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在线全文

正常孕妇及妊娠糖尿病患者*apoA1*基因启动子区－75 G/A多态性的研究*

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【摘要】 目的 研究载脂蛋白A1（apoA1）基因启动子区－75 G/A（*apoA*1 －75 G/A）单核苷酸多态性是否与妊娠糖尿病（GDM）有关联，为探讨本病的分子遗传基础提供依据。**方法** 应用聚合酶链反应-限制性片段长度多态性（PCR-RFLP）技术检测1 022名正常妊娠对照者和626例GDM患者*apoA*1 －75 G/A基因多态性。酶法测定总胆固醇（TC）、三酰甘油（TG）、高密度脂蛋白胆固醇（HDL-C）、低密度脂蛋白胆固醇（LDL-C）和血糖（Glu），化学发光法测定血浆胰岛素（INS）。免疫透射比浊法测定载脂蛋白A1（apoA1）和B（apoB）水平。**结果** *apoA*1 －75 G/A多态位点等位基因G、A频率在GDM组和对照组分别为0.718、0.282和0.713、0.287。两组人群基因型频率分布均符合Hardy-Weinberg平衡定律。*apoA*1 －75 G/A多态性基因型频率、等位基因G、A频率在GDM组和正常对照组间比较差异无统计学意义（$P>0.05$）。在GDM组*apoA*1 －75 G/A多态性AA基因型者较GG型者、GA型者在TC、HDL-C和apoA1水平均增高（P均<0.05）；GDM患者进一步划分为肥胖和非肥胖亚组后，*apoA*1基因型与apoA1水平的关系仅在肥胖亚组观察到，与TC和HDL-C的关系在非肥胖亚组观察到（$P<0.05$）。与GG基因型者比较，正常妊娠对照组AA和GA基因型者的收缩压（SBP）和HDL-C水平均有所升高（P均<0.05）；AA基因型者较GG型和GA型者Glu水平降低（$P<0.05$）。对照组人群按体质量指数（BMI）分亚组后基因型与SBP和HDL-C水平的关系仅在肥胖对照亚组观察到，与Glu水平的关系在肥胖和非肥胖亚组均存在。**结论** *apoA*1 －75 G/A多态性与GDM无关联，但该变异与GDM患者血浆apoA1、HDL-C和TC水平密切有关。该基因位点的变异在正常妊娠孕妇中与血浆HDL-C、Glu和SBP水平相关联。该变异在两组人群与血脂和血压水平改变的关系具有BMI依赖的特性。

【关键词】 载脂蛋白A1基因 糖尿病，妊娠 多态性，单核苷酸 血脂 血糖

－75 G/A Polymorphism of Apolipoprotein A1 Gene Promoter Region in Normal Pregnant Women and Patients With Gestational Diabetes Mellitus

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【Abstract】 Objective To investigate the －75 G/A single-nucleotide polymorphism in the promoter region of apolipoprotein A1 gene (*apoA*1) and its association with gestational diabetes mellitus (GDM) in pregnant women and to provide references for the exploration in the molecular genetic basis of GDM. **Methods** A total of 626 GDM patients and 1 022 normal pregnant women, ie, the controls, were included in the study. The genotyping of *apoA*1 －75 G/A polymorphism was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) analysis. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glucose (Glu) were measured by enzymatic methods. Plasma insulin (INS) was measured by chemiluminescence immunoassay. The protein levels of apoA1 and apoB were measured by the turbidimetric immunoassay. **Results** Allele frequencies of G and A were 0.718 and 0.282 in the GDM group and 0.713 and 0.287 in the control group, respectively. Distribution of the genotype frequencies was found to be in Hardy-Weinberg equilibrium in both the GDM and control groups. There was no significant difference in the frequencies of alleles G and A and the

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genotypes of *apoA*1 —75 G/A polymorphism between the GDM and the control group (P>0.05). In the GDM group, the carriers with the genotype AA were associated with significantly higher levels of TC, HDL-C, and apoA1 than those with genotypes GG and GA did (all P<0.05). After the GDM patients were divided into obese and non-obese subgroups, the genotype-related *apoA*1 variation was observed only in obese patients, while the genotype-related TC and HDL-C variations were evident in non-obese patients (P<0.05). In the control group, carriers of genotypes AA and GA had higher systolic blood pressure (SBP) and HDL-C than the carriers of genotype GG did (all P<0.05). Carriers of genotypes AA had significantly lower Glu levels than carriers of genotypes GG and GA did (P<0.05). The control subjects were further divided into subgroups according to their body mass index (BMI). Analysis of the subgroups showed that AA carriers were associated with higher SBP levels in the obese control women only, while lower Glu levels were evident in both obese and non-obese control women. **Conclusion** These results suggest that —75 G/A polymorphism in the *apoA*1 gene is not associated with GDM. However, the genetic variation is closed associated with the plasma apoA1, HDL-C, and TC levels in GDM patients and plasma HDL-C, Glu, and SBP levels in the control subjects. The *apoA*1 variant-associated lipids and SBP variation is BMI dependent in both groups.

【Key words】 Apolipoprotein A1 gene Diabetes, gestational Polymorphism, single nucleotide Lipids Glucose

妊娠糖尿病(gestational diabetes mellitus, GDM)是妊娠期最常见的代谢紊乱性疾病[1], 我国20 ~ 49岁育龄期妇女妊娠糖尿病的患病率为8.6%[2]。GDM患者常出现其他产科合并症, 包括妊娠高血压疾病、巨大胎儿和难产等, 严重影响母儿健康。GDM患者及其子代还存在远期2型糖尿病和心血管疾病等发生风险的增加。GDM患者以糖耐量降低为特征, 并伴有血脂水平的异常。GDM的病因目前尚不十分清楚, 研究表明该病与遗传因素[3]、血脂异常[4]、氧化应激[5]、炎症[6]等相关。

载脂蛋白A1(apolipoprotein A1, apoA1)是高密度脂蛋白(high-density lipoprotein, HDL)的主要结构蛋白, 参与激活卵磷脂胆固醇酰基转移酶(LCAT)、识别HDL受体, 促进血浆HDL从外周组织接受游离的胆固醇形成胆固醇酯而参与胆固醇的逆向转运, 是脂质代谢的重要调节分子。apoA1对脂质分子有高亲和力, 因而具有抗动脉粥样硬化、抗内毒素血症、抗炎和抗氧化作用。已有研究表明*apoA*1基因—75 bp G/A多态性位点突变可影响血清HDL、apoA1以及三酰甘油(triglycerides, TG)水平。另外一些研究发现*apoA*1单核苷酸多态性与脂代谢存在关联, 并与多种疾病如动脉粥样硬化/冠心病、肥胖、2型糖尿病、阿尔茨海默病、胆囊结石等的发生有关[7]。鉴于血脂水平的变化与*apoA*1 —75 G/A多态性密切相关, *apoA*1基因已成为GDM的候选基因。迄今关于*apoA*1 —75 G/A多态性是否与GDM以及妊娠妇女血脂水平等的变化存在关联尚未见报道。本研究的主要目的是比较GDM孕妇和正常妊娠孕妇*apoA*1基因—75 G/A变异的频率和分布是否存在差异, 以明确其变异是否与GDM发病有关联, 探索*apoA*1基因的变异与临床及相关代谢指标的关系, 为探讨GDM发生的遗传学病因以及妊娠妇女代谢异常的机制提供实验室依据。

1 对象与方法

1.1 对象

GDM组: 按国际糖尿病研究协会(IADPSG)推荐的GDM诊断标准[8], 即空腹血糖(glucose, Glu)≥5.1 mmol/L, 餐后1 h Glu≥10.0或餐后2 h Glu≥8.5 mmol/L, 满足任意一项即确诊为GDM。对照组: 选择正常妊娠孕妇作为对照组。以上两组均经询问病史和体检, 排除孕前糖尿病及其他妊娠期疾病和多胎妊娠, 以及心、肺、肝、肾及其他内分泌疾病, 均为来自成都地区的汉族人。本研究经四川大学华西第二医院伦理委员会批准(批准号2017-033), 所有研究对象均已签署了知情同意书。

1.2 血液基因组DNA的分离及聚合酶链反应扩增

参照ERLICH[9]微量DNA全血提取法从500 μL外周血中分离基因组DNA。聚合酶链反应(polymerase chain reaction, PCR)引物参照文献[10]合成。PCR引物序列为: 上游5′-AGGGACAGAGCTGATCCTTGAACTCTTAAG-3′, 下游5′-TTAGGGGACACCTAGCCCTCAGGAAGAGCA-3′, 由上海生工生物有限公司合成, 扩增*apoA*1基因片段长度为404 bp。PCR反应体系含2.0 mmol/L $MgCl_2$、1.0 μL DNA、0.15 μL *Taq* DNA聚合酶、引物各0.5 μmol/L、2. 5 mmol/L dNTP、2.5 μL PCR Buffer、1.25 μL DMSO试剂, 总体积为25 μL(以上试剂购于上海生工生物工程公司或成都同正生物技术有限公司)。PCR反应条件为94 ℃预变性5 min后, 94 ℃ 1 min, 60 ℃ 1 min, 72 ℃ 1 min, 30个循环后72 ℃最后延伸10 min。

1.3 PCR扩增产物的消化及电泳

参照文献的方法[11], 取PCR产物1.2 μL, 加入*Msp* Ⅰ限

制性内切酶8 U(NEB产品), 10倍酶切缓冲液1 μL, 加灭菌超纯水配成10 μL体积, 于37 ℃消化过夜, 取消化产物加入2.0%琼脂糖凝胶板(含Genecolour荧光试剂), 在TBE缓冲液中电泳40 min, 紫外光下显示DNA带并拍照。

1.4　血生化指标分析

使用化学发光法测定血浆INS, 采用酶法试剂盒测定Glu、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)、TG和总胆固醇(total cholesterol, TC)。apoA1和载脂蛋白B(apoB)的测定用免疫透射比浊法(ITA)。

胰岛素抵抗水平的分析指标HOMA稳态模型(HOMA-IR)计算方法如下: 空腹血糖(mmol/L)×空腹胰岛素水平(μU/mL)/22.5[12]。

1.5　统计学方法

采用SPSS 26.0软件统计。GDM组和对照组基因型频率采用基因计数法, 两组等位基因频率的比较用卡方检验。组间临床指标和代谢水平比较用*t*检验, 不同基因型亚组间的差异用one-way ANOVA和post hoc(独立样本单因子变异数分析)分析。*apoA*1基因的基因型进行Hardy-Weinberg平衡检验。$P<0.05$为差异有统计学意义。

2　结果

2.1　GDM组和对照组临床和代谢指标的比较

由表1可见, 与正常妊娠对照组比较, GDM组孕妇的年龄、孕前体质量指数(BMI)、空腹胰岛素(insulin, INS)、空腹Glu、HOMA-IR水平均升高($P<0.001$), 而在孕周、孕期增重、LDL-C和apoA1水平降低($P<0.01$或0.001)。分娩时的BMI、收缩压(SBP)、舒张压(DBP)、TC、HDL-C和apoB水平两组之间差异无统计学意义。

表 1　GDM组和对照组临床和代谢指标的比较

Table 1　Comparison of clinical and metabolic parameters between the GDM and the control groups

Parameter	GDM group (n=626)	Control group (n=1 022)	P
Age/yr.	35.57±4.03	34.54±4.99	<0.001
Gestational age/week	38.94±1.08	39.08±1.16	0.006
Prepregnancy BMI/(kg/m^2)	22.27±3.11	21.23±2.75	<0.001
Weight gain during pregnancy/kg	11.45±4.20	13.92±4.25	<0.001
Delivery BMI/(kg/m^2)	26.83±3.35	26.60±2.77	0.102
SBP/mmHg	115.83±11.01	115.11±9.98	0.124
DBP/mmHg	72.76±8.60	72.59±7.75	0.649
Fasting INS/(pmol/L)	13.92±17.20	10.35±4.62	<0.001
Fasting blood Glu/(mmol/L)	4.73±0.58	4.38±0.36	<0.001
HOMA-IR	3.18±5.24	2.02±0.92	<0.001
TC/(mmol/L)	5.98±1.24	6.04±1.09	0.236
HDL-C/(mmol/L)	1.97±0.45	1.97±0.42	0.921
LDL-C/(mmol/L)	2.98±0.97	3.17±0.98	<0.001
apoA1/(g/L)	2.30±0.41	2.36±0.44	0.001
apoB/(g/L)	1.15±0.26	1.15±0.26	0.731

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; INS: insulin; Glu: glucose; HOMA-IR: homeostasis model assessment of insulin resistance; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; apoA1: apolipoprotein A1; apoB: apolipoprotein B. 1 mmHg=0.133 kPa.

2.2　*apoA*1 －75 G/A多态性分析

PCR产物经*Msp* Ⅰ限制性内切酶水解后, 出现3种基因型: GG纯合子为178 bp、119 bp、107 bp 3条带; AA纯合子为285 bp、119 bp 2条带; AG杂合子为285 bp、178 bp、119 bp、107 bp 4条带(图1)。由于119 bp、107 bp 条带接近, 因此琼脂糖凝胶电泳上未能分开, 但这并不影响对基因型的判读。

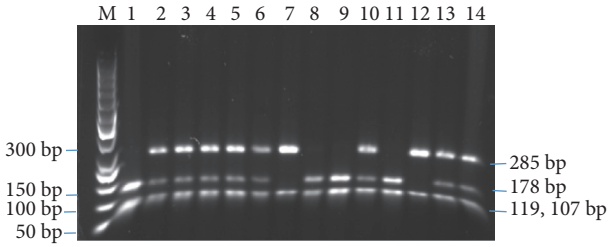

图 1　*apoA*1 －75 G/A基因多态性位点*Msp* Ⅰ酶切电泳图

Fig 1　Electrophoretic map of *apoA*1 －75 G/A polymorphic locus *Msp* Ⅰ

M: DNA standard reference; 1, 8, 9, and 11: GG genotype; 2, 3, 4, 5, 6, 10, 13, and 14: AG genotype; 7 and 12: AA genotype.

2.3　*apoA*1基因型和等位基因频率的分布和比较

GDM组和对照组*apoA*1 －75 G/A多态性基因型频率分布均符合Hardy-Weinberg平衡遗传定律(P均>0.05), 该位点达到遗传平衡, 具有群体代表性。由表2可见, GDM组和对照组G和A等位基因频率分别为0.718、0.282和0.713、0.287。未见两组之间基因型和等位基因频率的分布差异有统计学意义。

表 2　GDM组和对照组*apoA*1 －75 G/A基因型及等位基因频率分布

Table 2　Distribution of *apoA*1 －75 G/A genotypes and allele frequency in the GDM and the control groups

Genotype/Allele	GDM group (n=626)	Control group (n=1 022)	P
Genotype			0.704
GG	0.505 (316)	0.506 (517)	
GA	0.427 (267)	0.415 (424)	
AA	0.069 (43)	0.079 (81)	
Allele			0.770
G	0.718 (899)	0.713 (1 458)	
A	0.282 (353)	0.287 (586)	

The numbers in the brackets indicate the number of subjects with each genotype or the number of alleles of each type.

2.4　*apoA*1基因不同基因型亚组间临床和代谢指标的比较

由表3可见, GDM组*apoA*1基因－75位点AA基因型携带者其TC、HDL-C和apoA1水平较GG和GA基因型者

表 3 *apoA*1 —75 G/A多态性不同基因型亚组临床和代谢指标在GDM组和对照组的比较

Table 3 Comparison of clinical and metabolic parameters of subgroups with different genotypes of *apoA*1 —75 G/A polymorphism in the GDM and the control groups

Parameter	GDM group genotype			Control group genotype		
	GG (*n*=316)	GA (*n*=267)	AA (*n*=43)	GG (*n*=517)	GA (*n*=424)	AA (*n*=81)
Delivery BMI/(kg/m^2)	26.97±3.81	26.61±2.88	27.01±2.86	26.61±2.76	26.63±2.54	26.98±2.88
SBP/mmHg	116.78±10.11	114.92±12.37	115.29±9.09	114.74±10.11	115.57±10.10	117.28±9.59*
DBP/mmHg	73.46±8.05	72.40±9.40	71.04±7.97	72.10±7.73	72.10±7.52	73.16±7.81
Fasting INS/(μU/mL)	15.66±20.56	12.09±12.95	11.17±8.60	10.54±4.94	9.79±3.92	10.62±4.71
Fasting blood Glu/(mmol/L)	4.72±0.58	4.72±0.52	4.63±0.40	4.41±0.37	4.38±0.34	4.24±0.37$^{**,\#}$
HOMA-IR	3.54±5.61	2.72±4.28	2.31±1.57	2.07±1.00	1.92±0.79	2.00±0.90
Triglycerides/(mmol/L)	3.99±1.77	3.80±1.51	3.67±1.44	3.66±1.42	3.62±1.36	3.84±1.80
TC/(mmol/L)	5.97±1.05	5.93±1.13	6.45±2.53$^{*,\#}$	6.08±1.14	6.11±1.00	6.11±1.06
HDL-C/(mmol/L)	1.98±0.42	1.97±0.45	2.13±0.50$^{*,\#}$	1.96±0.42	2.05±0.40**	2.03±0.38
LDL-C/(mmol/L)	2.98±1.01	2.93±0.87	3.05±0.95	3.23±1.06	3.18±0.91	3.11±0.95
apoA1/(g/L)	2.28±0.35	2.29±0.40	2.42±0.36$^{*,\#}$	2.34±0.46	2.41±0.40	2.38±0.33
apoB/(g/L)	1.16±0.25	1.15±0.26	1.16±0.26	1.16±0.27	1.15±0.25	1.11±0.25

The abbreviations are explained in the note to Table 1. * *P*<0.05, ** *P*<0.01, vs. GG genetype carriers in the same group; $^{\#}$ *P*<0.05, vs. GA genetype carriers in the same group.

均升高(*P*均<0.05);对照组AA型者收缩压(SBP)水平高于GG型携带者(*P*<0.05),空腹葡萄糖水平则分别低于GG和GA型者(*P*均<0.05),而GA型者HDL-C水平高于GG型者(*P*<0.05)。

将GDM组进一步划分为肥胖(BMI≥25 kg/m^2)和非肥胖(BMI<25 kg/m^2)亚组进行统计分析后,仅在非肥胖亚组观察到*apoA*1多态性与TC和HDL-C水平的关系,而*apoA*1多态性与apoA1水平的关系仅在肥胖患者观察到(表4)。对照组划分为肥胖和非肥胖亚组后,*apoA*1基因型与空腹血糖水平的关系在肥胖和非肥胖组孕妇均能观察到,而与SBP和HDL-C水平的关系仅在肥胖亚组观察到(表5, *P*<0.05)。

表 4 肥胖和非肥胖GDM孕妇*apoA*1基因—75 G/A多态性不同基因型亚组临床和代谢指标

Table 4 Clinical characteristics and metabolic profile of *apoA*1 —75 G/A genotypes in overweight/obese and non-obese GDM patients

Parameter	Obese GDM genotype			Non-obese GDM genotype		
	GG (*n*=229)	GA (*n*=188)	AA (*n*=32)	GG (*n*=87)	GA (*n*=79)	AA (*n*=11)
Delivery BMI/(kg/m^2)	28.32±3.62	27.96±2.18	28.12±2.31	23.47±1.04	23.37±1.33	23.57±1.10
Neonatal birth weight/g	3 387.94±427.53	3 377.72±414.28	3 511.32±508.26	3 252.72±424.86	3 171.63±403.42	3 197.27±259.62
SBP/mmHg	117.74±10.16	115.80±13.09	115.35±9.46	114.19±9.67	112.77±10.30	115.09±8.24
DBP/mmHg	73.57±8.02	72.71±9.60	70.82±7.93	73.26±8.19	71.61±8.95	71.73±8.46
Fasting insulin/(μU/mL)	18.13±23.64	12.69±14.11	11.86±9.54	8.87±5.07	10.73±10.17	8.55±2.29
Fasting blood Glu/(mmol/L)	4.75±0.61	4.76±0.54	4.65±0.40	4.64±0.52	4.66±0.50	4.57±0.45
HOMA-IR	4.16±6.49	2.88±4.83	2.46±1.73	1.85±1.15	2.36±2.70	1.76±0.63
Triglycerides/(mmol/L)	4.08±1.72	3.91±1.61	3.84±1.27	3.76±1.88	3.50±1.21	3.16±1.83
TC/(mmol/L)	5.92±1.09	5.88±1.17	6.09±1.06	6.12±0.94	6.05±1.05	7.52±4.65$^{**,\#\#}$
HDL-C/(mmol/L)	1.94±0.41	1.96±0.45	2.03±0.34	2.11±0.44	2.01±0.46	2.40±0.76$^{\#}$
LDL-C/(mmol/L)	2.92±0.85	2.86±0.88	2.98±0.88	3.14±1.34	3.10±0.83	3.26±1.17
apoA1/(g/L)	2.26±0.35	2.30±0.39	2.47±0.36*	2.34±0.34	2.26±0.40	2.28±0.33
apoB/(g/L)	1.16±0.26	1.14±0.27	1.15±0.25	1.17±0.22	1.18±0.24	1.19±0.32

The abbreviations are explained in the note to Table 1. * *P*<0.05, ** *P*<0.01, vs. GG genetype carriers in the same group; $^{\#}$ *P*<0.05, $^{\#\#}$ *P*<0.01, vs. GA genetype carriers in the same group.

表 5　肥胖和非肥胖对照组孕妇*apoA*1基因－75 G/A多态性不同基因型亚组临床和代谢指标

Table 5　Clinical and metabolic parameters of *apoA*1 gene －75 G/A genotypes in obese and non-obese control subjects

Parameter	Obese control genotype			Non-obese control genotype		
	GG (*n*=374)	GA (*n*=317)	AA (*n*=64)	GG (*n*=143)	GA (*n*=107)	AA (*n*=17)
Delivery BMI/(kg/m^2)	27.79±2.26	27.71±1.94	28.00±2.28	23.58±1.09	23.51±1.01	23.23±1.29
SBP/mmHg	115.44±10.31	116.37±10.11	118.40±9.09*	113.26±9.44	113.36±9.81	112.37±10.77
DBP/mmHg	72.21±7.79	72.58±7.34	73.67±8.12	71.92±7.62	70.74±7.95	71.16±6.10
Fasting INS/(μU/mL)	10.96±4.94	10.34±4.07	11.27±4.99	9.37±4.80	8.10±2.90	8.75±3.35
Fasting blood Glu/(mmol/L)	4.42±0.38	4.40±0.35	4.26±0.35*	4.39±0.36	4.35±0.32	4.11±0.30*
HOMA-IR	2.16±1.00	2.03±0.81	2.12±0.91	1.82±0.95	1.57±0.58	1.61±0.66
Triglycerides/(mmol/L)	3.74±1.50	3.68±1.38	4.01±2.02	3.47±1.20	3.43±1.31	3.18±0.66
TC/(mmol/L)	6.01±1.13	6.05±1.04	6.02±1.08	6.28±1.18	6.26±0.88	6.48±0.98
HDL-C/(mmol/L)	1.93±0.40	2.02±0.40*	1.99±0.35	2.06±0.45	2.12±0.41	2.13±0.39
LDL-C/(mmol/L)	3.17±1.07	3.14±0.94	3.05±0.99	3.40±1.03	3.30±0.82	3.44±0.84
apoA1/(g/L)	2.35±0.47	2.41±0.41	2.38±0.33	2.34±0.45	2.42±0.39	2.32±0.34
apoB/(g/L)	1.15±0.27	1.14±0.26	1.10±0.26	1.19±0.28	1.19±0.24	1.19±0.22

The abbreviations are explained in the note to Table 1. * P<0.05, vs. GG genetype carriers in the same group.

3　讨论

本研究对成都地区1 648名孕妇*apoA*1基因－75 G/A多态性等位基因频率进行了分析，结果显示A等位基因频率在GDM组和正常妊娠对照组分别为0.282（28.2%）和0.287（28.7%），高于非洲人的10.1%、欧洲人的15%~19%、美国白人的18%~20%以及澳大利亚白人的18%~22%[13]，提示汉族人*apoA*1基因－75 G/A多态性位点等位基因频率与国外其他种族人群之间存在差异。

关于*apoA*1基因－75 G/A多态性与apoA1和HDL-C水平变化的关系研究较多。本研究在GDM孕妇发现，AA基因型携带者较GG和GA型携带者apoA1和HDL-C水平显著增加，在对照妊娠妇女观察到GA基因型携带者较GG型者HDL-C水平显著增加，提示*apoA*1基因多态性对脂蛋白HDL-C代谢在两组妊娠人群均存在影响，且存在一定的差异。*apoA*1基因启动子区－75 bp G/A多态位点G→A置换，改变了GGGCCGG序列。这一富含GC区域为*apoA*1基因转录的调控元件，具有激活转录的作用，当该序列发生变化时可能会影响基因的转录和表达，从而影响apoA1合成。而apoA1是构成HDL-C的主要载脂蛋白，因而apoA1的表达变化也影响HDL-C的形成和功能。一些报道显示*apoA*1 －75 G/A位点A等位基因与血浆apoA1和HDL-C水平密切相关，AA基因型携带者apoA1和HDL-C水平显著升高，并认为这是因为A碱基的置换促进了*apoA*1基因的表达和生物合成[14]。但另有研究[15-16]显示血浆HDL含量在*apoA*1基因－75 bp位点三种基因型间无显著差异，而且SMITH等[16]还发现apoA1生成速率在A等位基因者低于G等位基因携带者，故认为该位点变异并不影响血清apoA1和HDL含量，A等位基因与血浆apoA1和HDL-L水平升高无相关性。本研究在GDM人群和正常妊娠妇女的研究结果与PAPAZAFIRI等[14]的研究结果一致。

本研究还显示GDM患者*apoA*1基因A碱基置换引起血浆TC水平显著升高（P<0.05），与LARSON等[17]在德国人及XU等[18]在意大利儿童的研究结果一致。其机制可能为G>A变异的直接效应或与*apoA*1基因其他位点或相邻基因多态性位点发生连锁不平衡，从而影响胆固醇的代谢，导致血TC升高有关[17]。在正常妊娠妇女未观察到*apoA*1多态性与TC水平改变的关系。本研究在GDM患者观察到*apoA*1 －75 G/A多态性不仅与HDL-C和apoA1水平有关联，而且还与其他血脂表型如TC水平的改变有关，提示*apoA*1基因变异对GDM患者较正常妊娠妇女血脂代谢功能的影响可能更大。

此外，本研究在正常对照孕妇观察到*apoA*1 －75 G/A变异与空腹胰岛素水平存在关联。LI等[19]研究发现，一些与脂代谢相关基因的变异不仅影响血脂水平，也与葡萄糖代谢的表型（如空腹血糖、糖化血红蛋白和HOMA-IR水平）有关，而基因型对血脂和血糖的水平作用的效应呈相反的关系，即血脂升高或降低的等位基因分别与血糖指标的降低或升高有关。本研究在正常妊娠孕妇的结

果显示GG基因型携带者(较低的HDL-C水平者)较AA型者Glu水平显著升高,与在另一人群观察到的*apoA*1基因—75G等位基因与代谢综合征的表型相关的结果相似[20]。本研究在汉族正常妊娠人群的发现,提示脂代谢基因*apoA*1可能是糖脂代谢相关的又一多效性基因。基因变异对糖脂水平影响多效性作用关系的机制尚不清楚,涉及到糖脂代谢之间存在的复杂遗传调控和代谢方面的相互作用关系,需要进一步通过系统生物学的途径加以研究。

多个研究表明,脂代谢与血压等心血管功能表型具有共同的遗传学基础。即一些基因的多态性对血脂和血压等均具有影响作用。例如,在瑶族人群中发现*ABCA*1 V825I多态性与增高的收缩压、舒张压及脉压水平存在关联[21]。本课题组最近在GDM患者观察到*ABCG*1基因rs57137919位点G等位基因与收缩压增高有关[22]。此外,另一项对9个脂质相关基因多态性的研究表明,其中一些基因的变异与吸烟因素的相互作用对血压水平具有影响[23]。本研究观察到脂代谢相关的重要基因*apoA*1的变异与正常妊娠妇女血压水平存在关联,提示*apoA*1 —75 G/A位点的变异可能也是同时影响血压水平的多效性基因。而血压水平的升高是心血管病发生风险的重要因素。

综上所述,本研究结果表明*apoA*1基因启动子区—75 G/A变异不是GDM发生的遗传危险因素,但该变异与GDM患者血浆TC、HDL-C和apoA1水平有关。该基因位点的变异在正常妊娠孕妇中与血浆HDL-C、Glu和血压水平密切相关。*apoA*1基因的变异与血脂和血压水平增高的关系具有BMI依赖的特性。

* * *

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