

ACAT1 rs11545566多态性与非酒精性脂肪性肝病易感性的相关性

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摘 要

目的: 探究中国青岛地区乙酰辅酶A乙酰转移酶1 (acetyl-CoA acetyltransferase 1, ACAT1) 基因 rs11545566位点多态性与非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)易感性的相关性。方法: 纳入于青岛市市立医院收集的NAFLD患者226例, 健康对照141例。收集所有受试者血液标本, 提取DNA, 通过聚合酶链反应的方法扩增DNA, 并检测ACAT1基因rs11545566位点的基因型。收集并分析患者的临床资料及实验室指标。符合正态分布的计量资料采用t检验, 不符合正态分布的计量资料采用Wilcoxon秩和检验进行组间比较, 使用 χ^2 检验分析NAFLD和对照组的基因型及等位基因分布差异。结果: ACAT1 rs11545566位点在NAFLD组和对照组的基因型与等位基因分布差异均无统计学意义($P > 0.05$)。ACAT1 rs11545566位点G等位基因携带者比非携带者ALT水平更低($P = 0.038$)。结论: 在中国青岛汉族人群中, ACAT1 rs11545566位点多态性与NAFLD易感性无显著相关性。ACAT1 rs11545566位点G等位基因携带可能与低ALT水平有关。

关键词

非酒精性脂肪肝, 乙酰辅酶A乙酰转移酶1, 单核苷酸多态性

Association between ACAT1 rs11545566 Polymorphism and Susceptibility to Non-Alcoholic Fatty Liver Disease

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Abstract

Objective: To explore the polymorphism of acetyl-CoA acetyltransferase 1 (ACAT1) rs11545566 locus and non-alcoholic fatty liver disease in Qingdao region of China association with susceptibility to NAFLD. **Methods:** 226 patients with NAFLD and 141 healthy controls admitted to Qingdao Municipal Hospital were included. Blood samples were collected from all subjects and DNA was extracted. Then DNA was amplified by polymerase chain reaction and we genotyped the rs11545566 locus of the ACAT1 gene. Clinical data and laboratory indicators were collected and analyzed. T-test was used for measurement data conforming to normal distribution, and Wilcoxon rank sum test was used for comparison between groups for measurement data not conforming to normal distribution. χ^2 test was used to analyze the differences in genotype and allele distribution between NAFLD and control group. **Results:** There were no significant differences in genotype and allele distribution of ACAT1 rs11545566 between NAFLD group and control group ($P > 0.05$). ACAT1 rs11545566 G allele carriers have lower ALT levels than non-carriers ($P = 0.038$). **Conclusion:** There is no significant correlation between ACAT1 rs11545566 polymorphism and NAFLD in Qingdao Han population. ACAT1 rs11545566 G allele is associated with lower levels of ALT.

Keywords

Non-Alcoholic Fatty Liver Disease, Acetyl-CoA Acetyltransferase 1, Single Nucleotide Polymorphism

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1. 引言

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)近年来发病率逐年上升, 已经成为了全球最普遍的一种肝脏疾病, 在普通成人中患病率高达 6.3%~45% [1]。NAFLD 的诊断需影像学或病理学见弥漫性肝细胞脂肪变, 并且要排除酒精滥用等可以导致肝脂肪变的其他病因[2]。NAFLD 是一种异质性疾病, 疾病谱涉及到肝脏单纯性脂肪变性, 非酒精性脂肪性肝炎, 肝硬化, 肝细胞癌[3] [4]。在 NAFLD 发生发展的过程中, 基因扮演了重要的角色, 在基因层面探究与 NAFLD 发生相关的因素, 对于 NAFLD 的诊断和治疗具有重要的意义。许多遗传学研究已经确定了与 NAFLD 相关的单核苷酸多态性, 研究较多的基因有: TM6SF2 [5]、PNPLA3 [6]、PPARGC1A [7] [8]、PEMT [9]、ADPN [10]等。

胆固醇存在于动物细胞膜上, 是胆汁酸、维生素 D 和类固醇激素的前体, 对细胞生长和活动至关重要, 多余的胆固醇以胆固醇酯的形式储存, 乙酰辅酶 A 乙酰转移酶 1 (acetyl-CoA acetyltransferase 1, ACAT1)是一种将胆固醇转化为胆固醇酯的酶, 其主要在肝脏, 肾上腺, 巨噬细胞和肾脏中表达。ACAT1 基因表达增强可促进胆固醇酯积累和巨噬细胞源性泡沫细胞形成[11]。脂滴中胆固醇酯的积累是巨噬细胞起泡的主要特征, 可导致动脉粥样硬化疾病。ACAT1 基因 rs11545566 位点具有 A 和 G 两种等位基因, 2017 年中国学者证实了 rs11545566 位点多态性与冠心病的发生有相关性[12]。Wang YT 等[12]在冠状动脉疾病人群和健康人群中的研究表明, G 等位基因携带者冠心病的发病风险显著高于非携带者(OR = 1.67, 95% CI = 1.22~2.29, $P = 0.001$), 且该位点 G 等位基因携带者受试者 Gensini 评分大于 AA 基因型组受试

者($P = 0.002$), 即该位点与冠心病的严重程度亦具有相关性。NAFLD 的发生与脂质代谢相关, 其与冠心病病因有一定的相似之处, 荟萃分析表明, NAFLD 与心血管事件结局之间存在显著关联[13]。鉴于 NAFLD 与冠心病同属代谢相关性疾病, 我们设计此研究, 旨在探究 ACAT1 rs11545566 位点与 NAFLD 的相关性。

2. 资料与方法

2.1. 研究对象

收集自 2020 年 12 月至 2022 年 6 月于青岛市市立医院就诊的 NAFLD 患者及健康查体者, 参考《非酒精性脂肪性肝病防治指南(2018 更新版)》[2], NAFLD 的诊断应用彩超及肝脏瞬时弹性超声(Fibroscan), 同时排除酒精性肝病、基因 3 型丙型肝炎病毒感染、自身免疫性肝炎、肝豆状核变性等可导致脂肪肝的特定肝病, 并除外药物(他莫昔芬、乙胺碘呋酮、丙戊酸钠、甲氨蝶呤、糖皮质激素等)、全胃肠外营养、炎症性肠病、乳糜泻、甲状腺功能减退症、库欣综合征、 β 脂蛋白缺乏血症、脂质萎缩性糖尿病、糖原性肝病等导致脂肪肝的特殊情况[14]。两组均为长期生活于青岛地区的汉族人群, 无血缘关系。本研究在青岛市市立医院伦理委员会的许可下进行。纳入的受试者均知情同意, 并签署了知情同意书。

2.2. 资料收集

受试者在禁食 12 小时后于次日清晨测量身高、体重、血压, 后计算身体质量指数(Body Mass Index, BMI), $BMI = \text{体重}/\text{身高}^2$ 。受试者在禁食 12 小时后于次日清晨抽取静脉血送检, 检验指标包括空腹血糖(Fasting Blood Glucose, GLU), 总胆固醇(Total Cholesterol, TC), 甘油三酯(Triglyceride, TG), 低密度脂蛋白(Low-Density Lipoprotein, LDL), 高密度脂蛋白(High-Density Lipoprotein, HDL), 游离脂肪酸(Non-Esterified Fatty Acid, NEFA), 载脂蛋白 A1(ApoA1), 载脂蛋白 B(ApoB), 谷丙转氨酶(Alanine Aminotransferase, ALT), 谷草转氨酶(Aspartate Transaminase, AST), 谷丙转氨酶(Alanine Transpeptidase, GGT), 碱性磷酸酶(Aspartate Aminotransferase, ALP), 总胆红素(Total Bilirubin, TBIL)及白蛋白(Alb)等。

2.3. ACAT1 基因 rs11545566 位点测定

采用聚合酶链式反应对目的基因进行扩增, 并对 ACAT1 rs11545566 位点多态性分析。PCR 引物序列: 上游引物: ACGTTGGATGTAGCTTAGCAGGCGACGTTG, 下游引物: ACGTTGGATGAGAGCCGGG AAGCGGTCACA。提取 DNA 后, 由博淼生物科技(北京)有限公司完成该位点核苷酸多态性检测。

2.4. 统计学方法

采用 SPSS 25.0 软件对受试者的一般资料、实验室指标进行分析和比较, 符合正态分布的计量资料, 用均数 $\pm$ 标准差表示, 应用独立样本 t 检验分析各组间的差异, 非正态分布的计量资料, 采用中位数(第一四分位数, 第三四分位数)表示, 各组间的比较应用 Wilcoxon 秩和检验分析, 计数资料用例数表示, 组间比较应用卡方检验, 以 $P < 0.05$ 表明差异有统计学意义。

3. 结果

3.1. 所有受试者的一般临床资料及实验室指标比较

本次研究纳入的受试者共有 367 例。其中 NAFLD 组共有 226 例(男 111 人/女 115 人), 对照组共 141 例(男 69 人/女 72 人), 对所有受试者、健康对照组、NAFLD 组分别进行基线数据描述, 对健康对照组和 NAFLD 两组之间的一般临床资料及实验室指标比较, 结果见表 1。

Table 1. Comparison of general clinical data and related indicators between NAFLD and control group
表 1. NAFLD 组与健康对照组临床资料及相关指标对比

指标	总体(n = 367)	健康对照(n = 141)	NAFLD (n = 226)	统计值 t/z/ χ^2	P 值
性别(男/女)	170/187	69/72	111/115	0.001	0.973
年龄(岁)	49 (3760)	41 (30, 53.5)	53 (41.75, 63)	-6.859	<0.001
BMI, kg/m ²	25.94 (23.47, 28.73)	24.22 (21.80, 27.46)	27.13 (24.32, 29.66)	-5.058	<0.001
SBP, mmHg	127 (119, 138)	122 (114, 126)	130 (120.5, 142)	-3.981	<0.001
DBP, mmHg	76 (71, 84)	75 (69, 83)	77 (71, 85)	-1.735	0.083
ALT, U/L	22.24 (14.26, 35.01)	16.37 (12.65, 24.75)	28.37 (17.56, 41.32)	-6.663	<0.001
AST, U/L	21.82 (18.00, 28.46)	18.99 (16.02, 23.08)	24.29 (19.77, 32.91)	-6.648	<0.001
GGT, U/L	24.59 (17.00, 44.44)	18.00 (12.64, 27.50)	31.00 (21.51, 56.51)	-7.797	<0.001
ALP, U/L	85.15 (70.40, 100.47)	78.15 (62.74, 92.37)	87.01 (72.48, 104.40)	-3.373	0.001
FPG, mmol/L	5.06 (4.54, 5.78)	4.90 (4.49, 5.28)	5.12 (4.60, 5.86)	-2.768	0.006
TG, mmol/L	1.38 (0.93, 2.07)	1.05 (0.79, 1.53)	1.72 (1.14, 2.42)	-7.007	<0.001
NEFA, mmol/L	0.38 (0.31, 0.49)	0.34 (0.28, 0.40)	0.43 (0.35, 0.54)	-5.734	<0.001
TC, mmol/L	5.08 (4.34, 5.77)	4.93 (4.27, 5.59)	5.09 (4.46, 5.86)	-1.513	0.130
HDL, mmol/L	1.22 (1.05, 1.4)	1.29 (1.13, 1.54)	1.16 (1.00, 1.35)	-4.311	<0.001
LDL, mmol/L	3.10 (2.58, 3.56)	2.98 (2.47, 3.52)	3.13 (2.64, 3.58)	-1.611	0.107
ApoA1, g/L	1.24 (1.10, 1.41)	1.33 (1.19, 1.55)	1.21 (1.07, 1.38)	-3.228	0.001
ApoB, g/L	1.07 (0.86, 1.25)	1.02 (0.76, 1.20)	1.09 (0.89, 1.26)	-1.836	0.066
ApoA1: ApoB	1.20 (1.02, 1.50)	1.41 (1.15, 1.80)	1.15 (1.00, 1.40)	-4.348	<0.001
Lp(a), mg/dL	15.30 (8.62, 29.46)	25.18 (14.38, 33.77)	13.09 (7.68, 28.05)	-2.531	0.011
Alb, g/L	42.59 (40.27, 45.58)	43.56 (39.99, 46.01)	42.24 (40.33, 45.54)	-0.854	0.393
TBil, μ mol/L	12.50 (10.08, 16.60)	12.20 (10.00, 16.20)	12.70 (10.20, 16.80)	-0.723	0.470

注：① 缩写：丙氨酸氨基转移酶(ALT)、天冬氨酸氨基转移酶(AST)、 γ -谷氨酰转移酶(GGT)、碱性磷酸酶(ALP)、空腹血糖(FPG)、甘油三脂(TG)、游离脂肪酸(NEFA)、总胆固醇(TC)、高密度脂蛋白(HDL)、低密度脂蛋白(LDL)、载脂蛋白 A1 (ApoA1)、载脂蛋白 B (ApoB)、脂蛋白 a (Lp(a))、白蛋白(Alb)、总胆红素(TBil)；② 符合正态分布的数据资料使用均数 $\pm$ 标准差来表示，不符合正态分布的资料使用 p50 (p25, p75)表示；③ 以 $P < 0.05$ 为差异有统计学意义。

3.2. Hardy-Weinberg 遗传平衡检验

ACAT1 rs11545566 位点有 AA、AG、GG 三种基因型，通过进行 Hardy-Weinberg (H-W)遗传平衡检验，得出受试者 ACAT1 rs11545566 基因型分布符合 H-W 遗传平衡($\chi^2 = 0.8156, P = 0.67$)， $P > 0.05$ 表明受试者来自同一孟德尔人群，入组受试者具有群体代表性。

3.3. 基因型及等位基因分布频率比较

经检验，ACAT1 基因 rs11545566 位点的基因型、隐性基因模型、显性基因模型和等位基因频率的分布差异在 NAFLD 组和健康对照组之间无统计学意义(见表 2)。

Table 2. Distribution and comparison of ACAT1 rs11545566 genotypes and alleles in NAFLD group and control group
表 2. NAFLD 组与对照组 ACAT1 rs11545566 位点基因分布及比较

		NAFLD (n = 226)	健康对照(n = 141)	OR	95% CI	χ^2	P 值
基因型	AA	47 (20.8)	27 (19.1)	-	-	0.327	0.849
	GG	64 (28.3)	38 (27.0)				
	GA	115 (50.9)	76 (53.9)				
等位基因	A	209 (46.2)	130 (46.1)	0.994	0.738~1.340	0.001	0.971
	G	243 (53.8)	152 (53.9)				
隐性模型	GG	64 (28.3)	38 (27.0)	-	-	0.081	0.776
	AA + GA	162 (71.7)	103 (73.0)				
显性模型	AA	47 (20.8)	27 (19.1)	-	-	0.146	0.702
	GG + AG	179 (79.2)	114 (80.9)				

3.4. 应用非条件 Logistic 回归分析各组间 ACAT1 rs11545566 位点基因型的发病风险比较

应用二元 logistic 回归模型分析 ACAT1 基因 rs11545566 位点与 NAFLD 易感性的关系结果, 在完成年龄、性别、BMI 校正后没有统计学意义(见表 3)。

Table 3. Logistic regression analysis of risk factors for NAFLD
表 3. NAFLD 危险因素的 Logistic 回归分析

		OR	95% CI	P
隐性基因	GG	1.410	0.776, 2.561	0.260
	AA + GA			
显性基因	AA	0.675	0.343, 1.331	0.256
	GG + AG			

注: ① OR、95% CI、P 值为校正性别、年龄、BMI 后的 OR、95% CI 及 P 值; ② $P < 0.05$ 认为差异具有统计学意义。

3.5. 携带 G 等位基因者与未携带者的临床资料及实验室指标的比较

在两组受试者中, 各项定量资料均不符合正态分布。对 ACAT1 基因 rs11545566 不同基因型之间生物化学指标进行比较, 结果显示, ACAT1 基因 rs11545566 位点 G 等位基因携带者比非携带者拥有更低的 ALT 水平($P < 0.05$), 而在 BMI、FPG、ALT、AST、ALP、GGT、TC、TG、LDL、HDL、TBil 之间两者没有统计学差异($P > 0.05$) (见表 4)。

Table 4. Comparison of general biochemical indexes between G alleles and non-G alleles
表 4. 携带 G 等位基因及未携带 G 等位基因组一般生化指标的比较

指标	AA	GA + GG	统计值 $t/z/\chi^2$	P 值
性别(男/女)	39/35	141/152	0.496	0.481
年龄(岁)	46.50 (34.00, 60.25)	49.00 (38.00, 60.00)	-0.978	0.328
BMI, kg/m ²	25.95 (23.36, 29.47)	25.92 (23.52, 28.70)	-0.192	0.848
SBP, mmHg	128.00 (119.00, 138.00)	127.00 (118.00, 136.00)	-0.258	0.796
DBP, mmHg	79.00 (67.00, 85.00)	76.00 (71.00, 83.00)	-0.567	0.571
ALT, U/L	28.11 (16.00, 45.33)	21.11 (14.03, 34.00)	-2.073	0.038

续表

AST, U/L	22.72 (19.01, 32.71)	21.36 (17.75, 27.99)	-1.634	0.102
γ -GGT, U/L	23.87 (17.00, 48.92)	24.81 (16.76, 42.97)	-0.527	0.598
ALP, U/L	84.12 (72.48, 100.61)	85.70 (69.03, 100.65)	-0.215	0.830
FPG, mmol/L	5.03 (4.44, 5.57)	5.06 (4.55, 5.79)	-0.587	0.557
TG, mmol/L	1.35 (0.90, 2.01)	1.40 (0.93, 2.15)	-0.569	0.569
NEFA, mmol/L	0.37 (0.31, 0.53)	0.39 (0.31, 0.49)	-0.130	0.897
TC, mmol/L	5.12 (4.34, 5.87)	5.00 (4.34, 5.77)	-0.462	0.644
HDL, mmol/L	1.25 (1.03, 1.45)	1.20 (1.06, 1.40)	-0.487	0.626
LDL, mmol/L	3.11 (2.57, 3.53)	3.10 (2.58, 3.56)	-0.023	0.982
ApoA1, g/L	1.26 (1.07, 1.49)	1.24 (1.11, 1.41)	-0.013	0.990
ApoB, g/L	1.07 (0.89, 1.25)	1.07 (0.86, 1.26)	-0.016	0.987
ApoA1: ApoB	1.21 (1.06, 1.41)	1.19 (1.01, 1.50)	-0.088	0.930
Lp(a), mg/dL	17.53 (7.47, 42.14)	15.00 (8.82, 27.77)	-0.874	0.382
Alb, g/L	42.35 (40.71, 44.55)	42.61 (40.00, 45.80)	-0.010	0.992
TBIL, μ mol/L	13.55 (10.13, 18.58)	12.25 (10.00, 16.00)	-1.314	0.189

4. 讨论

NAFLD 的发生受到环境因素和遗传因素的共同作用。2006 年一项动物实验表明, ACAT1 基因缺失的小鼠巨噬细胞游离胆固醇的合成和排出会增加[15]。此后的动物实验表明泛素蛋白连接酶 E3A (UBE3A)与丙酮酸脱氢酶 E1 亚基 α 1 (PDHA1)和 ACAT1 之间存在泛素化介导的调节轴,在高脂饮食诱导下,肝细胞可以利用该轴适当调节糖酵解、生酮和脂质合成,以响应饮食变化[16]。在正常成人中, ACAT1 是肝细胞和巨噬细胞的主要同工酶,在巨噬细胞中, ACAT1 在泡沫细胞形成中起关键作用[17]。ACAT1 基因参与人体内脂质代谢,与超重、高血压、高脂血症、冠状动脉粥样硬化性心脏病等代谢相关性疾病的发生有密切的关系[18] [19]。此外, ACAT1 抑制会损害胆固醇酯化,从而增强抗肿瘤作用并增强 CD8+ T 细胞的细胞增殖[20]。既往研究显示, ACAT1 是结直肠癌、膀胱癌、肾透明细胞癌、三阴性乳腺癌、胶质母细胞瘤等恶性肿瘤及阿尔兹海默症的可能治疗靶基因[21]-[26]。Yang W 等人根据 T 细胞胆固醇代谢的调节途径,提出了一种抗肿瘤免疫治疗新概念,阿伐麦布作为一种 ACAT1 抑制剂可以增强 CD8+ T 细胞的抗肿瘤活性,具有显著的抗肿瘤效果[27]。2024 年中国学者发现 ACAT1 位点是一种天然有效抑制肿瘤生长的物质——绿源酸的主要靶蛋白之一,这有助于后续抗肿瘤治疗的临床应用[28]。

ACAT1 基因 rs11545566 位点的多态性与冠心病的发生及其严重程度相关[12]。NAFLD 与冠心病的发生均与脂质代谢相关。本研究首次探究了 ACAT1 基因 rs11545566 位点多态性与 NAFLD 发病风险的相关性。经检验, ACAT1 基因 rs11545566 位点的基因型、隐性基因模型、显性基因模型和等位基因频率的分布差异在 NAFLD 组和健康对照组之间无统计学意义。我们发现与非 G 等位基因携带者相比, G 等位基因的携带者的 ALT 水平更低, G 等位基因是否在肝脏细胞的破坏和炎症反应中发挥着积极的作用,值得我们进一步的研究。

5. 结论

在中国青岛汉族人群中, ACAT1 基因 rs11545566 位点与 NAFLD 的易感性无相关性。ACAT1 基因 rs11545566 位点 G 等位基因携带与更低水平的 ALT 相关。

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