Impact of patatin-like phospholipase domain-containing-3 rs738409 polymorphism in chronic liver disease: a meta-analysis of 27,365 subjects

Yang Zheng [1#], Lei Wang [1#], Jia-Hui Wang [1], Tian-Jian Liang [1*], Tie-Jian Zhao [2*]

[1]Department of Medicine, Faculty of Chinese Medicine science Guangxi University of Chinese Medicine, Nanning, Guangxi 530021, P. R. China.

[2]Department of Physiology, College of basic Medicine, Guangxi University of Chinese Medicine, Nanning, Guangxi 530021, P. R. China.

***Corresponding to**: Tian-Jian Liang, Department of Medicine, Faculty of Chinese Medicine science Guangxi University of Chinese Medicine,13 Wuhe Road, Nanning, Guangxi, P. R. China; E-mail: zycc5@sina.com.

Tie-Jian Zhao, Department of Physiology, College of basic Medicine, Guangxi University of traditional Chinese Medicine, 13 Wuhe Road, Nanning, Guangxi, P. R. China; E-mail: 13014989836@163.com.

Abstract: Background: Some genetic association studies have investigated the potential role of patatin-like phospholipase domain-containing-3 (PNPLA3) polymorphisms in chronic liver disease, retrieving inconsistent results. Therefore, we performed a meta-analysis to further explore *PNPLA3* rs738409 in a large pooled population with chronic liver disease. **Methods:** Eligible studies were selected from PubMed, Embase, and CNKI databases. Studies heterogeneity was assessed using I^2 statistics: when I^2 >50% the random effects model was used to pool the data; otherwise, a fixed effects model was used. **Results:** In total, 36 studies were selected, comprising 14,855 cases and 12,510 controls. The analysis showed that rs738409 was significantly associated with chronic liver disease in the general population (dominant model: $P < 0.0001$, OR=1.62, 95% CI=1.43–1.83, I^2=81.2%; recessive model: $p<0.0001$, OR=2.01, 95% CI=1.75–2.30, I^2=74.1%; allele model: P=0.001, OR=1.53, 95% CI=1.39–1.68, I^2=84.8%). These significant correlations were further confirmed in Asian and Caucasian populations. A stratified analysis also showed a positive correlation between rs738409 and hepatocellular carcinoma (HCC), cirrhosis, and non-alcoholic fatty liver disease (NAFLD), but not with chronic hepatitis B infection or alcoholic liver disease. **Conclusions:** Altogether, *PNPLA3* rs738409 may help identify individuals at higher susceptibility to chronic liver disease, in particular for HCC, cirrhosis, and NAFLD.

Key words: chronic liver disease, meta-analysis, rs738409, single nucleotide polymorphism, patatin-like phospholipase domain-containing-3, PNPLA3

***Acknowledgments*:** This study was supported by the National Natural Science Foundation of China (grant numbers 81960751 and 81660705) and the Guangxi University Young and Middle-aged Teachers' Research Ability Improvement Project (grant number 2020KY59009).

***Authors' Contributions*:** #Yang Zheng and Lei Wang contributed equally to this study and should be considered as co-first authors. Yang Zheng was responsible for writing the manuscript, Lei Wang was responsible for data processing, Jia-Hui Wang was responsible for document retrieval and screening, and Tie-Jian Zhao and Tian-Jian Liang were responsible for the design of the article's ideas and revision of the manuscript.

***Abbreviations*:** PNPLA3, patatin-like phospholipase domain-containing-3; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; SNP, single nucleotide polymorphism; CNKI, China National Knowledge Infrastructure; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa Scale; OR, odds ratio; CI, confidence interval; REMS, random effects model; FEMS, fixed effects model; CHB, chronic hepatitis B infection; ALD, alcoholic liver disease; MPE, molecular pathological epidemiology.

***Competing interests*:** The authors declare that there are no financial conflicts of interest.

***Citation*:** Zheng Y, Wang L, Wang JH, Liang TJ, Zhao TJ. Impact of patatin-like phospholipase domain-containing-3 rs738409 polymorphism in chronic liver disease: a meta-analysis of 27,365 subjects. *Gastroenterol Hepatol Res*. 2020;2(4):119-124. doi: 10.12032/ghr2020-12-025.

***Executive Editor*:** Xin Cheng.

***Submitted*:** 18 December 2020, ***Accepted*:** 12 November 2020, ***Published*:** 12 December 2020

Background

The main feature of chronic liver disease is the chronic lesions that occur in the liver, most of which are caused by viral hepatitis, non-alcoholic fatty liver, alcoholic liver disease, cirrhosis and liver cancer [1]. About 200 million people worldwide die of chronic liver disease every year, among which cirrhosis and liver cancer are the 11th and 16th most common cause of death, respectively [2]. The etiology of chronic liver disease is very complex. Chronic inflammation, excessive alcohol consumption, obesity, and viral infections have all been proven to be the causative factors of different types of chronic liver diseases [3, 4]. However, the possibility that people exposed to the above factors will further develop chronic liver disease is uncertain, which shows that genetic factors play an important role in the pathogenesis of chronic liver disease.

The patatin-like phospholipase domain–containing 3 (PNPLA3) gene, which belongs to the patatin-like phospholipase family, is located on chromosome 22 and encodes a soluble non-secretory protein consisting of 481 amino acids that is mainly expressed in adipocytes and liver cells. The protein has lipase and glyceride transacetylase activity, and regulates the triglyceride metabolism in the liver [5]. The single nucleotide polymorphism (SNP) rs738409 in *PNPLA3* causes the replacement of the isoleucine at position 148 by a methionine. This change inhibits the triglyceride hydrolase activity of PNPLA3, resulting in increased hydrolysis of triglycerides and their accumulation in liver cells. Studies have confirmed that rs738409 polymorphim in *PNPLA3* can promote non-alcoholic fatty liver disease (NAFLD) and cirrhosis [6, 7]. Since then, several genetic association studies were conducted in different populations to estimate the potential association between the rs738409 SNP and chronic liver disease, but with inconsistent results [8-10]. Therefore, we conducted a comprehensive systematic analysis of all related articles to evaluate the influence of PNPLA3 polymorphism on the susceptibility of individuals to chronic liver disease in a large number of people.

Methods

Literature retrieval and inclusion criteria

Eligible studies were selected from several databases, including PubMed, Web of Science, Embase, and China National Knowledge Infrastructure (CNKI). The following search strategy was used: (patatin-like phospholipase domain 3 or PNPLA3) AND (polymorphism or mutation or mutation or mutation or genome-wide association study or gene association study) AND (chronic liver disease or chronic hepatitis or HBV or HCV or non-alcoholic fatty liver disease or non-alcoholic fatty liver or alcoholic liver disease or cirrhosis or hepatocellular carcinoma). The bibliographic search was conducted in February 2020. In addition, we screened references for all retrieved articles to identify other potentially relevant studies.

All included studies met the following conditions: (A) research on the association between *PNPLA3* rs738409 polymorphism and susceptibility to chronic liver disease in humans; (B) indication of the genotype/allele frequency of rs738409 in case and control groups; (C) full text available in English or Chinese. Studies that complied with one of the following criteria were excluded from the analysis: (A) did not evaluated *PNPLA3* rs738409 polymorphism in chronic liver disease; (B) studies that have not been performed on humans; (C) case reports or case series; (D) reviews, comments, or meeting reports; (E) not consistent with Hardy–Weinberg equilibrium.

Data extraction and quality assessment

We extracted the following data from the selected studies: first author name, year of publication, country and ethnicity of the study, sample size, and genotype/allele distribution of the *PNPLA3* rs738409 SNP in cases and controls. The probability value (*p*-value) of Hardy-Weinberg equilibrium (HWE) was calculated. When necessary, we wrote to the corresponding authors of the studies to request additional information. We used the Newcastle-Ottawa Scale (NOS) to assess the quality of eligible studies [11], with scores above 7, in a scale range from 0 to 9, being indicative of high quality. Data extraction and quality assessment were performed by two independent reviewers, and any differences between them were resolved through discussion until a consensus was reached.

Statistical analyses

We use Stata 12.0 software for statistical analysis. We calculated the odds ratio (OR) and 95% confidence interval (CI) to estimate the association strength in all possible genetic models. The statistical significance of the combined analysis was determined by the Z test. A p-value lower than or equal to 0.05 was considered statistically significant. Heterogeneity between studies was assessed using I^2 statistics. In cases where I^2 was greater than 50%, taking into account significant heterogeneity, a random effects model (REMS) was used to pool the data. Otherwise, a comprehensive analysis was performed using a fixed effects model (FEMS). Subgroup analysis was performed according to the race and disease type of the study subjects. Sensitivity analysis was conducted to evaluate the stability of the synthesis results, and funnel plots were used to evaluate publication bias.

doi: 10.53388/ghr2020-12-025

Results

Characteristics of included studies

The initial literature search retrieved 243 potentially relevant studies, among which a total of 36 studies met the inclusion criteria and were selected for the meta-analysis (Figure 1). Eligible articles had NOS scores ranging from 7 to 8, suggesting that all included studies were of high quality. The baseline characteristics of the selected studies are shown in Table 1.

Overall and subgroup analyses

The overall and subgroup analyses results are summarized in Table 1. A total of 14,855 cases and 12,510 controls were included in the analyses. Pooled data analyses showed that the rs738409 polymorphism was significantly associated with chronic liver disease, regardless of the analysis model used (dominant model: $P < 0.0001$, OR = 1.62, 95% CI = 1.43–1.83, and I^2 = 81.2%; recessive model: $P < 0.0001$, OR = 2.01, 95% CI = 1.75–2.30, I^2 = 74.1%; allele model: $P = 0.001$, OR = 1.53, 95% CI = 1.39–1.68, I^2 = 84.8%). These significant findings were also confirmed in both Asian (dominant, recessive, and allele models) and Caucasian (dominant, recessive and allele models) populations. Stratified analyses by type of disease further revealed similar positive results in hepatocellular carcinoma (HCC), cirrhosis, and NAFLD, but not in chronic hepatitis B infection (CHB) and alcoholic liver disease (ALD) (Table 2).

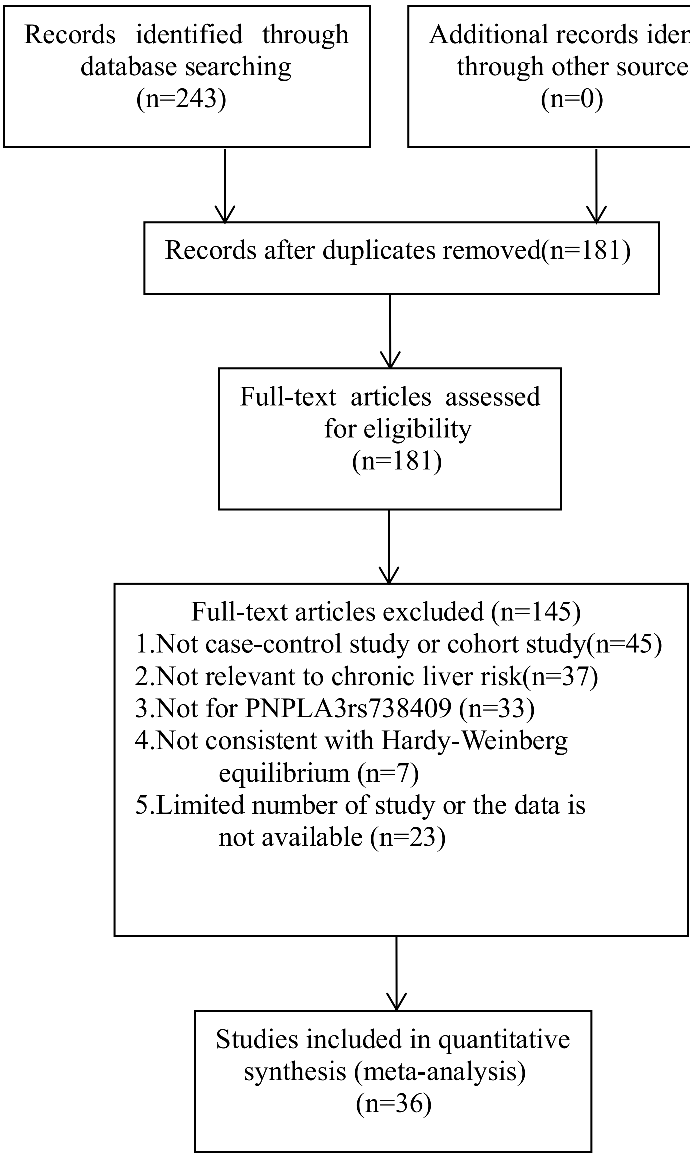

Figure 1. The studies identified in this meta-analysis based on the inclusion and exclusion criteria.

Table 1. The characteristics of included studies for PNPLA3 rs738409 polymorphism and chronic liver disease.

First author (year)	Country	Ethnicity	Type of disease	Sample size	Genotype distribution Cases	Genotype distribution Controls	p-value for HWE	NOS score
Eric2011	Belgium	Caucasian	ALD	330/328	140/148/42	181/118/92	0.331	7
Wang2018	China	Asian	HCC	407/358	165/185/57	143/173/42	0.801	7
Wang2018	China	Asian	CHB	673/358	244/337/92	143/173/42	0.801	7
Wang2018	China	Asian	Cirrhosis	657/358	278/296/83	143/173/42	0.801	7
Xu2013	China	Asian	NAFLD	315/336	45/128/142	155/139/42	0.562	7
Jiang2014	China	Asian	CHB	185/164	91/70/24	103/50/11	0.556	8
An2016	China	Asian	NAFLD	296/321	55/136/105	103/162/56	0.875	8
Luca2012	Italy	Caucasian	NAFLD	144/257	55/68/21	146/95/16	0.995	7
Luca2012	Italy	Caucasian	CHC	261/257	133/103/25	146/95/16	0.995	7
Kikuko2010	Japan	Asian	NAFLD	253/575	45/111/97	175/296/104	0.558	8
Chen2019	China	Asian	NAFLD	512/451	114/236/162	196/194/61	0.503	8
Juozas2017	Lithvania	Caucasian	Cirrhosis	317/498	162/124/31	341/140/17	0.823	8
Shahinul2017	Bengal	Asian	NAFLD	99/75	37/43/19	45/27/3	0.856	7
Casper2016	Germany	Caucasian	HCC	44/174	13/18/13	104/62/8	0.947	8
Sayeh2014	Africa	Caucasian	CHC	230/132	90/106/34	66/54/12	0.947	7
Edmondo2011	Italy	Caucasian	Cirrhosis	483/428	168/220/95	218/175/35	0.997	8
Wang2016	China	Asian	NAFLD	376/382	122/191/63	169/174/39	0.813	8
Gao2017	China	Asian	CHB	672/358	244/337/92	143/173/42	0.655	8
Gao2017	China	Asian	Cirrhosis	557/358	278/296/83	143/173/42	0.655	8
Gao2017	China	Asian	HCC	408/358	166/185/57	143/173/42	0.655	8
Eylul2014	Turkey	Asian	NAFLD	80/303	13/49/18	118/133/52	0.397	8
Sang2014	Korea	Asian	NAFLD	155/184	31/75/49	55/92/37	0.995	7
Lin2011	China	Asian	NAFLD	102/418	24/52/26	167/192/59	0.966	7
Marzuillo2019	Italy	Caucasion	NAFLD	327/264	152/123/52	133/96/35	0.178	8
Mazo2019	Brazil	Caucasion	NAFLD	248/134	77/117/54	66/55/13	0.919	8
Manal2013	America	Caucasion	HCC	257/494	130/94/33	274/197/23	0.227	8
Daniele2016	Italy	Caucasion	HCC	170/304	71/64/35	148/128/28	0.982	8
Park2015	Korea	Asian	NAFLD	602/761	172/293/137	280/364/117	0.999	8
Yu2015	China	Asian	Cirrhosis	154/150	48/56/50	68/45/37	0.887	7
Chen2019	China	Asian	ALD	140/100	56/58/26	57/36/7	0.865	7
Gao2014	China	Asian	HCC	67/69	29/26/12	41/24/4	0.980	7
Takahisa2012	Japan	Asian	NAFLD	529/932	88/236/203	247/468/217	0.986	8
Peng2012	China	Asian	NAFLD	552/553	183/276/93	235/259/59	0.606	8
Yuya2016	Japan	Asian	HCC	130/86	18/60/52	11/39/36	0.986	7
Felix2018	Germany	Caucasion	HCC	751/1165	205/346/200	508/505/152	0.313	8
Tian2009	America	Caucasion	Cirrhosis	694/392	59/264/371	83/198/111	0.955	8
Tian2009	America	Caucasion	ALD	662/392	91/266/305	83/198/111	0.955	8
Luca2011	Italy	Caucasion	CHC	819/179	424/310/85	118/56/5	0.883	8
Samar2019	Egypt	Caucasion	CHC	151//179	79/57/15	64/103/12	0.07	8
Zhang2018	China	Asian	ALD	504/642	122/223/159	251/300/91	0.993	8
Ning2019	China	Asian	HCC	217/164	81/93/43	79/70/15	0.967	7
Wang2015	China	Asian	Cirrhosis	224/200	77/106/41	94/89/17	0.802	7

Abbreviations: PNPLA3,patatin-like phospholipase domain-containing-3; HCC, Hepatocellular carcinoma; NAFLD, Nonalcoholic fatty liver disease; ALD, Alcoholic liver disease; CHB, Chronic hepatitis B infection; CHC, Chronic hepatitis C infection; HWE, Hardy–Weinberg equilibrium; NOS, Newcastle-Ottawa scale.

Table 2. Results of pooled analyses for PNPLA3 rs738409 polymorphism and chronic liver disease

Population	Sample size	Dominant comparison p-value	Dominant comparison OR(95%CI)	Dominant comparison I^2statistic	Recessive comparison p-value	Recessive comparison OR(95%CI)	Recessive comparison I^2statistic	Allele comparison p-value	Allele comparison OR(95%CI)	Allele comparison I^2statistic
Overall	14855/12510	<0.0001	1.62(1.43-1.83)	81.2%	<0.0001	2.01(1.75-2.30)	74.1%	0.001	1.53(1.39-1.68)	84.8%
Asian	8866/9014	<0.0001	1.60(1.36-1.88)	82.8%	<0.0001	1.83(1.53-2.18)	77.7%	0.001	1.53(1.36-1.71)	84.4%
Caucasian	5888/5079	<0.0001	1.65(1.37-1.98)	77.0%	0.027	2.39(2.02-2.84)	45.9%	0.001	1.54(1.30-1.82)	86.3%
CHB	1504/880	0.201	1.25(0.98-1.56)	37.6%	0.395	1.27(0.98-1.65)	0%	0.113	1.23(1.01-1.49)	54.1%
CHC	1461/880	<0.0001	1.07(0.62-1.85)	87.3%	0.362	1.90(1.29-2.79)	6.3%	0.001	1.26(0.88-1.82)	82.7%
NAFLD	4590/5946	<0.0001	1.99(1.65-2.39)	75.1%	<0.0001	2.08(1.63-2.65)	80.9%	<0.0001	1.73(1.50-1.99)	81.9%
ALD	1636/1462	0.758	1.83(1.56-2.15)	0%	0.168	2.27(1.75-2.94)	40.6%	0.292	1.78(1.55-1.97)	19.6%
Cirrhosis	2529/2026	<0.0001	1.60(1.12-2.28)	88.8%	<0.0001	1.92(1.32-2.79)	81.2%	<0.0001	1.32(1.01-1.75)	40.8%
HCC	2451/3172	<0.0001	1.41(1.08-1.85)	78.9%	<0.0001	2.18(1.57-3.01)	71.8%	<0.0001	1.52(1.24-1.86)	81.5%

Note: The values in bold represent there is statistically significant differences between cases and controls. **Abbreviations**: H CC, Hepatocellular carcinoma; ALD, Alcoholic liver disease; NAFLD, Nonalcoholic fatty liver disease; CHB, Chronic hepati tis B infection; CHC, Chronic hepatitis C infection; OR, Odds ratio; CI, Confidence interval.

Sensitivity analyses

Sensitivity analyses were performed to test the impact of individual studies on the pooled results. No significant changes were observed in the overall and subgroup comparisons, indicating that our findings were statistically robust.

Publication bias

No obvious asymmetry was observed in the funnel plots of the different models, which suggested that our findings were unlikely to be impacted by severe publication biases (**Figure S1**).

Discussion

According to our search, this study is the first systematic analysis of the correlation between PNPLA3 rs738409 polymorphism and chronic liver disease. Our results show that rs738409 is significantly associated with chronic liver disease in Asians and Caucasians. However, further stratified analysis showed that there are similar positive results in HCC, cirrhosis and NAFLD, but not in CHB and ALD.

Some studies have suggested that PNPLA3 is an important regulator of triglycerides, holding a dual function of phosphatase and acyltransferase; however, the underlying physiological mechanism and the target organ remains poorly known [12]. Although the effect of *PNPLA3* on liver physiology is unclear, it is clear that its rs738409 SNP not only affects the deposition of hepatic triglycerides, but also has an significant effect on disease progression in patients with fatty liver [13-15]. To date, relevant studies have focused on understanding the pathogenic mechanisms involving *PNPLA3* mutation on NAFLD, revealing that is mainly related to liver lipid decomposition. Studies have shown that the liver triglycerides levels increased in mice upon expression of mutated PNPLA3, similar to what was observed in *in vitro* cultured *PNPLA3* mutant hepatocytes [16]. Therefore, we can know that the mutation of PNPLA3 has a certain inhibitory effect on its substrate binding ability. Thus, this mutation inhibits the triglyceride hydrolase activity of PNPLA3 [16].

There are several things worth noting about the present study. First, several different types of chronic liver disease were pooled for analysis. Heterogeneity among studies in the overall analysis indicates that these results should be treated with caution. Second, Subgroup analysis based on disease type showed that liver cancer, liver cirrhosis and NAFLD are closely related to rs738409 SNP. However, it is worth noting that the correlation trend between CHB and ALD with rs738409 SNP was the same as for the overall analysis. Considering that the analysis had a small sample size for ALD and CHB, But our research cannot solve the specific molecular regulation mechanism of rs738409 SNP in specific liver diseases. Therefore, in-depth research with a larger sample size is still needed to more accurately evaluate the relationship between rs738409 polymorphism and chronic liver disease, especially the correlation with ALD and CHB, and to explore its specific molecular regulation mechanism in conjunction with basic experiments. Third, The etiology and pathogenesis of chronic liver disease are very complex, so the regulatory role of a single gene in this disease is very limited. Fourth, In order to accurately assess the impact of endogenous/exogenous factors on the disease, molecular pathological epidemiology (MPE) analysis should be performed. However, because the included studies focused only on the effects of rs738409 SNP on susceptibility to chronic liver disease, such analyses were not applicable to the present meta-analyses. In order to explore the pathogenesis of chronic liver disease in depth, further research should evaluate the interaction between rs738409 polymorphism and potential pathogenic environmental factors. Lastly, this meta-analysis only explores the relationship between *PNPLA3* rs738409 polymorphism and chronic liver disease. Therefore, additional studies are warranted to further analyze the *PNPLA3* polymorphism and its full impact on chronic liver diseases.

In conclusion, our meta-analysis suggests that the *PNPLA3* rs738409 polymorphism may affect the individual susceptibility to chronic liver disease in Asians and Caucasians, potentially contributing for HCC, cirrhosis, and NAFLD, but not for ALD, CHB, and CHC. Further research is necessary to explore the potential role of other *PNPLA3* polymorphisms in the occurrence and development of chronic liver diseases.

Conclusions

Overall, this is the first systematic analysis of the correlation between PNPLA3 polymorphism and the risk of chronic liver disease. Our research shows that PNPLA3 rs738409 may be closely related to chronic liver disease and can be a marker of susceptibility to HCC, liver cirrhosis and NAFLD.

Supplementary materials

The Figure S1 (Funnel diagram of the three models) is available at https://doi.org/10.12032/ghr2020-12-025.

References

1. Teschke R, Danan G. Drug-induced liver injury: Is chronic liver disease a risk factor and a clinical issue?. *Expert Opin Drug Metab Toxicol*. 2017;13 (4):425–438.
2. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol*. 2019;70(1):151–171.
3. Pimpin L, Cortez-Pinto H, Negro F, et al. Burden of liver disease in Europe: Epidemiology and

analysis of risk factors to identify prevention policies. *J Hepatol*. 2018;69(3):718–735.
4. Marra F, Tacke F. Roles for chemokines in liver disease. *Gastroenterology*. 2014;147(3):577–594.
5. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nature genetics*. 2008,40:1461-1465.
6. Trépo E, Romeo S, Zucman-Rossi J, Nahon P. PNPLA3 gene in liver diseases. *J Hepatol*. 2016 Aug;65(2):399-412.
7. Kupcinskas J, Valantiene I, Varkalaitė G, et al. PNPLA3 and RNF7 Gene Variants are Associated with the Risk of Developing Liver Fibrosis and Cirrhosis in an Eastern European Population. *J Gastrointestin Liver Dis*. 2017,26(1):37-43.
8. Karamfilova V, Gateva A, Assyov Y, et al. PNPLA3 I148M Polymorphism in Patients with Nonalcoholic Fatty Liver Disease, Obesity and Prediabetes. *J Gastrointestin Liver Dis*. 2019,28 (4):433-438.
9. Shen JH, Li YL, Li D, et al. The rs738409 (I148M) variant of the PNPLA3 gene and cirrhosis: a meta-analysis. *J Lipid Res*. 2015,56(1):167-75.
10. Huang Z, Guo X, Zhang G, Liang L, Nong B. Correlation between PNPLA3 rs738409 polymorphism and hepatocellular carcinoma: a meta-analysis of 10,330 subjects. *Int J Biol Markers*. 2019,34(2):117-122.
11. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol*. 2014,14:45.
12. Li YL, Chao X, JONATHAN C. COHEN. Genetic Variant in PNPLA3 is Associated with Nonalcoholic Fatty Liver Disease in China. *Hepatology*, 2012,1:327-328.
13. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet*. 2008,40:1461-1465.
14. Rotman Y, Koh C, Zmuda JM, Kleiner DE, Liang TJ. The association of genetic variability in patatin-like phospholipase domain-containing protein 3(PNPLA3) with histological severity of nonalcoholic fatty liver disease. *Hepatology*. 2010,52:894-903.
15. Valenti L, Al-Serri A, Daly AK, et al. Homozygosity for the patatin-like phospholipase -3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. *Hepatology*. 2010,51:1209-1217.
16. He S, McPhaul C, Li JZ, et al. A sequence variation (I148M) in PNPLA3 associated with nonalcoholic fatty liver disease disrupts triglyceride hydrolysis. *J Biol Chem*. 2010, 285: 6706-6715.