ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-6326

The Association of the Polymorphic Marker of +795 G>A in the Adiponectin Receptor 2 Gene with Biopsy-confirmed Metabolic Dysfunction-associated Steatotic Liver Disease

Kosar Babaeian Roshani[1], Zahra Ourang[1], Mitra Rostami[1], Atefeh Dehghanitafti[1], Mobina Hosseini[1], Touraj Mahmoudi[1], Ronak Soltanirazlighi[1], Aidin Mahban[2], Radmehr Shafiee[3], Helia Sadat Kaboli[1], Gholamreza Rezamand[4,5], Asadollah Asadi[6], Reza Dabiri[7], Seidamir Pasha Tabaeian[4,5]

1) Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran; 2) Department of Business Management, Science and Research Branch, Islamic Azad University, Tehran, Iran; 3) Sterile Services Department (CSSD), Practice Plus Group Hospital, Emersons Green, Bristol, United Kingdom; 4) Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; 5) Colorectal Research Center, Iran University of Medical Sciences, Tehran, Iran; 6) Department of Biology, Faculty of Science, University of Mohaghegh Ardabili, Ardabil, Iran; 7) Internal Medicine Department, Semnan University of Medical Sciences, Semnan, Iran

Address for correspondence:
Seidamir Pasha Tabaeian, Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Shahid Hemmat Highway, Tehran, Iran
noblautoumah@gmail.com

Received: 27.02.2025
Accepted: 05.08.2025

ABSTRACT

Background & Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) with the prevalence of around 25% is the most prevailing cause of chronic liver disease. In this study, we aimed to investigate the association of the rs16928751 or +795 G>A variant in adiponectin receptor 2 gene (*ADIPOR2*) with MASLD.
Methods: Genomic DNA was isolated from the whole blood of 130 patients with biopsy-confirmed MASLD, and 130 controls according to the phenol-chloroform extraction and ethanol precipitation approach. Then the polymorphic marker of +795 G>A was genotyped by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).
Results: The +795 G>A variant met the Hardy-Weinberg equilibrium ($p > 0.05$) in both control and patient groups; hence, the samples had good population representativeness. The genotype count of *ADIPOR2* gene +795 G>A differed significantly between these two groups. The +795 G>A „AA" genotype in comparison to the „GG" was more frequent in the patients with MASLD (p=0. 037; OR=2.24, 95%CI: 1.20–6.47).
Conclusions: To our knowledge, this study is the first one that found a significant association between the +795 G>A variant of the *ADIPOR2* gene and biopsy-confirmed MASLD; nonetheless, it needs to be corroborated by further research in different populations.

Key words: adiponectin – *ADIPOR2* – MASLD – rs16928751 – variant.

Abbreviations: *ADIPOR2*: adiponectin receptor 2 gene; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; DBP: diastolic blood pressure; GGT: gamma glutamyl transferase; HWE: Hardy-Weinberg equilibrium; IR: insulin resistance; MAF: minor allele frequency; MASLD: metabolic dysfunction-associated steatotic liver disease; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; SBP: systolic blood pressure; SNP: single nucleotide polymorphism; T2D: type 2 diabetes mellytus.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) which once was called nonalcoholic fatty liver disease (NAFLD) is the most prevailing cause of chronic liver disease and is a worldwide major public health burden. MASLD is present when more than five percent of liver hepatocytes are steatotic in the absence of excessive alcohol consumption. The broad spectrum of MASLD ranges from simple steatosis to more complex forms, consisting of nonalcoholic steatohepatitis (NASH), hepatic fibrosis, and cirrhosis. Cirrhosis can even develop into hepatocellular carcinoma. MASLD, whose prevalence is rising, affects approximately 25% of the adult population [1]. Although MASLD has been extensively researched, its molecular mechanisms remain unclear. Evidence proposes direct strong links between MASLD and insulin resistance (IR), obesity, type 2 diabetes mellitus (T2D), dyslipidemia, and high blood pressure. The release of free fatty acids from adipocytes and their influx into liver is expedited by IR. MASLD is also associated with single nucleotide polymorphisms (SNPs) in insuling signaling pathway genes [2-5].

Adiponectin, a 30 kDa collagen-like protein encoded by the *ADIPOQ* gene, is a hepatoprotective adipokine involved in glucose and lipid metabolism. It is mainly secreted by adipocytes and is the most abundant gene product of adipose tissue. Adiponectin has insulin-sensitising, anti-inflammatory,

and hepatoprotective properties [6, 7]. The dysfunctional regulation of adiponectin has been shown in IR, obesity, T2D, metabolic syndrome, and hypertension. Low serum level of adiponectin is significantly correlated with IR, T2D and obesity [8-11]. Additionally, serum adiponectin level is believed to be inversely related to MASLD [9, 12-14]. Finally, significant associations have been found between the adiponectin gene (*ADIPOQ*) polymorphisms and MASLD [15, 16].

Adiponectin exerts its effects by binding to adiponectin receptors which are G protein-coupled receptors. Obesity reduces the expression of adiponectin receptor 1 (ADIPOR1) and adiponectin receptor 2 (ADIPOR2), thereby decreasing adiponectin signaling and leading to IR [8-11]. ADIPOR2, encoded by the *ADIPOR2* gene, mediates the biological effects of adiponectin and is largely expressed in skeletal muscle and the liver. ADIPOR2 is expressed in pancreatic β-cells too and fatty acids play a role in control of its expression level in these cells [17]. The activation of ADIPOR2 raises fatty acid oxidation and glucose utilization by adiponectin [18]. However, until now there has been no study investigating the possible association between the *ADIPOR2* polymorphisms and susceptibility to MASLD. In the present study, we examined whether the polymorphic marker rs16928751 or +795 G>A in the *ADIPOR2* gene is implicated in susceptibility to MASLD. The selection of the +795 G>A variant was based on the following criteria: First, this SNP has a comparatively high minor allele frequency (MAF). Second, the +795 G>A has been commonly studied in prior research. Lastly, the position of this polymorphism in the exon region (exon 6) of the *ADIPOR2* gene implies that it may influence the functionality of ADIPOR2.

METHODS

Study Population

A total of 130 Iranian unrelated patients with MASLD and 130 controls were studied (Table II). The study protocol was approved by the Ethics Committee of the Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences in Tehran, Iran, and all participants gave informed consent. The MASLD patients were selected according to: a) ultrasonographic findings of steatosis b) elevated levels of liver enzymes – aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT) c) Patients with hepatitis due to excessive intake of alcohol (>70g per week for women or >140g per week for men), hepatitis due to drug use, viral hepatitis B and C, Wilson's disease (a rare inherited condition), and alpha-1 antitrypsin deficiency were excluded from the study. d) liver biopsy findings of MASLD diagnosis. The severity of liver steatosis and necroinflammation was graded from 0 to 3, and fibrosis severity was staged from 0 to 4. 27% of the patients had hypertension, 24% had type 2 diabetes, and 31% had metabolic syndrome. Selected control subjects were unrelated people who were age-, body mass index (BMI)- and gender-matched with the patient group. They were chosen from the research staff and medical students of Shahid Beheshti University of Medical Sciences seeking a routine health checkup. The subjects with elevated AST, ALT, and GGT (examined by blood tests), viral hepatitis infection (examined by blood tests) as well as history of liver steatosis (examined by abdominal ultrasonography) were excluded from the control group. Subjects with evidence of being alcoholic or being on regular medications were not included as controls too. Information on demographics, anthropometric, and clinical parameters was obtained using self-administered questionnaires or laboratory tests. Body mass index was calculated as body weight in kilograms / the square of body height in meters [19, 20]. The study was conducted in accordance with the relevant guidelines and regulations of the Declaration of Helsinki.

SNP Genotyping

Blood samples from the patients and controls were drawn and collected in EDTA tubes and DNA samples were extracted according to the phenol-chloroform extraction and ethanol precipitation approach. The storage of the isolated DNA was done at minus 20 degrees Celsius for later use. As characterized in Table I, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays were used to determine the *ADIPOR2* +795 G>A alleles. The PCR products were digested using the restriction enzyme of Bse1I or BseNI or BsrI for 16h at 65°C (Fermentas, Leon-Rot, Germany). To visualize the digested fragments, an agarose gel (2.5%) was used, then stained with ethidium bromide and exposed under ultraviolet light [21]. There were three genotypes for the *ADIPOR2* gene +795 G>A variant: AA, which has a single band at 301bp; AG, which has three separate bands at 301bp, 169bp and 132bp; and GG, which has two bands at 169bp and 132bp. Twenty percent of the participants were chosen at random and re-genotyped for checking the genotyping process; the genotyping error rate was 0%.

Statistical Analysis

Data were analyzed with the SPSS program (version 25.0; SPSS Inc., Chicago, IL, USA). To compare quantitative data (presented as mean±standard deviation) or qualitative data (expressed as number±percent) between the patient and control groups we used t-test or chi-square (χ^2) test, as appropriate. The test for evaluating the compatibility of the *ADIPOR2* +795 G>A genotype distributions with Hardy-Weinberg equilibrium (HWE) was conducted using χ^2. This test was also applied to assess the possible differences in the allele

Table I. Detection of rs16928751 or +795 G>A SNP within the adiponectin receptor 2 gene (ADIPOR2)

Gene (SNP ID)	Location (Base change)	Primers (forward and reverse)	PCR program (32 cycles)	PCR fragment size (bp)	Restriction enzyme, Incubation temperature	RFLP fragments size (bp)
ADIPOR2 (rs16928751)	Exon 6 (G>A)	5'-CTCTGGTATTGCTCTTCTGATTATGGGAA-3' 5'-TTCTTCATCTTGGCATCACAAATACACAG-3'	94 °C 35s, 58 °C 40s, 72 °C 30s	301	Bse1I, 65 °C	A: 301 G: 169+132

frequencies between the two groups. To evaluate the association between the genotype frequencies of the *ADIPOR2* gene +795 G>A and MASLD, logistic regression analysis was employed. We used multivariate logistic regression analysis to confirm the independent association of the +795 G>A polymorphism with MASLD and interaction with other risk factors including age, BMI, gender, smoking history, systolic blood pressure (SBP), diastolic blood pressure (DBP), AST, ALT, and hypertension. The association of this SNP with MASLD was analyzed by determining the odds ratio (OR) and 95% confidence interval (95% CI). The critical level of significance was accepted at *p* value less than 0.05 [22].

RESULTS

Clinical characteristics of the MASLD patients and control individuals are summarized in Table II. Compared to the controls, MASLD patients had significantly elevated SBP, DBP, and AST, ALT, and GGT levels (p<0.001).

Table II. Clinical and metabolic characteristics of the patients with metabolic dysfunction-associated steatotic liver disease and control subjects[a]

Variables	Controls (n=130)	Patients (n=130)	p[b]
Age (years) Range	32.5 (5.9) 28–54	34.1(6.8) 29–61	0.106
BMI (kg/m^2)	25.6 (3.4)	27.2 (3.7)	0.115
Females (n)	54 (41.5)	49 (37.7)	0.487
Current or former smoker	20 (15.4)	23 (17.7)	0.691
SBP (mmHg)	113.1 (12.9)	126.3 (15.4)	<0.001
DBP (mmHg)	70.3 (8.7)	79.6 (9.8)	<0.001
AST (IU/L)	19.0 (7.3)	37.5 (16.3)	<0.001
ALT (IU/L)	19.4 (8.8)	66.7 (34.9)	<0.001
GGT (IU/L)	20.1 (8.3)	54.2 (30.6)	<0.001
Steatosis grade			
0		-	
1		21 (16.2)	
2		68 (52.3)	
3		41 (31.5)	
Necroinflammation grade			
0		26 (20.0)	
1		46 (35.4)	
2		51 (39.2)	
3		7 (5.4)	
Fibrosis stage			
0		50 (38.4)	
1		53 (40.8)	
2		16 (12.3)	
3		8 (6.2)	
4		3 (2.3)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; DBP: diastolic blood pressure; GGT: gamma glutamyl transferase; SBP: systolic blood pressure. [a] Data are expressed as mean (standard deviation) or number (percent). [b] The p-values were calculated by t-test or chi-squared test where appropriate.

Table III shows the genotype and allele counts of the *ADIPOR2* gene +795 G>A variant in the case and control groups. The polymorphic marker studied followed the HWE in controls and patients (p>0.05), hence the samples of both groups had good population representativeness. A significant difference in genotypic frequencies of the +795 G>A between the controls and MASLD patients was observed either before or after adjustment for confounding factors such as age and BMI. Analysis of the frequencies of this SNP demonstrated that the "AA" genotype of the *ADIPOR2* gene +795 G>A variant compared with the "GG" genotype was significantly overrepresented in the biopsy-confirmed MASLD patients even after adjustment for confounding factors including age, BMI, sex, smoking status, SBP, DBP, and hypertension (p=0.037; OR=2.24, 95%CI: 1.20–6.47). Study of the *ADIPOR2* +795 G>A allelic frequencies showed no significant difference between the case and control groups (p>0.05).

DISCUSSION

To our knowledge, this is the first study that analyzed the role of *ADIPOR2* gene polymorphisms in MASLD; the "AA" genotype of the *ADIPOR2* +795 G>A (rs16928751) compared to the "GG" genotype appeared to be a marker of increased MASLD susceptibility. The present research, however, identifies an association between the *ADIPOR2* +795 G>A and MASLD, not a direct causative effect.

With the increasing prevalence of MASLD worldwide, it has become paramount to understand the role of genes involved in its pathophysiology. In the pathogenesis that results in MASLD, both hereditary predisposition and lifestyle and nutrition habits are considered key elements. Consequently, investigations of variants in candidate genes implicated in the MASLD pathogenesis are of the utmost practical importance. To identify a polymorphism, it must occur at least in one percent of the general population. Adipokines including adiponectin may be involved in the link between obesity and IR and risk of MASLD. Adiponectin is the most abundant adipocytokine. The amount of adiponectin decreases in inverse proportion to the amount of adipose mass and visceral fat. Adiponectin plays a significant role in energy metabolism, modulating insulin action, and the regulation of glucose metabolism and inflammation. It improves hepatic insulin resistance by a fall in glycogenesis and lipogenesis and a rise in glucose consumption. To the best of our knowledge, however, no studies have evaluated the association between the *ADIPOR2* polymorphisms and MASLD up to now. Genetic variations in *ADIPOR2* may have effects on IR-related phenotypes such as MASLD [9, 23-25].

The *ADIPOR2* gene comprising 8 exons and 7 introns spans 97 kb on chromosome 12p13. This gene encodes the ADIPOR2 protein – a cell-surface receptor – containing 387 amino acids. ADIPOR2 increases the expression of glucose consumption related genes by activating PPAR-α signaling pathway [26]. In the current research, the *ADIPOR2* +795 G>A "AA" genotype compared to the "GG" genotype was associated with a 2.24-fold increase in MASLD. The +795G>A – a common SNP studied in the *ADIPOR2* gene – is situated in exon 6 which does not alter the amino acid sequence of

Table III. Association of the rs16928751 or +795 G>A variant in ADIPOR2 gene with biopsy-confirmed MASLD[a]

Gene	Polymorphism	Genotypes/Alleles	Controls (n=130)	Patients (n=130)	P-value[b]	Adjusted OR (95% CI)[b]
ADIPOR2	rs16928751	GG	90 (69.2)	79 (60.8)	-	1.00 (reference)
		GA	34 (26.2)	40 (30.8)	0.541	1.30 (0.72–1.64)
		AA	6 (4.6)	11 (8.4)	0.037	2.24 (1.20–6.47)
		GA+AA	40 (30.8)	51 (39.2)	0.268	1.69 (0.83–2.05)
		AA versus others	6 (4.6)	11 (8.5)	0.092	1.85(0.92–2.71)
		G	214 (82.3)	198 (76.2)	-	1.00 (reference)
		A	46 (17.7)	62 (23.8)	0.085	1.29 (0.59–1.88)

ADIPOR2: adiponectin receptor 2 gene; MASLDL metabolic dysfunction-associated steatotic liver disease; OR: odds ratio; CI: confidence interval. [a] Variables presented as number (%). [b] p-values, ORs, and 95% CIs were calculated after adjusting for age, body mass index, sex, smoking status, systolic blood pressure, diastolic blood pressure, and hypertension in genotype-wise comparisons.

the ADIPOR2 (a synonymous SNP); nonetheless, previous reports support the hypothesis that the *ADIPOR2* +795 G>A "AA" genotype may be implicated in the MASLD pathogenesis. Fatty acid oxidation and glucose utilization is increased by the activation of ADIPOR2 [18]. The expression level of ADIPOR2 is positively associated with insulin sensitivity [27] and is negatively associated with serum AST and ALT levels and T2D and MASLD [28, 29]. Furtheremore, adiponectin signaling decreases with the downregulation of the ADIPOR2 expression and low ADIPOR2 levels may reduce the biological effects of adiponectin, hence further aggravate the detrimental effects of low adiponectin level. According to former studies, serum adiponectin level is inversely associated with adipose tissue mass, obesity, metabolic syndrome, T2D, IR, and serum levels of glucose, insulin, total cholesterol, and triglycerides [8-11, 30, 31]. MASLD patients also have a lower serum level of adiponectin [9, 12-14]. More interestingly, the "AA" genotype or the "GA+AA" genotypes compared with the "GG" genotype are associated with higher BMI [11], IR, triglycerides levels, blood pressure, and higher likelihood of T2D [32]. Alternatively, maybe the +795 G>A polymorphism is not functional by itself. Instead, this SNP may be in linkage disequilibrium with other *ADIPOR2* gene SNPs and cause changes in the receptor activity, although such a mechanism is speculative but biologically plausible. The *ADIPOR2* rs767870 variant which is in high LD with +795 G>A is associated with liver fat content and its surrogate markers [33]. Some other *ADIPOR2* variants show significant associations with ADIPOR2 protein expression [34] and rate of fat oxidation [35].

Some limitations of the current study which were due largely to the budget constraints warrant a mention. Firstly, no measurements of serum adiponectin levels are available for this report. Thus, it is almost impossible to prove whether the *ADIPOR2* +795 G>A variant influences MASLD susceptibility by affecting the adiponectin levels. Secondly, the selected locus does not represent whole SNPs in the *ADIPOR2* gene. Therefore, if there was enough funding available, we should have analyzed more polymorphisms in this gene. Thirdly, the modest sample size of the present study. Fourthly, the lack of functional assays to validate the biological significance of the +795 G>A polymorphism restricts a deeper understanding of the mechanistic pathways through which this SNP is associated with MASLD. Fifthly, this study is limited to a specific population (the Iranian population) and may not be generalizable to other populations with different ethnic and/or cultural backgrounds. Sixthly, in the present study, we did not use any matching strategies beyond age, BMI, and gender, and because the controls were selected from the staff of research institutes and hospitals and medical students, this could introduce bias since these individuals may have different lifestyle factors compared to the general population. Our study, however, has several strengths too. First, using liver biopsy as the gold standard method for the diagnosis of MASLD. Second, the novel and interesting finding regarding the potential association of the *ADIPOR2* gene +795 G>A polymorphism with MASLD.

CONCLUSIONS

To our knowledge, this is the first study identifying the *ADIPOR2* +795 G>A variant as a potential risk factor for biopsy-confirmed MASLD, with the 'AA' genotype showing a 124% increased risk. If the association between the *ADIPOR2* gene polymorphisms and MASLD is confirmed by future research in different populations and races, this gene may act as a potentially diagnostic biomarker and a promising therapeutic target for MASLD.

Conflicts of interest: None to declare.

Authors' contributions: T.M. conceived and designed the study. K.B.R., Z.O., M.R., A.D., M.H., R.S., A.M., R.S., H.S.K., G.R., A.A., R.D. and S.P.T. collected the data and were involved in the genetic analysis. T.M. analysed and interpreted the results. K.B.R., T.M. and S.P.T. drafted the manuscript. K.B.R. coordinated the study. T.M. and S.P.T supervised the project. All the authors read and approved the final version of the manuscript.

Acknowledgements: The authors thank all patients and healthy blood donors for providing blood samples. This work was supported by a grant from the Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences [grant number 1430].

REFERENCES

1. Díaz LA, Fuentes-López E, Ayares G, et al. The establishment of public health policies and the burden of non-alcoholic fatty liver disease in the

Americas. Lancet Gastroenterol Hepatol 2022;7:552-559. doi:10.1016/S2468-1253(22)00008-5
2. Eguchi Y, Eguchi T, Mizuta T, et al. Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease. J Gastroenterol 2006;41:462-469. doi:10.1007/s00535-006-1790-5
3. Dietrich P, Hellerbrand C. Non-alcoholic fatty liver disease, obesity and the metabolic syndrome. Best Pract Res Clin Gastroenterol 2014;28:637-653. doi:10.1016/j.bpg.2014.07.008
4. Atay K, Canbakan B, Koroglu E, et al. Apoptosis and Disease Severity is Associated with Insulin Resistance in Non-alcoholic Fatty Liver Disease. Acta Gastroenterol Belg 2017;80:271-277.
5. Nobakht H, Mahmoudi T, Sabzikarian M, et al. Insulin and insulin receptor gene polymorphisms and susceptibility to nonalcoholic fatty liver disease. Arq Gastroenterol 2020;57:203-208. doi:10.1590/S0004-2803.202000000-39
6. Tsochatzis E, Papatheodoridis GV, Archimandritis AJ. The evolving role of leptin and adiponectin in chronic liver diseases. Am J Gastroenterol 2006;101:2629-2640. doi:10.1111/j.1572-0241.2006.00848.x
7. Vachliotis ID, Valsamidis I, Polyzos SA. Tumor Necrosis Factor-Alpha and Adiponectin in Nonalcoholic Fatty Liver Disease-Associated Hepatocellular Carcinoma. Cancers (Basel) 2023;15:5306. doi:10.3390/cancers15215306
8. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006;116:1784-1792. doi:10.1172/JCI29126
9. Machado MV, Coutinho J, Carepa F, Costa A, Proença H, Cortez-Pinto H. How adiponectin, leptin, and ghrelin orchestrate together and correlate with the severity of nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2012;24:1166-1172. doi:10.1097/MEG.0b013e32835609b0
10. Ahasic AM, Zhao Y, Su L, Sheu CC, Thompson BT, Christiani DC. Adiponectin gene polymorphisms and acute respiratory distress syndrome susceptibility and mortality. PLoS One 2014;9:e89170. doi:10.1371/journal.pone.0089170
11. Shramko I, Ageeva E, Krutikov E, et al. Polymorphism in Adiponectin and Adiponectin Receptor Genes in Diabetes Mellitus Pathogenesis. Pathophysiology 2022;29:81-91. doi:10.3390/pathophysiology29010008
12. Mendez-Sanchez N, Chavez-Tapia NC, Villa AR, et al. Adiponectin as a protective factor in hepatic steatosis. World J Gastroenterol 2005;11:1737-1741. doi:10.3748/wjg.v11.i12.1737
13. Pagano C, Soardo G, Esposito W, et al. Plasma adiponectin is decreased in nonalcoholic fatty liver disease. Eur J Endocrinol 2005;152:113-118. doi:10.1530/eje.1.01821
14. Gupta AC, Misra R, Sakhuja P, Singh Y, Basir SF, Sarin SK. Association of adiponectin gene functional polymorphisms (-11377C/G and +45T/G) with nonalcoholic fatty liver disease. Gene 2012;496:63-67. doi:10.1016/j.gene.2011.12.023
15. 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. doi:10.1002/hep.22142
16. Wang BF, Wang Y, Ao R, Tong J, Wang BY. AdipoQ T45 G and G276 T Polymorphisms and Susceptibility to Nonalcoholic Fatty Liver Disease Among Asian Populations: A Meta-Analysis and Meta-Regression. J Clin Lab Anal 2016;30:47-57. doi:10.1002/jcla.21814
17. Kharroubi I, Rasschaert J, Eizirik DL, Cnop M. Expression of adiponectin receptors in pancreatic beta cells. Biochem Biophys Res Commun 2003;312:1118-1122. doi:10.1016/j.bbrc.2003.11.042
18. Namvaran F, Rahimi-Moghaddam P, Azarpira N, Dabbaghmanesh MH. Polymorphism of adiponectin (45T/G) and adiponectin receptor-2 (795G/A) in an Iranian population: relation with insulin resistance and response to treatment with pioglitazone in patients with type 2 diabetes mellitus. Mol Biol Rep 2012;39:5511-5518. doi:10.1007/s11033-011-1354-5
19. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 1999;94:2467-2474. doi:10.1111/j.1572-0241.1999.01377.x
20. Mahmoudi T, Majidzadeh-A K, Karimi K, et al. Gly972Arg variant of insulin receptor substrate 1 gene and colorectal cancer risk in overweight/obese subjects. Int J Biol Markers 2016;31:e68-e72. doi:10.5301/jbm.5000159
21. Mahmoudi T, Karimi K, Arkani M, et al. Lack of associations between Vitamin D metabolism-related gene variants and risk of colorectal cancer. Asian Pac J Cancer Prev 2014;15:957-961. doi:10.7314/apjcp.2014.15.2.957
22. Mahmoudi T, Karimi K, Arkani M, et al. Resistin -420C>G promoter variant and colorectal cancer risk. Int J Biol Markers 2014;29:e233-e238. doi:10.5301/jbm.5000079
23. Mahmoudi T, Arkani M, Karimi K, et al. The -4817 G>A (rs2238136) variant of the vitamin D receptor gene: a probable risk factor for colorectal cancer. Mol Biol Rep 2012;39:5277-5282. doi:10.1007/s11033-011-1325-x
24. Mahmoudi T, Karimi K, Arkani M, et al. Parathyroid hormone gene rs6256 and calcium sensing receptor gene rs1801725 variants are not associated with susceptibility to colorectal cancer in Iran. Asian Pac J Cancer Prev 2014;15:6035-6039. doi:10.7314/apjcp.2014.15.15.6035
25. Mahmoudi T, Majidzadeh-A K, Karimi K, et al. An exon variant in insulin receptor gene is associated with susceptibility to colorectal cancer in women. Tumour Biol 2015;36:3709-3715. doi:10.1007/s13277-014-3010-x
26. Yamauchi T, Nio Y, Maki T, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007;13:332-339. doi:10.1038/nm1557
27. Civitarese AE, Jenkinson CP, Richardson D, et al. Adiponectin receptors gene expression and insulin sensitivity in non-diabetic Mexican Americans with or without a family history of Type 2 diabetes. Diabetologia 2004;47:816-820. doi:10.1007/s00125-004-1359-x
28.. Kaser S, Moschen A, Cayon A, et al. Adiponectin and its receptors in non-alcoholic steatohepatitis. Gut 2005;54:117-121. doi:10.1136/gut.2003.037010
29. Namvaran F, Rahimi-Moghaddam P, Azarpira N, Nikeghbalian S. The association between adiponectin (+45T/G) and adiponectin receptor-2 (+795G/A) single nucleotide polymorphisms with cirrhosis in Iranian population. Mol Biol Rep 2012;39:3219-3223. doi:10.1007/s11033-011-1089-3
30. Broedl UC, Lehrke M, Fleischer-Brielmaier E, et al. Genetic variants of adiponectin receptor 2 are associated with increased adiponectin levels and decreased triglyceride/VLDL levels in patients with metabolic syndrome. Cardiovasc Diabetol 2006;5:11. doi:10.1186/1475-2840-5-11
31. He J, Stryjecki C, Reddon H, al. Adiponectin is associated with cardio-metabolic traits in Mexican children. Sci Rep 2019;9:3084. doi:10.1038/s41598-019-39801-2
32. Potapov VA, Chistiakov DA, Dubinina A, Shamkhalova MS, Shestakova MV, Nosikov VV. Adiponectin and adiponectin receptor gene variants in relation to type 2 diabetes and insulin resistance-related phenotypes. Rev Diabet Stud 2008;5:28-37. doi:10.1900/RDS.2008.5.28

33. Kotronen A, Yki-Jarvinen H, Aminoff A, et al. Genetic variation in the ADIPOR2 gene is associated with liver fat content and its surrogate markers in three independent cohorts. Eur J Endocrinol 2009;160:593-602. doi:10.1530/EJE-08-0900
34. Halvatsiotis I, Tsiotra PC, Ikonomidis I, et al. Genetic variation in the adiponectin receptor 2 (ADIPOR2) gene is associated with coronary artery disease and increased ADIPOR2 expression in peripheral monocytes. Cardiovasc Diabetol 2010;9:10. doi:10.1186/1475-2840-9-10
35. Loos RJ, Ruchat S, Rankinen T, Tremblay A, Pérusse L, Bouchard C. Adiponectin and adiponectin receptor gene variants in relation to resting metabolic rate, respiratory quotient, and adiposity-related phenotypes in the Quebec Family Study. Am J Clin Nutr 2007;85:26-34. doi:10.1093/ajcn/85.1.26