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EDITORIAL

Genetic polymorphisms in non-alcoholic fatty liver disease: Clues to pathogenesis and disease progression

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Abstract

The spectrum of non-alcoholic fatty liver disease (NAFLD) ranges from simple steatosis through steatohepatitis to advanced fibrosis and cirrhosis. Although the reason why only a minority of patients develop progressive forms of disease still remains largely unclear, recent research has identified genetic factors as a possible basis for this variation in disease presentation. Most of the studies have been focused on finding associations between advanced disease forms and selected single nucleotide polymorphisms in genes encoding various proteins involved in disease pathogenesis. Although there are many limitations regarding the study design and interpretation of published data, further carefully planned studies together with implementation of new genetic technologies will likely bring new insights into disease pathogenesis and potential benefits to the management of patients with NAFLD.

Key words: Genetics; Liver fibrosis; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Single nucleotide polymorphisms

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as the most common form of chronic liver disease. The spectrum of NAFLD ranges from simple steatosis through steatohepatitis (NASH) to advanced fibrosis and cirrhosis, and the minority of patients progress to end-stage liver disease requiring liver transplantation or develop hepatocellular carcinoma[1]. However, the vast majority of patients only have simple steatosis with a benign long-term prognosis. It has been observed that even when considering patients with similar environmental and metabolic NAFLD risk factors (diet, exercise, obesity and insulin resistance being the most important factors), they still differ largely in terms of disease phenotype and degree of progression[2]. This led to the research focus more recently being placed on genetic factors that may possibly have a role in NAFLD etiology, and genetic variability is now implied to be one of the most important determinants of disease phenotype and progression in individual patients.

GENETIC INFLUENCES IN NAFLD

Possible genetic risk for advanced NAFLD was initially suggested in studies which showed coexistence of NASH and/or cryptogenic cirrhosis within several kindreds, and it was not invariably associated with similar major metabolic risk factors[3,4]. Further evidence comes from reports of ethnic differences in the prevalence of steatosis, NASH and cryptogenic cirrhosis. The prevalence of all forms of NAFLD was shown to be highest in Hispanic and lowest in African American populations, and this variability did not always correlate with differences in the prevalence of major risk factors[5-7]. Furthermore, it was reported that Asian patients with NAFLD had a significantly lower body mass index (BMI) than all other racial groups[8].

As most of the common diseases today, NAFLD

is considered to be a genetically complex disorder. In complex diseases, several or many different genes interact with environmental factors in determining disease presence or its phenotype, and individual genes only have a small effect on disease risk and can therefore be very difficult to identify. Methods for detecting genes in complex disorders have included family-based linkage studies, hypothesis-based candidate gene allele association studies, genome-wide single nucleotide polymorphism (SNP) scanning and, recently, microarray and proteomic studies. Almost all of the data available on genes associated with NAFLD has so far come from the candidate gene association studies, where candidate genes are usually selected on the basis of their suggested role in disease pathogenesis, and the frequency of one or more known SNPs within or close to those genes is compared in cases and controls, in the search for a positive or negative association with the disease. Genes that are candidates for study in NAFLD have included genes influencing insulin resistance, fatty acid metabolism, oxidative stress, immune regulation and fibrosis development.

GENETIC POLYMORPHISMS

Peroxisome proliferator-activated receptor γ coactivator 1α (PPARGC1A)

PPARGC1A has been involved with different metabolic pathways, such as regulation of gene expression in glucose and lipid metabolism and transcriptional control of cellular metabolism, mainly through control of mitochondrial function and biogenesis[9,10]. Several studies have shown that *PPARGC1A* regulates several key hepatic gluconeogenic genes, is directly involved in the homeostatic control of systemic energy metabolism, and *PPARGC1A* Gly482Ser polymorphism has also been associated with the development of insulin resistance, obesity and diabetes[11-14]. *PPARGC1A* knockout mice are prone to develop hepatic steatosis due to a combination of reduced mitochondrial respiratory capacity and an increased expression of lipogenic genes[15]. Yoneda *et al*[16] therefore examined 15 SNPs in the *PPARGC1A* gene and found that the rs2290602 polymorphism was significantly associated with NAFLD (more closely with NASH than with simple steatosis), and the frequency of the T allele (allele with rs2290602 polymorphism) was significantly higher in the NASH patients than in the control subjects. They also found that intrahepatic *PPARGC1A* mRNA expression was significantly lower in the TT genotype group than in the GG or GT group. On the other hand, Hui *et al*[17] did not find any association between the Gly482Ser variant and NAFLD in Chinese Han people. However, they have reported a correlation between C161T PPAR-γ gene SNP, consequent lower plasma levels of adiponectin and increased susceptibility to NAFLD.

Microsomal triglyceride transfer protein (MTTP)

A higher incidence of -493G/T polymorphism in the MTTP gene promoter has been reported in patients with NAFLD; GG homozygosity was associated with more severe liver histology and has been considered as a risk factor for NAFLD[18]. Gambino *et al*[19] suggested that NASH patients with GG homozygosity have more atherogenic postprandial lipoprotein profiles and lipoprotein metabolism, which leads to increased peroxidative liver injury.

Leptin

Leptin is an adipocytokine whose main role is regulation of food intake. It probably has an important role in the pathogenesis of NAFLD; leptin-deficient ob/ob mice develop steatohepatitis when fed with a methionine-choline-deficient diet[20]. Common variants in the human leptin receptor (*LEPR)* gene have been associated with traits of metabolic syndrome such as obesity, insulin resistance, type 2 diabetes mellitus and altered lipid metabolism, and possibly with NAFLD[21-23]. The *LEPR* 3057 variant may link obesity to NAFLD in Chinese patients with type 2 diabetes mellitus through interference with leptin receptor signaling and regulation of lipid metabolism and insulin sensitivity[24].

Adiponectin

Adiponectin, an adipocyte-derived cytokine has an important role in mobilization, transport and muscle oxidation of free fatty acids leading to improvements in lipid profiles and insulin sensitivity[25,26]. High levels of tumor necrosis factor-α (TNF-α) mRNA in adipose tissue and high plasma TNF-α concentrations were detected in adiponectin-knockout mice, resulting in severe diet-induced insulin resistance[27]. Musso *et al*[28] reported that the adiponectin SNPs 45TT and 276GT/TT were more prevalent in Italian NAFLD patients than in the general population; these polymorphisms independently predicted the severity of liver disease in NASH and exhibited a blunted postprandial adiponectin response and higher postprandial triglyceride levels.

Hepatic lipase

Zhan *et al*[29] investigated the prevalence of the hepatic lipase gene promoter polymorphism at position -514 in Chinese patients with NAFLD. They reported a higher frequency of the CC genotype and C allele in the NAFLD group and both the CC genotype and CT genotypes were associated with higher relative risk for development of NAFLD[29].

Phosphatidylethanolamine N-methyltransferase (PEMT)

Phosphatidylcholine is required for hepatic formation and secretion of very low density lipoproteins, and it has been shown that a choline-deficient diet leads to accumulation of fat droplets in hepatocyte cytosol and the development of fatty liver[30]. PEMT catalyzes *de novo* synthesis of phosphatidylcholine and is responsible for approximately 30% of phosphatidylcholine formed in liver, the rest of it being synthesized by another pathway from dietary choline. Song *et al*[31] showed that SNP (G to A substitution in exon 8) that leads to Val to Met substitution at residue 175 of PEMT is associated

Table 1 Studies of genetic polymorphisms in non-alcoholic fatty liver disease (NAFLD) included

Gene	Polymorphism	Ref.	No. of patients with NAFLD included in the study
Peroxisome proliferator-activated receptor γ coactivator 1α (*PPARGC1A*)	rs2290602	Yoneda *et al*[16], 2008	115
	Gly482Ser	Hui *et al*[17], 2008	96
Microsomal triglyceride transfer protein (MTTP)	-493G/T	Namikawa *et al*[18], 2004	63
		Gambino *et al*[19], 2007	29
Human leptin receptor	G3057A	Lu *et al*[24], 2009	104
Adiponectin	45G/T and 276G/T	Musso *et al*[28], 2008	70
Hepatic lipase	-514C/T	Zhan *et al*[29], 2008	106
Phosphatidylethanolamine *N*-methyltransferase (PEMT)	Val175Met	Song *et al*[31], 2005	28
		Dong *et al*[32], 2007	107
Methylenetetrahydrofolate reductase (MTHFR)	C677T and A1298C	Sazci *et al*[33], 2008	57
Tumor necrosis factor-α (TNF-α)	-238 and -308	Valenti *et al*[38], 2002	99
	-1031, -863, -857, -308 and -238	Tokushige *et al*[39], 2007	102
Angiotensinogen	G-6A	Dixon *et al*[45], 2003	105
Transforming growth factor-β1 (TGF-β1)	Pro25Arg		

with significantly diminished activity of the enzyme, and determined the frequency of this polymorphism in NAFLD patients and controls. The loss of function AA genotype (Met/Met) occurred significantly more frequently in NAFLD patients than in control subjects, which led to the conclusion that genetically inherited low PEMT activity is an important risk factor for developing NAFLD. This was further proven in a Japanese study published by Dong *et al*[32]. Although the polymorphism is much rarer in the Japanese population than in Caucasians, the frequency of A allele was significantly higher in NASH patients compared with controls. NASH patients who were carriers of the Val175Met variant had significantly lower BMI and were more frequently non-obese than NASH patients who were wild-type homozygotes, further proving the role of this polymorphism as an independent risk factor for NAFLD development.

Methylenetetrahydrofolate reductase (MTHFR)

Sazci *et al*[33] investigated whether the C677T and A1298C polymorphisms of the MTHFR gene which lead to hyperhomocysteinemia and development of liver steatosis were associated with NASH. They found that the MTHFR 1298C allele was associated with increased risk for NASH in patients of both genders, C1298C genotype and C677C/C1298C compound genotype in female and C677C/A1298C compound genotype in male NASH patients.

TNF-α

TNF-α has long been proven to be one of the key cytokines in the development of all chronic liver diseases. In NAFLD, it has been shown that it may cause hepatocyte injury and apoptosis, neutrophil chemotaxis, and hepatic stellate cell activation, as well as contribute to systemic and hepatic insulin resistance[34-36]. Crespo *et al*[37] found that obese patients with NASH compared to those without NASH have significantly increased liver expression of TNF-α and its receptor p55, as well as increased expression of TNF-α in adipose tissue. Valenti *et al*[38] investigated the relationship between insulin resistance, occurrence of NAFLD and -238 and -308 TNF-α promoter polymorphisms known to be associated with an increased release of this cytokine. The prevalence of the 238 TNF-α polymorphism was higher in subjects with NAFLD than controls, and patients with these polymorphisms had higher insulin resistance indices. Tokushige *et al*[39] determined the prevalence of several TNF-α promoter region polymorphisms (positions -1031, -863, -857, -308 and -238) in a group of Japanese NAFLD patients and control subjects. There were no significant differences in the allele frequencies of any of the six polymorphisms among the group of patients with NAFLD and the control group, including the -238 polymorphism which was previously reported to be associated with NAFLD in Italian patients, but this polymorphism was much less frequent in the Japanese population[38]. However, the frequency of the -1031C polymorphism was significantly higher in the NASH group compared to the simple steatosis group, as was the frequency of the -863A polymorphism. The frequency of other polymorphisms did not differ significantly between the two groups. These two polymorphisms were also associated with higher levels of insulin resistance measured by HOMA-IR.

Transforming growth factor-β1 (TGF-β1) and angiotensin Ⅱ

TGF-β1 and angiotensin Ⅱ are two molecules that have been extensively studied in models of liver fibrogenesis. TGF-β1 has a major role in development of liver fibrosis by activation of hepatic stellate cells and stimulation of production of extracellular matrix proteins[40]. Besides its well-known effects in the cardiovascular and renal systems, angiotensin Ⅱ also has an established role in liver fibrogenesis, and based on those observations, studies with angiotensin Ⅱ receptor antagonists have been performed in patients with NASH[41,42]. There have been several suggestions that profibrotic effects of angiotensin Ⅱ in heart and kidney are mediated by induction of transcription of TGF-β1[43,44]. Considering these data, and based on their previous study in hepatitis C patients, Dixon *et al*[45] investigated the relationship between the

presence of advanced fibrosis and angiotensinogen G-6A polymorphism or TGF-β1 Pro25Arg polymorphism in a group of severely obese patients. There was no correlation between either high angiotensin or TGF-β1 producing genotypes alone and hepatic fibrosis. However, patients who inherited both high angiotensin and TGF-β1 producing polymorphisms had a higher risk of advanced fibrosis. These data also support the hypothesis that angiotensin Ⅱ stimulated TGF-β1 production promotes hepatic fibrosis.

A comprehensive list of the above-mentioned polymorphism studies is shown in Table 1.

CONCLUSION

While all this and other evidence clearly indicates that genetic factors have a key role in determining susceptibility to advanced forms of NAFLD and its progression, the majority of studies mentioned here had small sample sizes and therefore limited statistical power, which makes it rather difficult to draw definitive conclusions. However, we believe that the development and wider availability of high throughput genetic technologies together with careful design and performance of large multicenter studies with adequate statistical power will soon provide new insights in this vast and very interesting area. Further study and new data on genetic effects have many potential benefits - advancement in understanding the pathogenesis of NAFLD, identification of new potential treatment targets, and, eventually, categorization of patients with respect to disease prognosis, leading to a change in management approach in specific subgroups of patients. Despite the currently limited data on genetic influences in NAFLD and all the difficulties in studying them, we believe that most of the variability in NAFLD presentation will eventually be attributed to and explained by variations in SNP frequencies and their effects on the function of factors involved in the pathogenesis of the disease.

REFERENCES

1 **Duvnjak M**, Lerotić I, Barsić N, Tomasić V, Virović Jukić L, Velagić V. Pathogenesis and management issues for non-alcoholic fatty liver disease. *World J Gastroenterol* 2007; **13**: 4539-4550

2 **Wanless IR**, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology* 1990; **12**: 1106-1110

3 **Struben VM**, Hespenheide EE, Caldwell SH. Nonalcoholic steatohepatitis and cryptogenic cirrhosis within kindreds. *Am J Med* 2000; **108**: 9-13

4 **Willner IR**, Waters B, Patil SR, Reuben A, Morelli J, Riely CA. Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. *Am J Gastroenterol* 2001; **96**: 2957-2961

5 **Browning JD**, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387-1395

6 **Browning JD**, Kumar KS, Saboorian MH, Thiele DL. Ethnic differences in the prevalence of cryptogenic cirrhosis. *Am J Gastroenterol* 2004; **99**: 292-298

7 **Caldwell SH**, Harris DM, Patrie JT, Hespenheide EE. Is NASH underdiagnosed among African Americans? *Am J Gastroenterol* 2002; **97**: 1496-1500

8 **Farrell GC**. Non-alcoholic steatohepatitis: what is it, and why is it important in the Asia-Pacific region? *J Gastroenterol Hepatol* 2003; **18**: 124-138

9 **Kelly DP**, Scarpulla RC. Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. *Genes Dev* 2004; **18**: 357-368

10 **Puigserver P**, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* 1998; **92**: 829-839

11 **Esterbauer H**, Oberkofler H, Linnemayr V, Iglseder B, Hedegger M, Wolfsgruber P, Paulweber B, Fastner G, Krempler F, Patsch W. Peroxisome proliferator-activated receptor-gamma coactivator-1 gene locus: associations with obesity indices in middle-aged women. *Diabetes* 2002; **51**: 1281-1286

12 **Hara K**, Tobe K, Okada T, Kadowaki H, Akanuma Y, Ito C, Kimura S, Kadowaki T. A genetic variation in the PGC-1 gene could confer insulin resistance and susceptibility to Type II diabetes. *Diabetologia* 2002; **45**: 740-743

13 **Ridderstråle M**, Johansson LE, Rastam L, Lindblad U. Increased risk of obesity associated with the variant allele of the PPARGC1A Gly482Ser polymorphism in physically inactive elderly men. *Diabetologia* 2006; **49**: 496-500

14 **Xie G**, Guo D, Li Y, Liang S, Wu Y. The impact of severity of hypertension on association of PGC-1alpha gene with blood pressure and risk of hypertension. *BMC Cardiovasc Disord* 2007; **7**: 33

15 **Leone TC**, Lehman JJ, Finck BN, Schaeffer PJ, Wende AR, Boudina S, Courtois M, Wozniak DF, Sambandam N, Bernal-Mizrachi C, Chen Z, Holloszy JO, Medeiros DM, Schmidt RE, Saffitz JE, Abel ED, Semenkovich CF, Kelly DP. PGC-1alpha deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. *PLoS Biol* 2005; **3**: e101

16 **Yoneda M**, Hotta K, Nozaki Y, Endo H, Uchiyama T, Mawatari H, Iida H, Kato S, Hosono K, Fujita K, Yoneda K, Takahashi H, Kirikoshi H, Kobayashi N, Inamori M, Abe Y, Kubota K, Saito S, Maeyama S, Wada K, Nakajima A. Association between PPARGC1A polymorphisms and the occurrence of nonalcoholic fatty liver disease (NAFLD). *BMC Gastroenterol* 2008; **8**: 27

17 **Hui Y**, Yu-Yuan L, Yu-Qiang N, Wei-Hong S, Yan-Lei D, Xiao-Bo L, Yong-Jian Z. Effect of peroxisome proliferator-activated receptors-gamma and co-activator-1alpha genetic polymorphisms on plasma adiponectin levels and susceptibility of non-alcoholic fatty liver disease in Chinese people. *Liver Int* 2008; **28**: 385-392

18 **Namikawa C**, Shu-Ping Z, Vyselaar JR, Nozaki Y, Nemoto Y, Ono M, Akisawa N, Saibara T, Hiroi M, Enzan H, Onishi S. Polymorphisms of microsomal triglyceride transfer protein gene and manganese superoxide dismutase gene in non-alcoholic steatohepatitis. *J Hepatol* 2004; **40**: 781-786

19 **Gambino R**, Cassader M, Pagano G, Durazzo M, Musso G. Polymorphism in microsomal triglyceride transfer protein: a link between liver disease and atherogenic postprandial lipid profile in NASH? *Hepatology* 2007; **45**: 1097-1107

20 **Leclercq IA**, Farrell GC, Schriemer R, Robertson GR. Leptin is essential for the hepatic fibrogenic response to chronic liver injury. *J Hepatol* 2002; **37**: 206-213

21 **Wauters M**, Considine RV, Chagnon M, Mertens I, Rankinen T, Bouchard C, Van Gaal LF. Leptin levels, leptin receptor gene polymorphisms, and energy metabolism in women. *Obes Res* 2002; **10**: 394-400

22 **Chagnon YC**, Rankinen T, Snyder EE, Weisnagel SJ, Pérusse L, Bouchard C. The human obesity gene map: the 2002 update. *Obes Res* 2003; **11**: 313-367

23 **Liu CY**, Wang YQ, Liu HY, Ji JF, Li WH, Bie HL, Li LX. [Relationship of variation 3057 G-->A of exon 20 of leptin receptor gene to lipid metabolism and fat distribution of children with obesity] *Zhonghua Yixue Yichuanxue Zazhi*

2004; **21**: 252-256
24 **Lu H**, Sun J, Sun L, Shu X, Xu Y, Xie D. Polymorphism of human leptin receptor gene is associated with type 2 diabetic patients complicated with non-alcoholic fatty liver disease in China. *J Gastroenterol Hepatol* 2009; **24**: 228-232
25 **Czaja MJ**. Liver injury in the setting of steatosis: crosstalk between adipokine and cytokine. *Hepatology* 2004; **40**: 19-22
26 **Mantzoros CS**, Li T, Manson JE, Meigs JB, Hu FB. Circulating adiponectin levels are associated with better glycemic control, more favorable lipid profile, and reduced inflammation in women with type 2 diabetes. *J Clin Endocrinol Metab* 2005; **90**: 4542-4548
27 **Maeda N**, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 2002; **8**: 731-737
28 **Musso G**, Gambino R, De Michieli F, Durazzo M, Pagano G, Cassader M. Adiponectin gene polymorphisms modulate acute adiponectin response to dietary fat: Possible pathogenetic role in NASH. *Hepatology* 2008; **47**: 1167-1177
29 **Zhan Q**, Li YY, Nie YQ, Zhou YJ, DU YL, Sha WH, Wang H. [Association of hepatic lipase gene promoter polymorphism -514C/T with nonalcoholic fatty liver disease] *Zhonghua Ganzangbing Zazhi* 2008; **16**: 375-378
30 **Buchman AL**, Dubin MD, Moukarzel AA, Jenden DJ, Roch M, Rice KM, Gornbein J, Ament ME. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology* 1995; **22**: 1399-1403
31 **Song J**, da Costa KA, Fischer LM, Kohlmeier M, Kwock L, Wang S, Zeisel SH. Polymorphism of the PEMT gene and susceptibility to nonalcoholic fatty liver disease (NAFLD). *FASEB J* 2005; **19**: 1266-1271
32 **Dong H**, Wang J, Li C, Hirose A, Nozaki Y, Takahashi M, Ono M, Akisawa N, Iwasaki S, Saibara T, Onishi S. The phosphatidylethanolamine N-methyltransferase gene V175M single nucleotide polymorphism confers the susceptibility to NASH in Japanese population. *J Hepatol* 2007; **46**: 915-920
33 **Sazci A**, Ergul E, Aygun C, Akpinar G, Senturk O, Hulagu S. Methylenetetrahydrofolate reductase gene polymorphisms in patients with nonalcoholic steatohepatitis (NASH). *Cell Biochem Funct* 2008; **26**: 291-296
34 **Arkan MC**, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, Wynshaw-Boris A, Poli G, Olefsky J, Karin M. IKK-beta links inflammation to obesity-induced insulin resistance. *Nat Med* 2005; **11**: 191-198
35 **Nagai H**, Matsumaru K, Feng G, Kaplowitz N. Reduced glutathione depletion causes necrosis and sensitization to tumor necrosis factor-alpha-induced apoptosis in cultured mouse hepatocytes. *Hepatology* 2002; **36**: 55-64
36 **Ding WX**, Yin XM. Dissection of the multiple mechanisms of TNF-alpha-induced apoptosis in liver injury. *J Cell Mol Med* 2004; **8**: 445-454
37 **Crespo J**, Cayón A, Fernández-Gil P, Hernández-Guerra M, Mayorga M, Domínguez-Díez A, Fernández-Escalante JC, Pons-Romero F. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. *Hepatology* 2001; **34**: 1158-1163
38 **Valenti L**, Fracanzani AL, Dongiovanni P, Santorelli G, Branchi A, Taioli E, Fiorelli G, Fargion S. Tumor necrosis factor alpha promoter polymorphisms and insulin resistance in nonalcoholic fatty liver disease. *Gastroenterology* 2002; **122**: 274-280
39 **Tokushige K**, Takakura M, Tsuchiya-Matsushita N, Taniai M, Hashimoto E, Shiratori K. Influence of TNF gene polymorphisms in Japanese patients with NASH and simple steatosis. *J Hepatol* 2007; **46**: 1104-1110
40 **Friedman SL**. Cytokines and fibrogenesis. *Semin Liver Dis* 1999; **19**: 129-140
41 **Bataller R**, Sancho-Bru P, Ginès P, Brenner DA. Liver fibrogenesis: a new role for the renin-angiotensin system. *Antioxid Redox Signal* 2005; **7**: 1346-1355
42 **Yokohama S**, Tokusashi Y, Nakamura K, Tamaki Y, Okamoto S, Okada M, Aso K, Hasegawa T, Aoshima M, Miyokawa N, Haneda M, Yoneda M. Inhibitory effect of angiotensin II receptor antagonist on hepatic stellate cell activation in non-alcoholic steatohepatitis. *World J Gastroenterol* 2006; **12**: 322-326
43 **Gibbons GH**, Pratt RE, Dzau VJ. Vascular smooth muscle cell hypertrophy vs. hyperplasia. Autocrine transforming growth factor-beta 1 expression determines growth response to angiotensin II. *J Clin Invest* 1992; **90**: 456-461
44 **Noble NA**, Border WA. Angiotensin II in renal fibrosis: should TGF-beta rather than blood pressure be the therapeutic target? *Semin Nephrol* 1997; **17**: 455-466
45 **Dixon JB**, Bhathal PS, Jonsson JR, Dixon AF, Powell EE, O'Brien PE. Pro-fibrotic polymorphisms predictive of advanced liver fibrosis in the severely obese. *J Hepatol* 2003; **39**: 967-971

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