研究为将来开展基于遗传背景的个性化儿童肥胖干预提供了科学依据。

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