A panel design of gene polymorphism detection of metabolic dysfunction-associated fatty liver disease in East Asian population

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Abstract: The aim of this study was to design a panel of gene polymorphism detection of MAFLD in East Asian population based on current research. Literature search was conducted in PubMed database using the keywords "metabolism-related fatty liver" or "non-alcoholic fatty liver" and "Asia" or "East Asia" and "gene". 41 studies met the inclusion criteria, and 12 key genetic loci were screened out involving FTO, KLB, PNPLA3, TRIB1, PPARα, LEPR, APOA5, TM6SF2, APOC3, GCKR, SREBP2, MTTP, associating with obesity, insulin resistance, glucose metabolism, fatty acid metabolism, and inflammatory fibrosis pathways. The panel was designed successfully, while the sensitivity and specificity remain to be further clinically validated.

Keywords: Panel, Metabolic dysfunction-associated fatty liver disease, MAFLD, Gene, East Asian

1. Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD), previously known as non-alcoholic fatty liver disease (MAFLD), is a complex liver disease which is marked by fat accumulation in hepatocytes. The pathogenesis is associated with the genetic factors, environmental factors, and metabolism-related factors[1].

MAFLD is currently recognized as the most common liver disease worldwide and the leading cause of end-stage liver diseases in the coming decades. Globally, the prevalence of MAFLD is approximately 24%, and in Asia the prevalence is 27%. Meanwhile, MAFLD has become the leading cause of hepatocellular liver cancer in the United States, United Kingdom, and France. The incidence of hepatocellular liver cancer induced by steatohepatitis is estimated to be approximately 0.5%-2.6%,and the incidence is predicted to increase by 87%, 117%, and 122% in China, France, and the United States, respectively, in 2030[2].Factors that involve the pathogenesis of MAFLD include age, gender, race, alcohol consumption, dietary intake, intestinal flora, genetic susceptibility, and metabolic status. However, the pathogenesis of MAFLD has not been fully elucidated. The "second strike theory" has been used for MAFLD. The first strike is the lipid metabolism disorder associated with obesity, sedentary lifestyle, high-fat diet, and insulin resistance that causes hepatocellular steatosis, and the second strike is the inflammatory and fibrotic events associated with oxidative stress and lipid peroxidation[3]. However, the two-hit model cannot explain the complex etiology of MAFLD and the interactions between multiple influencing factors. Currently, MAFLD is a manifestation of systemic metabolic disorders in the liver, and insulin resistance plays a key role in the development of MAFLD, leading to increased production and decreased breakdown of new lipids in the liver[4]. In addition, intestinal flora is also involved in the development of MAFLD through factors such as affecting nutrient absorption and stimulating the production of pro-inflammatory factors by hepatocytes[5].Since the first genome-wide study association study in 2008 identified the association of PNPLA3 gene mutations with MAFLD, many studies have confirmed genetic factors in the pathogenesis of MAFLD, and these studies include family aggregation studies, twin studies, and ethnic susceptibility difference studies[6-8].The current studies on the gene polymorphism of MAFLD mainly focus on the Caucasian population in Europe and North America, and this paper reviews the current studies in the East Asian population.

The purpose of this study is to design a panel that can detect key gene mutations associated with MAFLD in East Asian populations in order to guide future clinical diagnosis and disease risk assessment.

2. Method

Literature search was conducted in PubMed database using the keywords "metabolism-related fatty liver" or "non-alcoholic fatty liver" and "Asia" or "East Asia" and "gene". The target population of the study was limited to East Asian ethnic groups and the publication time is limited to 2011-2021. After the effective articles were screened out, we select and classified the key genes in each article together.

Genes were selected based on the following: the sample size of the clinical study was no less than 300; the gene was significantly correlated (p-value < 0.05). Loci with high mutation rates are preferentially selected in the same gene pathway.

Afterwards, a panel was designed based on the screened genes and was plotted as a table.

3. Results

3.1. Selection of literature

The selected articles cover clinical studies for the validation of candidate genes or known related genes, as well as genome-wide association studies. A total of 12 studies met the inclusion criteria, of which one was East Asian population studies,one was a Japanese study and the rest were Chinese population studies. The selected articles were published between 2012 and 2020, and five of the articles were meta-analyses. One of the included studies used a transcriptomic assay, two used an exome assay, and most of the studies detected only the relevant SNP loci. The literature is listed in table 1.

Table 1: Relevant articles published in 2012 to 2020

Doi number	Time of publication	Country of origin	Targeted gene	Sample size
10.2147/CIA.S254740. eCollection 2020.	2020	China	FTO	741/825
10.18632/aging.102293. Epub 2019 Sep 23.	2019	China	KLB	545/1143
10.1186/s12944-019-0992-9.	2019	China	PNPLA3	512/451
10.1089/gtmb.2018.0203. Epub 2019 Feb 22.	2019	China	AGTR1	1591
10.2174/1566524018666180705110412.	2018	China	LEPR	1711/1732
10.1186/s12944-017-0570-y.	2017	Japan	PNPLA3,MTTP	950/3014
10.1007/s12072-015-9687-0. Epub 2016 Feb 10.	2016	China	ADIPOQ	302/310
10.1186/s12944-016-0181-z.	2016	Asian	TM6SF2	4692
10.3748/wjg.v20.i38.14010.	2014	China	APOC3	300/300
10.1089/gtmb.2014.0116. Epub 2014 Jul 3.	2014	China	SREBP-2	300/160
10.3945/ajcn.113.079749.	2014	China	GCKR,PNPLA3	797
10.1111/liv.12220. Epub 2013 Jun 5.	2014	China	MTTP	580/580

3.2. Selected gene loci

Genes selected for the panel meet the following requests: (1) Natural mutation rate is >1% in the East Asian population. (2) Significant correlation (p value <0.01) exists in clinical trials, and the sample size

of the enrolled clinical trials is not less than 300. (3) In the same gene pathway, preference is given to the loci with high mutation rate.

3.2.1. FTO

The FTO gene, also known as the obesity gene, is located on chromosome 16 (16q12.2), contains nine exons and is 410.50 kb in length. it is widely expressed in human tissues at all stages of development and is highly expressed in hypothalamus, skeletal muscle and adipose tissue. Experimental studies have shown that FTO gene expression is upregulated in the liver of MAFLD rats and that overexpression of FTO can characterize MAFLD by increasing oxidative stress and lipid overaccumulation in human hepatocytes[9].

Clinical trials found a significantly higher frequency of the C allele of rs1421085 in MAFLD patients (OR=1.353; 95% CI=1.095-1.671; P=0.005). rs8050136 allele was significantly more frequent in the MAFLD group (OR=1.371; 95% CI= 1.109-1.695; P = 0.004). In rs3751812, the frequency of the T allele was significantly higher in MAFLD (OR = 1.369; 95% CI = 1.108-1.691; P = 0.004). The frequency of the A allele was also significantly higher in MAFLD for rs9939609 (OR=1.369; 95% CI=1.108-1.691; P=0.004). The data results suggest that the C variant of rs1421085, the A variant of rs8050136, the T variant of rs3751812 and the variant of rs9939609 are associated with an increased risk of MAFLD in an elderly Chinese Han population.

3.2.2. KLB

KLB is a protein-coding gene located on chromosome 4p14, belonging to the glycoside hydrolase family 1 gene group and is predominantly expressed in fat and liver. It encodes a single transmembrane protein that acts as a co-receptor for the fibroblast growth factor receptor (FGFR)[10]. By mediating the binding of FGF21 to FGFR, KLB plays a key role in metabolic regulation. FGF21 expression is elevated in the liver, adipose tissue, pancreas and brain under fasting and some stress conditions, where signalling through the FGF21-KLB-FGFR1 complex affects multiple metabolic systems.

Clinical studies showed that the KLB SNPs rs7674434 and rs12152703 were significantly associated with ALT (P = 0.030 and P = 0.041, respectively) and γ-GT (P = 0.032 and P = 0.024, respectively) levels, while the SNP rs7670903 was associated with γ-GT levels (P = 0.034). rs7674434 of the minor G allele and the T allele of rs12152703 were positively associated with ALT and γ-GT levels, the A allele of rs7670903 was positively associated with γ-GT levels, and the G allele of rs499765 was positively associated with GF21 levels. The results of the data suggest that KLB is closely associated with obesity, the development of MAFLD in the obese population, and liver inflammation in patients with MAFLD.

3.2.3. PNPLA3

PNPLA3 is an important lipid regulator in hepatocytes and stellate cells. PNAPL3 is regulated by TGF-β and releases retinol from retinyl esters of stellate cells, involved in stellate cell activation and fibrosis. In hepatocytes, PNPLA3 is located in lipid droplets that hydrolyze triglycerides (TG) and catalyze the transfer of polyunsaturated fatty acids (PUFA) from di- and triacylglycerols to phosphatidylcholine. The PNPLA3-I148M mutant was associated with lower levels of arachidonic acid in hepatic TGs. The PNPLA I148M mutant has impaired hydrolytic activity and is not readily degraded by ubiquitination, which leads to the retention of triglycerides and PUFA-rich lipid droplets, creating conditions for hepatic fat accumulation.studies have shown that PNPLA3 I148M gene plays a role in the control of intrahepatic fat accumulation. Romeo demonstrated that in MAFLD development, a variant of the *PNPLA3* gene, rs738409 C > G , was significantly higher in the Hispanics (49%) compared to the European Americans (23%) and African Americans (17%). In addition, PNPLA3 has also been suggested to play a role in lipid remodelling in hepatic TGs. Human hepatocytes expressing PNPLA3 and PNPLA3-I148M had higher levels of very long-chain polyunsaturated fatty acids (PUFA) in the phospholipids. The PNPLA3-I148M mutant was associated with lower levels of arachidonic acid in hepatic TGs[11]. Arachidonic acid is the major substrate of MBOAT7, a mutant of which is implicated in alcoholic cirrhosis.

Clinical study found that the PNPLA3 I148M variant was significantly associated with the risk of MAFLD in an additive model (CG, OR = 2.092, 95% CI: 1.551-2.820, P = 0.000; GG, OR = 4.566, 95% CI: 3.141-6.638, P = 0.000, respectively). Meanwhile, rs143392071 (Tyr220Cys, PNPLA3) significantly increased (odds ratio = 3.52, P = 0.008) the MAFLD risk.

3.2.4. AGTR1

The AGTR1 gene,known as angiotensin II receptor 1 gene,is an important gene that involves the

activation in the renin-angiotensin system as well as metabolic diseases[12]. AGTR1 blocker was shown to have a preventive role of in the progression of NASH in both animal and human studies. ATGR1, is shown to have the ability to activate hepatic stellate cells and increase the expression level of TGF-β1, a profibrogenic cytokine that response to the liver injury[13].

Clinical studies have shown that subjects carrying the T/C genotype of rs2638360 in ATGR1 have a lower risk of MAFLD than those carrying T/T-C/C genotypes. Moreover,three-locus models (rs275646, rs5182, and rs1492100) and four-locus models (rs275646, rs2933249, rs1492100, and rs2638360) were apparently associated with an increased risk of MAFLD.

3.2.5. LEPR

LEPR, known as one of the family numbers of I-type cytokines, can bind to leptin and then affects the food intake in the human body. Previous researches have indicated LEPR K109R and Q223R to be susceptible factors for metabolic syndrome including obesity, BMI , and altered serum lipid profile. The study of Zain et al. has shown that the G allele of LEPR K109R can significantly decrease the risk of MAFLD in Malay population. Studies have shown that LEPR Q223R is associated with metabolic syndrome[14].

Clinical study have found that in the meta-analysis, including 1711 patients with MAFLD and 1732 healthy controls. Q223r was significantly correlated with MAFLD in both allelic and recessive models (allelic model: $P < 0.001$, or = 0.57, 95% CI [0.50-0.65]; recessive model: $P = 0.001$, or = 0.67, 95% CI [0.52-0.85]).

3.2.6. ADIPOQ

The adiponectin gene is a 16 kb sequence locating on chromosome 3q27 and is consists of three exons and two introns. Evidence demonstrates the SNPs of the adiponectin gene is associating with varying levels of circulating adiponectin. Variant alleles at rs266729, which is associated with lower adiponectin levels, have been shown to be related to obesity, type 2 diabetes, and insulin sensitivity. Another variant, rs1501299, is correlated with decreased adiponectin expression, which might in turn lead to increased body weight and insulin resistance[15].

Clinical study have found that there was an important association of the rs266729 (-11377 G/C) and rs822393 (-4522 C/T) polymorphism with increased risk of MAFLD. The interaction analysis showed a combined effect of rs266729 and rs822393 on MAFLD.

3.2.7. TM6SF2

Tm6sf2 is located on chromosome 19 and encodes a protein composed of 351 amino acids. It is estimated that its protein structure is composed of seven transmembrane functional domains, but they are different from the functional domains found so far. Tm6sf2 was mainly expressed in brain, kidney, liver and small intestine, and the expression was the highest in small intestine. Rs58542926 SNP on tm6sf2 leads to the substitution mutation of nucleotide 499 from cytosine to thymine, resulting in the mutation of residue 167 from glutamate to lysine (rs58542926c.499, C > t, p.glu167lys, e167k), which affects the function of the protein encoded by it. Tm6sf2 rs58542926 e167k single nucleotide polymorphism is significantly associated with the susceptibility to MAFLD, and studies have shown that it is also associated with nonalcoholic steatohepatitis, liver fibrosis and hepatocellular carcinoma[16].

Clinical studies have shown that rs58542926 had significant association with Japanese MAFLD. The minor allele (t) increased MAFLD risk (OR 1.682, 95 % CI 1.289–2.196, p value 0.00013).

3.2.8. APOC3

APOC3 is a major component of low-density lipoprotein cholesterol, and it inhibits the hydrolysis of TG-rich particles by lipoprotein lipase. Studies have confirmed that transgenic mice overexpressing APOC3 can develop hepatic steatosis, suggesting that this gene is associated with the development of metabolic fatty liver. A single nucleotide polymorphism in the promoter domain of the APOC3 gene (rs2854116, APOC3 (-455T>C)) has been reported to be associated with insulin resistance[17].

The clinical study that included 600 Han samples from southern China (300 metabolic fatty liver and 300 normal population) confirmed that TC and CC genotypes increase disease susceptibility to metabolic-associated fatty liver compared to TT genotype (OR=1.77, 95% CI: 1.16-2.72, p=0.009; OR=2.80, 95% CI : 1.64-4.79, p<0.001).

3.2.9. GCKR

GKRP regulates the activity of glucokinase in the liver based on blood glucose levels. During hypoglycemia, GKRP binds to glucokinase in the nucleus of hepatocytes and will be sequestered in the nucleus, while under hyperglycemic conditions, GKRP is released from glucokinase, allowing its translocation from the nucleus to the cytoplasm. Glucokinase activates glycogen synthesis and new adipogenesis. a single nucleotide polymorphism in the GCKR gene (rs780094) has also been shown to be associated with metabolic fatty liver and fibrosis severity[18].

The clinical study showed that the genetic variants in *GCKR* rs780094 is associated with an increased risk of MAFLD. And the T allele of rs780094 at *GCKR* were significantly higher in the subjects with MAFLD ($P = 0.016$ for rs780094).

3.2.10. SREBP2

SREBF2(Sterol regulatory element binding transcription factor 2) is encoded by a separate gene on human chromosome 22q13 and is closely associated with cholesterol synthesis. When cells are deprived of cholesterol, SREBP-2 binds to and activates the enzyme encoding the low-density lipoprotein (LDL) receptor or HMG-CoA reductase, whose transcription is regulated by the SREBP-2 gene. In addition, activation of the SREBP-2 gene may play a key role in enhancing cholesterol uptake and biosynthesis and may be directly involved in the regulation of intracellular cholesterol metabolism, thereby maintaining cholesterol homeostasis[19].

The clinical study that included 460 Chinese Han populations (300 metabolic fatty liver and 160 normal controls) showed that single nucleotide polymorphisms in the SREBP-2 gene (rs2228314, G > C) were strongly associated with susceptibility to metabolism-related de novo fatty liver (p< 0.001).

3.2.11. MTTP

MTTP(microsomal triglyceride transfer protein) plays a key role in the incorporation of triglycerides (TG) from the liver into very low density lipoproteins (VLDL). A recent meta-analysis suggested that the MTP -493G > T (rs1800591) polymorphism may have an impact on the susceptibility of metabolic patients[20].

Clinical study A case-control study that included 1160 Chinese Han populations (580 metabolic fatty liver and 580 normal controls) showed that rs1800804 (-164 T/C) of the MTP gene was associated with an increased risk of MAFLD in Chinese Han populations (p=0.047).

Based on the above studies, the panel is designed as follows in table 2:

Table 2: The design panel

Gene	SNP	Clinical Significance
FTO	rs1421085;rs8050136;rs3751812;rs9939609	The C variant of rs1421085, the A variant of rs8050136, the T variant of rs3751812 and the variant of rs9939609 are associated with an increased risk of MAFLD in the elderly Chinese Han population.
KLB	rs7674434;rs12152703;rs7670903	The rs7674434 is significantly associated with the development of MAFLD in an obese population and with the degree of liver inflammation in MAFLD. rs12152703 and rs7674434 exhibits a similar association.
PNPLA3	rs738409 ;rs143392071	The rs143392071(Tyr220Cys, PNPLA3) significantly increased the MAFLD risk.

ATGR1	rs2638360;	The T/C genotype of rs2638360 in ATGR1 have a lower risk of MAFLD than those carrying T/T-C/C genotypes.
LEPR	rs1137100;rs1137101	rs1137100 may be a susceptibility factor for MAFLD in Southeast Asian population. rs1137101 may be a susceptibility factor for MAFLD in Chinese population.
ADIPOQ	rs266729 ;rs822393	The rs266729 ,-11377 G/C and rs822393 ,-4522 C/T polymorphism is associated with increased risk of MAFLD.
TM6SF2	rs58542926 ;	The rs58542926 had significant association with Japanese MAFLD.
APOC3	rs2854116;	TC and CC genotype increases the disease susceptibility of MAFLD.
GCKR	rs780094;	The rs780094has also been shown to be associated with MAFLD and the severity of fibrosis.
SREBP2	rs2228314;	The rs2228314, G > C in SREBP-2 gene is closely related to the susceptibility to MAFLD.
MTTP	rs1800804 ;	The rs1800804 (- 164 T / C) is associated with increased risk of MAFLD in Chinese Han population.

4. Discussion

The pathogenesis of MAFLD has not been elucidated, but current studies suggest that its pathogenesis involves genetic factors, which implies that MAFLD may be a polygenic disease.

In present studies, a total of 7 groups of genes were found to be associated with MAFLD, which were classified into (1) genes relating to hepatic lipid export/oxidation (PNPLA3, TM6SF2, NR1I2, PPAR-α, PEMT, MTTP, APOC3, and APOE); (2) genes relating to glucose metabolism and insulin resistance (ENPP1/IRS1, GCKR, SLC2A1, GOAT, TCF7L2 and PPARG); (3) genes associated with steatosis/hepatic lipid input or synthesis (SLC27A5, FADS1 and LPIN1); (4) genes associated with oxidative stress (HFE, GCLC/GCLM, ABCC2 and SOD2); (5) genes associated with endotoxic inflammatory response (TLR4 and CD14); (6) genes relating to cytokines (TNF and IL6); (7) genes relating to fibrosis (AGTR1 and KLF6)[1, 21].

There are no definitive findings on MAFLD susceptibility genes, and current research is focused on how to identify MAFLD susceptible individuals early in the disease course so that they can be effectively intervened, staged and followed up in clinical work. It is not possible to perform Sanger sequencing for each individual, so it may reduce the cost and time by selecting some representative genes of MAFLD for second-generation sequencing. The characteristics of the genetic disease for which the gene panel is suitable are: (1) this disease has significant diversity in clinical phenotype; (2) this disease has overlapping phenotypes with other diseases, requiring differential diagnosis; (3) this disease has

heterogeneity of genetic loci, with multiple genes controlling one molecular pathway or functional structure at the same time. MAFLD has exactly these characteristics, and using the customized gene panel can quickly detect the candidate mutation loci. After bioinformatic analysis, MAFLD patients and susceptible individuals can get an accurate molecular diagnosis for guiding clinical treatment and lifestyle intervention afterwards. At current, studies of MAFLD-associated genes have mostly targeted Caucasian populations in Europe and North America. Moreover, with an increasing number of MAFLD-associated genes getting discovered, there is still no gene panel design for MAFLD. In this article, we have designed a gene polymorphism detection panel, regarding the current study of MAFLD-associated genes in East Asian populations, with the hope that it can help future clinical studies, diagnosis and risk assessment.

In this study, a total of 12 studies were selected to meet the inclusion criteria, and the selected articles were published between 2012 and 2020, including one Japanese study, one Asian studies, and the rest were Chinese Han population studies. 12 key genetic loci were screened, involving the pathways of obesity, insulin resistance, glucose metabolism, fatty acid metabolism, and inflammatory fibrosis.

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