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PNPLA3 rs3747207位点多态性与NAFLD易感性的相关性

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摘 要

目的：探讨青岛地区汉族人群中patatin样磷脂酶结构域蛋白3 (Patatin-like phospholipase domain-containin, PNPLA3)基因rs3747207位点多态性与非酒精性脂肪性肝病(Non-Alcoholic Fatty Liver Disease, NAFLD)发病风险的相关性。方法：随机纳入2020年12月~2022年6月就诊于青岛市市立医院的NAFLD患者223例，并选取同期健康对照人群168例。采集所有受试者的临床数据及血液样本，检测血液样本的生物化学指标并测定PNPLA3 rs3747207位点基因型。根据是否符合正态分布对定量资料进行t检验或非参数检验。定性资料两组间比较采用χ^2检验。采用二元logistic回归分析NAFLD发生的危险因素。结果：PNPLA3 rs3747207基因型分布及等位基因频率在NAFLD组和对照组之间分布无统计学意义(P均 > 0.05)。二元logistic回归分析表明，携带GG基因型未增加NAFLD发病风险(OR = 0.702, 95%CI: 0.428~1.152, P = 0.161)。GG基因型携带者低密度脂蛋白水平高于非携带者(P < 0.05)。结论：PNPLA3 rs3747207多态性与青岛地区汉族人群NAFLD发病风险无明显相关性。

关键词

非酒精性脂肪性肝病，基因多态性，PNPLA3 rs3747207

Correlation between PNPLA3 rs3747207 Polymorphism and Non-Alcoholic Fatty Liver Disease

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Abstract

Objective: To investigate the relationship between PNPLA3 rs3747207 polymorphism and the onset risk of non-alcoholic fatty liver disease in the Chinese Han population in Qingdao. Methods: A total of 223 patients with NAFLD who attended Qingdao Municipal Hospital from December 2020 to June 2022 were enrolled in NAFLD group; 168 healthy individuals were enrolled in control group. We collected the clinical date and blood sample of all subjects to measure related biochemical parameters and detect PNPLA3 rs3747207 genotype. The t-test was used for the comparison of normally distributed quantitative data between two groups, and the non-parametric test was used for the non-normally distributed quantitative data between two groups. The chi-square test was used for comparison of qualitative data between two groups. The binary logistic regression analysis was used to investigate the risk factors for NAFLD. Result: There was no significant difference in PNPLA3 rs3747207 genotype distribution and allele frequency between the control group and NAFLD group (P > 0.05). The binary logistic regression analysis showed that the risk of NAFLD in individuals with genotype GG was not increased compared with those in individuals with allele gene A (OR = 0.702, 95%CI: 0.428~1.152, P = 0.161). For all subjects, the subjects with GG genotype had a higher level of low density lipoprotein than those with allele gene A (P < 0.05). Conclusion: There is no significant association between PNPLA3 rs3747207 polymorphism and the risk of NAFLD in the Chinese Han population in Qingdao.

Keywords

Non-Alcoholic Fatty Liver Disease, Gene Polymorphism, Patatin like Phospholipase Domain Containing Protein 3

1. 引言

非酒精性脂肪性肝病(Non-Alcoholic Fatty Liver Disease, NAFLD)是指排除过量饮酒等继发性原因引起的以肝脏脂肪变性为主要特征的临床病理综合征[1]。流行病学显示，全球 NAFLD 患病率约为 32.4%，亚洲患病率约为 34% [2] [3]。NAFLD 促进肝细胞癌的发展，NAFLD 患病率的上升可能会在接下来的几十年中引发肝细胞癌发病率的过度增加[4] [5]。如何预防 NAFLD 发生、延缓乃至控制其进展是目前亟待解决的问题。NAFLD 的发病机制十分复杂，现有研究认为它与肥胖、代谢综合征、糖尿病、胰岛素抵抗、遗传、肠道微生物群等多种因素相关[6]。其中，遗传因素通过影响脂代谢、炎症通路和氧化应激等机制对 NAFLD 的流行和严重程度发挥重要作用[7]。

Patatin 样磷脂酶结构域蛋白 3 (tatin-like phospholipase domain-containin, PNPLA3)基因在人体内位于 22 号染色体(22q13. 31)，其编码的蛋白质是一种具有催化甘油三酯水解和溶血磷脂酸酰化作用的酶[8]。

2008 年，Romeo 等人首先发现了 PNPLA3 rs738409 位点的 C/G 变异与肝脏脂肪含量升高和肝脏炎症密切相关[9]。随着研究的深入，Peng 等人还发现 PNPLA3 基因的 rs139051、rs143392071、rs3747207 等位点与 NAFLD 发病风险相关[10] [11] [12] [13]。最近，Gong 等人在一项纳入了 971 名汉族人群的研究中指出，rs3747207 位点与年龄大于 55 岁的人群肝癌易感性增加相关[14]。国内目前尚无 rs3747207 与 NAFLD 发病风险相关研究，本研究旨在探索 PNPLA3 rs3747207 位点多态性与中国青岛地区汉族人群 NAFLD 发病风险的相关性，进而完善 NAFLD 相关遗传因素的研究。

2. 对象和方法

2.1. 研究对象

本研究已得到青岛市市立医院伦理委员会批准。所有受试者均已签署知情同意书。NAFLD 患者来自于 2020 年 12 月~2022 年 6 月就诊于青岛市市立医院的 NAFLD 患者，健康对照来自于同期体检中心的健康体检者。所有 NAFLD 患者均由 B 型超声进行诊断，符合《非酒精性脂肪性肝病防治指南(2018 更新版)》[15]诊断标准：1) 无过量饮酒史，即每日饮酒折合乙醇量男性 < 30 g，女性 < 20 g；2) 除外酒精性肝病、自身免疫性肝炎、基因 3 型丙型肝炎病毒感染等可致脂肪肝的特殊肝脏疾病；3) 未应用他莫西芬、丙戊酸钠、乙胺碘呋酮等可致脂肪肝的药物；4) 排除全胃肠外营养、乳糜泻、炎症性肠病等可致脂肪肝的特殊情况；5) 血清氨基酸转移酶和 γ-谷氨酰转移酶(GGT)增高，同时排除可致肝脏生化指标异常以及肝硬化的其他原因；6) 符合肝脏影响学诊断标准。所有健康体检者体检、影像和实验室等辅助检查未见明显异常，并排除 NAFLD 相关疾病。

2.2. 临床及化验评估

详细记录所有受试者的性别、年龄，对其身高及体质量进行标准测量并计算体质量指数(body mass index, BMI)。每个受试者于 12 h 空腹后在上午取静脉血 4 ml，将静脉血分别保存至 2 个 EDTA 抗凝管中用于后续研究：一管血液样本在青岛市市立医院检验科进行生物化学指标检测，包括 γ-谷氨酰转移酶、空腹血糖(FPG)、血清丙氨酸氨基转移酶(ALT)、天冬氨酸氨基转移酶(AST)、碱性磷酸酶(ALP)、总胆固醇(TC)、甘油三脂(TG)、低密度脂蛋白(LDL)、高密度脂蛋白(HDL)、总胆红素(TBil)；一管血液样本用于 DNA 提取及基因型鉴定。

2.3. 诊断标准

使用血液基因组 DNA 提取试剂盒(博淼生物科技公司)从血液样本中提取 DNA，然后使用多聚合酶链反应方法对 PNPLA3 目的基因进行扩增及基因型分析，基因扩增引物序列为“5’-ACGTTGGATGAAGTGTGCTCACACATCTCC-3’”和“5’-ACGTTGGATGTGAAAGGCAGTGAGGCATGG-3’”。基因扩增程序为首先在 94℃进行最初的 5 min 预变性，然后进行 45 个循环的扩增：94℃变性 20 s，56℃退火 30 s，72℃延伸 1 min。PNPLA3 rs3747207 位点的基因型通过基因测序方法进行鉴定。

2.4. 基因组 DNA 提取及基因分型

使用 SPSS 26.0 版软件对所得数据进行统计分析。使用 χ^2 检验分析 PNPLA3 rs3747207 基因型分布是否具有群体代表性。定性资料两组间比较应用卡方检验(χ^2)；连续变量经方差齐性检验后符合正态分布的资料用均数±标准差表示，两组间比较应用 t 检验；符合非正态分布的资料用中位数(四分位数)表示，两组间比较应用非参数检验。使用非条件 logistic 回归模型来评估 PNPLA3 rs3747207 位点多态性与 NAFLD 发病风险之间的风险，以 $P < 0.05$ 为差异有统计学意义。

3. 结果

3.1. 研究人员的基线特征

本研究共纳入了 223 例 NAFLD 患者，168 例健康对照。NAFLD 组和健康对照组的临床特征见表 1。两组间性别、TC、LDL、TBil 差异无统计学意义(P 均 > 0.05)。NAFLD 组的年龄、BMI、FPG、ALT、AST、ALP、TG 水平显著高于健康对照组，并且 NAFLD 组的高密度脂蛋白水平显著低于健康对照组(P 均 < 0.05)。

Table 1. Clinical date and biochemical parameters of all subjects
表 1. 所有受试者的临床资料及生物化学指标

各类指标	健康对照	NAFLD	统计值 χ^2/t/z	*P*
男/女	89/79	117/106	χ^2 = 0.010	0.920
年龄，岁	39 (30, 52)	53 (41, 63)	z = −6.598	<0.001
BMI, kg/m^2	24.22 (22.00, 27.50)	27.16 (24.80, 29.48)	z = −5.119	<0.001
FPG, mmol/L	4.92 (4.49, 5.22)	5.12 (4.57, 6.03)	z = −2.661	0.008
ALT, U/L	17.59 (12.96, 26.96)	28.08 (17.90, 41.11)	z = −5.380	<0.001
AST, U/L	20.00 (16.07, 24.00)	24.01 (19.54, 32.54)	z = −5.082	<0.001
GGT, U/L	18.00 (12.00, 26.25)	30.12 (21.76, 47.83)	z= −7.016	<0.001
ALP, U/L	74.66 (59.68, 87.06)	86.41 (71.99, 105.99)	z = −3.516	<0.001
TC, mmol/L	4.88 (4.27 ,5.49)	5.09 (4.33, 5.79)	z = −1.422	0.155
TG, mmol/L	1.04 (0.79, 1.45)	1.76 (1.18, 2.45)	z = −7.196	<0.001
HDL, mmol/L	1.30 (1.13, 1.49)	1.14 (1.02, 1.31)	z = −4.241	<0.001
LDL, mmol/L	3.00 (2.47, 3.45)	3.15 (2.63, 3.61)	z= −1.629	0.103
TBil，μmol/L	13.20 (10.38, 16.50)	12.60 (10.33, 16.78)	z = −0.266	0.790

注：空腹血糖(FPG)、血清丙氨酸氨基转移酶(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)、总胆固醇(TC)、甘油三脂(TG)、低密度脂蛋白(LDL)、高密度脂蛋白(HDL)、总胆红素(TBil)。

3.2. PNPLA3 rs3747207 基因型及等位基因的分布

χ^2 检验显示健康对照组及 NAFLD 组 PNPLA3 rs3747207 的基因型分布符合 Hardy-weinberg 平衡法则(P 分别为 0.878、0.935)，具有群体代表性(表 2)。两组的 PNPLA3 rs3747207 位点的基因型和等位基因分布差异无统计学意义(P 均 > 0.05) (表 3)。非条件 Logistic 回归模型分析结果显示：PNPLA3 rs3747207 位点基因型及等位基因分布与 NAFLD 发病风险无明显相关(P 均 > 0.05) (表 4)。

Table 2. Analysis of Hardy-Weinberg equilibrium of PNPLA3 rs3747207 in two groups
表 2. PNPLA3 rs3747207 在两组中的 Hardy-Weinberg 遗传平衡定律分析

基因型	χ^2	*P*
健康对照组	0.730	0.694
NAFLD 组	0.586	0.746

Table 3. PNPLA3 rs3747207 allele and genotype frequency distribution
表 3. PNPLA3 rs3747207 等位基因和基因型频率分布

		NAFLD (n = 223) n (%)	健康对照 (n = 168) n (%)	χ^2	*P*
基因型	GG	72 (32.3)	65 (38.7)	2.037	0.361
	GA	102 (45.7)	73 (43.5)		
	AA	49 (22.0)	30 (17.9)		
等位基因	G	246 (55.2)	203 (60.4)	2.168	0.141
	A	200 (44.8)	133 (39.6)		
显性模型	GG	46 (32.4)	51 (38.1)	1.726	0.189
	GA + AA	96 (67.6)	83 (61.9)		
隐性模型	AA	113 (80.0)	111 (82.8)	1.007	0.316
	GG + GA	29 (20.0)	23 (17.2)		

Table 4. Logistic regression analysis of risk factors for NAFLD
表 4. NAFLD 危险因素的 logistic 回归分析结果

		OR	95%CI	*P*	OR	95%CI	*P*'
等位基因	G A	0.806	(0.605, 1.074)	0.141			
显性模型	GG GA + AA	0.702	(0.428, 1.152)	0.161	0.593	(0.332, 1.062)	0.079
隐性模型	AA GG + GA	1.633	(0.866, 3.082)	0.130	1.733	(0.855, 3.509)	0.127

注：*P*'值为校正年龄、性别、BMI 后的 *P* 值。

3.3. PNPLA3 rs3747207 基因多态性与临床参数的相关性

在所有受试者中我们进行了 PNPLA3 rs3747207 不同基因型之间生物化学指标的比较。结果显示，在所有受试者中，PNPLA3 rs3747207 位点 GG 基因型携带者与 A 等位基因携带者相比有更高的 LDL 水平 ($P < 0.05$) (表 5)。

Table 5. Comparison of various indexes between GG genotype carriers and non-carriers in all subjects
表 5. 所有受试者中 GG 基因型携带者与非携带者各项指标比较

各类指标	GG	GA + AA	统计值 t/z	*P*
BMI, kg/m^2	26.00 (23.12, 28.20)	26.53 (23.95, 29.10)	z = −1.504	0.133
FPG, mmol/L	5.10 (4.62, 5.85)	5.04 (4.52, 5.79)	z = −0.677	0.498
ALT, U/L	21.13 (14.33, 33.87)	24.92 (15.30, 37.86)	z = −1.796	0.072
AST, U/L	21.41 (18.09, 26.54)	22.46 (18.27, 30.92)	z = −1.903	0.057
GGT, U/L	26.97 (19.00, 41.05)	25.38 (16.00, 45.42)	z = −0.560	0.575
ALP, U/L	82.98 (68.71, 97.25)	85.31 (69.23, 104.30)	z = −0.633	0.527

Continued

TC, mmol/L	5.22 (4.48, 6.04)	4.98 (4.28, 5.56)	z = −1.960	0.050
TG, mmol/L	1.47 (1.04, 2.02)	1.37 (0.92, 2.18)	z = −0.486	0.627
HDL, mmol/L	1.16 (1.04, 1.37)	1.22 (1.06, 1.38)	z = −0.868	0.385
LDL, mmol/L	3.30 (2.66, 3.71)	2.99 (2.53, 3.46)	z = −2.717	0.007
TBil，μmol/L	12.90 (10.00, 17.20)	12.84 (10.50, 16.65)	z = −0.482	0.630

注：空腹血糖(FPG)、血清丙氨酸氨基转移酶(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)、总胆固醇(TC)、甘油三脂(TG)、低密度脂蛋白(LDL)、高密度脂蛋白(HDL)、总胆红素(TBil)。

4. 讨论

个体间 NAFLD 的发生和相关并发症的变异性是由遗传和环境因素共同决定的[16]。本研究在 391 名青岛地区汉族人群中探讨了 PNPLA3 rs3747207 位点基因多态性与 NAFLD 发病风险的相关性。

目前研究认为，PNPLA3 基因的作用是协助调节脂肪细胞的发育以及肝细胞和脂肪细胞中脂肪的产生和分解[17]。该基因编码的蛋白质主要表达于肝细胞和肝星状细胞，在这两种细胞中均发挥着脂滴调节的作用[8]。近期，Ericson 等人的研究[18]利用人 PNPLA3 蛋白抗体测定了 NAFLD 患者肝活检组织中 PNPLA3 蛋白水平，他们发现 PNPLA3 蛋白水平的升高和 NAFLD 患者脂肪变性程度的增加显著相关(P = 0.000027)，并且在小叶性炎症(P = 0.009)、气球膨胀(P = 0.022)和显著纤维化(2~4 期：P = 0.014)的患者中 PNPLA3 蛋白水平也有显著升高。PNPLA3 基因多态性可通过促进脂肪变性(rs738409 位点[19] [20] [21])，促进炎症(rs738409 位点[22]、rs2281135 位点[23])和纤维化(rs738409 位点[24] [25] [26]、rs2281135 位点和 rs2143571 位点[27])来影响 NAFLD 的发生和发展。2019 年，Namjou 等人对欧洲血统受试者进行的全基因组关联研究(genome-wide association study, GWAS)显示 rs3747207 与 NAFLD 发病风险具有相关性[12]。研究结果显示 rs3747207 多态性与 NAFLD 易感性无明显相关性，与上述 GWAS 结果不一致。这可能由于种族特异性，本研究受试者均为中国汉族人群，而 GWAS 研究对象则为欧洲人群。此外，GWAS 研究对象通过肝活组织检查诊断，而本研究是通过 B 型超声进行诊断，对轻度脂肪肝的诊断灵敏度较低。尽管本研究 PNPLA3 rs3747207 基因型分布在 NAFLD 组和健康对照组之间没有差异，但不同基因型携带者的血脂水平有差异。

本研究比较携带 A 等位基因及未携带 A 等位基因受试者的各项指标，结果表明在所有受试者中，PNPLA3 rs3747207 位点 GG 基因型携带者与 A 等位基因携带者相比有更高的 LDL 水平。LDL 颗粒的主要成分是低密度脂蛋白胆固醇(low density lipoprotein cholesterin, LDL-C) [28]，先前的研究表明 LDL-C 与 NAFLD 发病风险增加有关[29] [30]。此外，LDL 可分为大而轻 LDL 和小而密 LDL (small and dense low-density lipoprotein, sdLDL) [31]。NAFLD 患者血脂异常的特征除血浆 TG 水平升高(P < 0.001)外，还包括 sdLDL 水平升高(P < 0.01)和 HDL 水平下降(P < 0.001) [32] [33] [34]。近期，Young 等人的研究[35]发现 NAFLD 患者的 sdLDL 水平不但高于健康人群[33]，而且随着肝脂肪变性和纤维化程度的加重而逐渐升高。因此，纵然本研究 rs3747207 位点多态性与 NAFLD 发病风险无明显相关，但鉴于该位点与 LDL 水平密切相关，且与肝癌易感性相关[14]，我们仍不能忽视该基因位点对 NAFLD 发生发展过程的影响。

综上所述，PNPLA3 rs3747207 基因多态性与 NAFLD 的发病风险无明显相关性，然而 GG 基因型携带与受试者 LDL 水平升高有关。由于本研究存在一定的局限性，下一步研究应招募更多受试者，完善肝活组织检查，进一步研究 PNPLA3 rs3747207 基因多态性对 NAFLD 的影响。

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