Gene 528 (2013) 328–334

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Short Communication

Association between the Pro12Ala polymorphism of PPAR-γ gene and the non-alcoholic fatty liver disease: A meta-analysis

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ARTICLE INFO

Article history:
Accepted 8 July 2013
Available online 23 July 2013

Keywords:
PPAR-γ
Non-alcoholic fatty liver disease
Polymorphism
Meta-analysis

ABSTRACT

Several studies have been conducted to examine the association between PPAR-γ2 Pro12Ala polymorphism and non-alcoholic fatty liver disease (NAFLD), but the results remain inconsistent. In this study, a meta-analysis was performed to assess the association of PPAR-γ Pro12Ala polymorphism with NAFLD risk. A total of 8 case–control studies, including 1697 cases and 2427 controls, were selected. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated using fixed- or random-effects model. Overall, no evidence has indicated that the Pro12Ala polymorphism was associated with the susceptibility to NAFLD. Besides, stratified analysis with ethnicity also indicated that no significant association between PPAR-γ Pro12Ala and the risk of NAFLD under all for genetic model in both Asian and Caucasian populations was observed. This meta-analysis indicated that the Pro12Ala polymorphism is not associated with NAFLD risk. Large and well-designed studies are warranted to validate our findings.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a major cause of liver disease worldwide (Lazo and Clark, 2008). And it is usually in the form of steatosis but may progress to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis, and occasionally to hepatocellular carcinoma (Adams et al., 2005). NAFLD is a hepatic component of metabolic syndrome (MS), which is characterized by obesity, type 2 diabetes, dyslipidemia and hypertension with insulin resistance being the main mechanisms (Mendez-Sanchez et al., 2007). Although the exact etiology of NAFLD is not known, however it is a complex metabolic condition in which both lifestyle and genetic factors have a pathogenic role (Angulo, 2002).

Peroxisome proliferator activated receptor-γ (PPAR-γ) is a member of the nuclear hormone receptor superfamily and is located on chromosome 3p25 and encodes a nuclear transcription factor involved in the expression of hundreds of genes (Stumvoll and Haring, 2002). PPAR-γ increases expression of lipoprotein lipase, an enzyme that serves to partition fat to adipocytes, limiting fatty acid flux to the liver (Di Rosa and Malaguarnera, 2012). There are several polymorphism sites in the PPAR-γ gene, and the CCA-to-GCA (Pro-to-Ala) mutation in codon 12 of exon B of the PPARγ2 is a common single nucleotide polymorphism (SNP). The Pro12Ala polymorphism (rs1801282) has been identified to have a key role in the development of obesity, insulin resistance and type 2 diabetes (Stickel and Hampe, 2012; Yen et al., 1997). Recently, there are several studies that investigated the association between the Pro12Ala polymorphism and the susceptibility of NAFLD in diverse populations. However, the results of these studies remain controversial.

In this study, we conduct a meta-analysis on 8 eligible case–control studies (Bhatt et al., 2013; Cao et al., 2012; Dongiovanni et al., 2010; Gawrieh et al., 2012; Gupta et al., 2010; Rey et al., 2010; Yang et al., 2012; Ye and Lv, 2007) to evaluate the association between the Pro12Ala polymorphism and NAFLD susceptibility.

2. Materials and methods

2.1. Search strategy

A literature research was conducted using PubMed and Web of Science up to December 2012 without language restrictions. Relevant studies were identified using the terms: ['peroxisome proliferator activated receptor-γ or PPAR-γ or peroxisome proliferator activated receptor gamma or PPAR-gamma'] AND ['genetic polymorphism or polymorphisms or variant'] AND ['non-alcoholic fatty liver disease or NAFLD']. The search was restricted to humans. Additional studies were identified by a hand search of references of original or review articles on this topic.

2.2. Inclusion criteria and exclusion criteria

Studies were included if they met the following criteria: (1) the diagnostic criteria for NAFLD were clear: studies were included when

Abbreviations: PPAR-γ, peroxisome proliferator activated receptor-γ; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MS, metabolic syndrome; SNP, single nucleotide polymorphism; CI, confidence interval; OR, odds ratio; HWE, Hardy–Weinberg equilibrium.

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http://dx.doi.org/10.1016/j.gene.2013.07.014

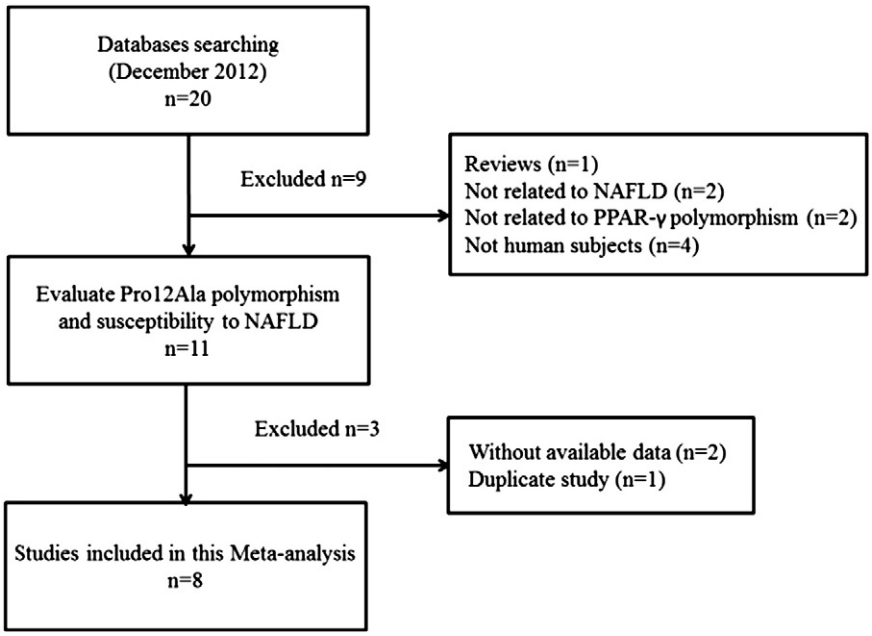

Fig. 1. Flow chart showing study selection procedure.

imaging features (ultrasound and/or computed tomography) of the liver reveal a diffuse fatty liver and/or confirmed histologically by liver biology, and studies were excluded by the following reasons: increased alcohol consumption (>30 g/day for males, >20 g/day for females), infectious (HBV and HCV), immunological, drug-induced, or hereditary causes of liver disease, and other serious diseases (including severe heart, lung, brain, or kidney diseases); (2) studies that evaluated the association between the Pro12Ala polymorphism and NAFLD, (3) in a case–control study design, and (4) had detailed genotype frequency of cases and controls or could be calculated from the article text. While major exclusion criteria were: (1) case-only study, case reports, and review articles, (2) studies without the raw data of the Pro12Ala genotype of PPAR-γ, and (3) studies that compared the PPAR-γ variants in alcoholic fatty liver disease.

2.3. Data extraction and quality assessment

The two investigators (Wang J and Guo XF) independently extracted data and reached consensus on all of the items. If the two investigators generated different results, they would check the data again and have a discussion to come to an agreement. If they could not reach an agreement, an expert (Dong WG) was invited to the discussion. Data extracted from the selected articles included the first author's name, year of publication, country of origin, ethnicity, source of controls, age, gender, diagnostic method of NAFLD, number of cases and controls, and minor allele frequency in the controls. Different ethnicity was categorized as Asian and Caucasian.

2.4. Statistical analysis

Meta-analysis was performed using the Cochrane Collaboration RevMan 5.0 (Copenhagen, 2008) and STATA package version 9.2 (Stata Corporation, College Station, Texas). The risk of NAFLD associated with the Pro12Ala polymorphism of the PPAR-γ gene was estimated for each study by odds ratio (OR) and 95% confidence interval (95% CI). A χ^2-test-based Q statistic test was performed to assess the between-study heterogeneity (Lau et al., 1997). We also quantified the effect of heterogeneity by I^2 test. When a significant Q test ($P < 0.1$) or $I^2 > 50\%$ indicated heterogeneity across studies, the random effects model was used (DerSimonian and Laird, 1986), or else the fixed effects model was used (Mantel and Haenszel, 1959). Before the effect estimation of PPAR-γ polymorphism in NAFLD, we tested whether genotype frequencies of controls were in Hardy–Weinberg equilibrium (HWE) using χ^2 test. We first estimated the risks of the heterozygote (Pro/Ala) and variant homozygote (Ala/Ala) compared with the wild-type homozygote (Pro/Pro), respectively, and then evaluated the risks of the combined

Table 1
Characteristics of studies included in the meta-analysis.

Study	Year	Country	Ethnicity	Source of controls	Age, mean ± SD, year		Gender (male, %)		NAFLD method	Genotype (case/control)			P_{HWE}
					Case	Control	Case	Control		Pro/Pro	Pro/Ala	Ala/Ala	
Bhatt	2013	India	Asian	HB	38.2 ± 7.0	37.1 ± 6.9	NR	NR	Ultrasound	124/144	28/23	10/6	0.0004
Cao	2012	China	Asian	PB	56 (49–65.5)[a]	56 (46–64)	24.85	25.61	Ultrasound + liver biopsy	159/656	10/43	0/0	0.401
Dongiovanni	2010	Italy	Caucasian	PB	47.4 ± 11	47.7 ± 12	80	79	Liver biopsy	166/295	33/50	3/1	0.461
Gawrieh	2012	USA	Caucasian	PB	44 ± 10	43 ± 13	31.7	29.1	Liver biopsy	162/32	47/25	3/5	0.970
Gupta	2011	India	Asian	HB	36 ± 7	32 ± 8	67.35	65	Ultrasound or liver biopsy	63/213	34/67	1/0	0
Rey	2010	Germany	Caucasian	HB	50.48 ± 15.25	NR	NR	NR	Liver biopsy	206/200	48/55	9/4	0.922
Yang	2012	China	Asian	PB	61.1 ± 8.3	59.3 ± 8.0	35.77	44.11	Ultrasound	406/409	30/58	0/0	0.152
Ye	2007	China	Asian	HB	NR	NR	NR	NR	Ultrasound	142/130	13/11	0/0	0.630

PB, population based; HB, hospital based; NR, not reported.
[a] Expressed as median (interquartile range).