ADIPOQ (RS1501299) G276 T POLYMORPHISMS AND SUSCEPTIBILITY TO NONALCOHOLIC FATTY LIVER DISEASE AMONG PATIENTS WITH UZBEK NATIONALITY

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Summary

Background. Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver injury and is an escalating medical problem worldwide. Genetic predisposition can play an important role in the development of this disease. AdipoQ (rs1501299) G276 T gene Polymorphisms have been found associated with the presence of NAFLD in a genome-wide association study. The purpose of this study was to determine the genotype distribution of single nucleotide polymorphism +276G > T (rs1501299) in ADIPOQ gene and an attempt to identify the impact of this polymorphism susceptibility to NAFLD in the Uzbek population

Keywords: Nonalcoholic fatty liver disease, AdipoQ (rs1501299) G276 T, genotypes, alleles, Uzbek population

Methods: In this case-control study, 94 patients with NAFLD and the age, gender and ethnically matched controls (n=49) were recruited. Genomic DNA was isolated and SNP genotyping was performed by using polymerase chain reaction with specific primers followed by restriction fragment length polymorphism analysis.

Results. Our investigations showed the accumulation of the GT-heterozygous state in patients with NAFLD of Uzbek nationality, while in healthy individuals the predominance of the GG homozygous genotype with a high frequency of the G-allele. The study of genetic models and the ratio of the chances of developing NAFLD in carriers of a certain combination of alleles and genotypes showed that for the multiplicative model, a significant association of the T allele with the risk of developing NAFLD was revealed ($p<0.001$; OR=2.33; 95% CI1.39 – 3.92). In other words, the presence of the T allele increases the risk of developing NAFLD in persons of Uzbek nationality by 2.3 times. In the group of healthy individuals, there is a significant predominance of carriers of the G / G genotype in comparison with the group of patients ($\chi 2=10.4$; df=1, p=0.001).

Conclusion. Our data suggest the reasonability of inclusion 276G>T (rs1501299) of the ADIPOQ test for identification of high risk groups for NASH in Uzbekistan.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver injury and is an escalating medical problem worldwide. The estimated global prevalence of NAFLD is between 24-30 %, whilst in Africa it is 13.5 % compared to the Middle East, Europe and America with rates of 31.8 %, 23.7 % and 30.4 %, respectively [1,2]. NAFLD is be defined as the hepatic manifestation of the metabolic syndrome that is characterized by increased hepatic lipid accumulation in the absence of excessive alcohol consumption and strongly associated with obesity and insulin resistance [3] The histologic spectrum of NAFLD ranges from simple steatosis, its inflammatory counterpart nonalcoholic steatohepatitis (NASH), which may advance to cryptogenic cirrhosis and hepatocellular carcinoma [4,5]

NAFLD is a multifactorial disease, the emergence and development of which depends on a number of interrelated factors: genetic polymorphisms, diet and lifestyle. [6]. Genetic factors play

an important role in the development of NAFLD [7]. Adiponectin, one of the major adipocyte-secreted proteins, has attracted scientific interest in recent years and has been extensively studied in both human and animal models. Adiponectin exerts insulin-sensitizing effects through binding to adiponectin receptors, leading to activation of adenosine monophosphate-activated protein kinase, peroxisome proliferators activated receptor-α, and potentially other unknown molecular pathways [8].

Currently, the National Center for Biotechnology Information genetic database contains information on 683 single-nucleotide polymorphisms (SNPs) mapped in the human adiponectin gene, 33 of these SNPs are cited in PubMed literature. Variants of SNPs in protein-coding regions cause changes in amino acids in key positions, which affect the functional activity of the protein. Moreover, latest research efforts focus on linking genetic markers of polymorphic variant of the SNP rs2241766 of the ADIPOQ gene, as well as rs266729 and rs822395, and significant association with diabetes mellitus 2 [9,10].

Furthermore, the rs2241766 polymorphism is closely related not only to diabetes, but also to obesity [11] and metabolic syndrome [12]. There is also a growing number of studies, which shows the association of SNPs in the ADIPOQ gene with changes in circulating serum adiponectin. The most common SNPs variants, such as rs266729 (-11377 C > G) and rs1501299 (+276 G > T) in the proximal part of the promoter and the intron region of the ADIPOQ gene, respectively, have been extensively studied in epidemiological studies. Allelic variants of rs266729, which is associated with low adiponectin content, also showed an association with obesity, body mass index, insulin sensitivity, endometrial cancer, and NAFLD [13, 14, 15, 10]. Another polymorphic variant, rs1501299, correlates with reduced adiponectin expression, resulting in increased body weight and insulin resistance [16, 17].

Also, a meta-analysis was conducted, which included publications in the PubMed and Embase databases devoted to the study of the association of polymorphism +276G>T (rs1501299) and NAFLD. The meta-analysis was based on 25 published results from studies involving 7,480 subjects. As a result, a significant association of G276T polymorphism with insulin resistance was proved [18]. Association of (rs1501299) of the ADIPOQ gene polymorphism with NAFLD was confirmed in several ethnic and geographic groups, but to date the assessment of this association has not been performed in the Central Asia populations. Uzbek population are the largest, youngest and fastest growing population in Central Asia. Uzbeks is very interesting with regard to cultural, socioeconomic, and genetic perspectives. It is remarkable to note that this population has been formed by admixture of two or more ancestral populations, thus it offers a unique opportunity for studying the interaction between gene polymorphisms, ethnic-specific genetic backgrounds and environmental contributions to disease occurrence.

The purpose of this study was to determine the genotype distribution of SNPs +276G > T (rs1501299) in ADIPOQ and an attempt to identify the impact this polymorphism susceptibility to NAFLD in Uzbek population.

Material and Methods. The study included 94 patients with NAFLD aged from 22 to 60 years and 49 healthy, age-matched, randomly selected persons with no history of metabolic diseases, no alcohol intake (no more than 30/20 g / day in men/women) and normal biochemical parameters, who underwent the treatment at the Republican Specialized Scientific-Practical Medical Center of Therapy and Rehabilitation. Molecular and genetic studies were carried out at the Center for Advanced Technologies under the Ministry of Innovative Development.

Study was conducted in accordance with the guidelines of the Helsinki Declaration of the World Medical Association's "Ethical Principles for Medical Research Involving Human Subjects" with amendments (2013). All patients who participated in this study gave written informed consent and the protocol was approved by the National Ethics Committee of Uzbekistan.

The diagnosis of NAFLD was established on the basis of clinical history, clinical examination, laboratory tests and liver ultrasound.

Abdominal ultrasonography (USG). Diagnosis of NAFLD was verified by the presence of "bright liver" echo pattern and hepatorenal echo contrast. Abdominal USG was performed by the same operator using Accuvix V20 apparatus (Samsung Medison Co., Ltd.,Seoul, South Korea).

Laboratory data. All blood samples were collected from the median cubital vein in the morning, after an overnight fast. Alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ -GTP), Serum triglycerides (TGs), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) were measured.

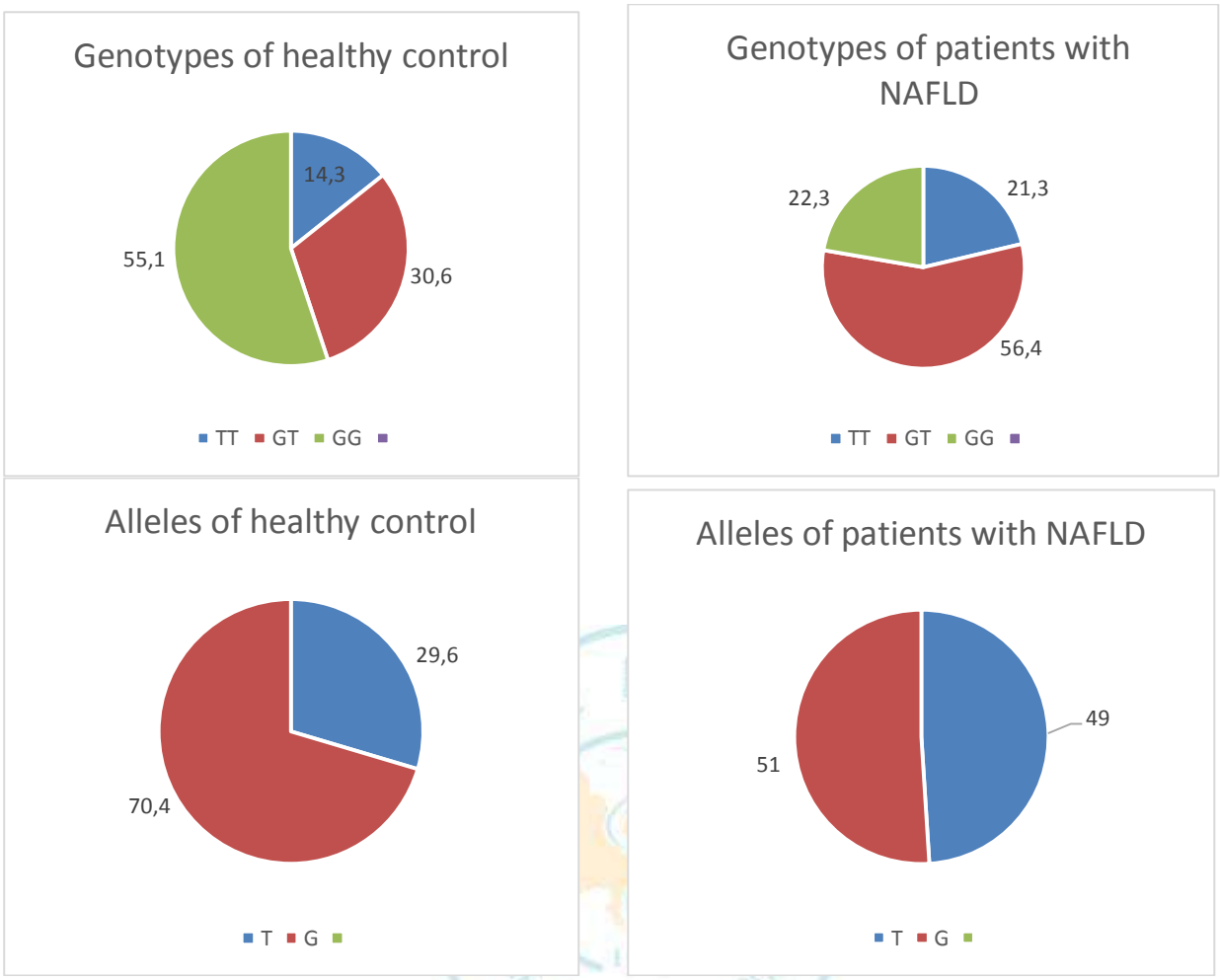
Genotyping. DNA samples were isolated from peripheral blood leucocytes by using DNA extraction kit Diatom™ DNA Prep 200 ("IsoGen Laboratory", Moscow, Russia). 276G>T (rs1501299) of the ADIPOQ gene was genotyped by PCR-RFLP method. A 468-bp region if the ADIPOQ (rs1501299) gene was by PCR using specific primers (forward primer: 5'-TCTCTCCATGGCTGACAGTG -3' and reverse primer: 5'- AGATGCAGCAAAGCCAAAGT -3'). PCR mixture(25 µl) consisted of 13 µl of ddH2O, 2.5 µl 10xPCR buffer, 2.5 µl 25 mM $MgCl_2$, 2.5 µl 2.5 mM dNTP Mix, 1,5 µl (10pkmol/µl) of each oligonucleotide primer, 0.3 ul (1.5 units.) "hot-start" Taq-polymerase and 3 µl of DNA. PCR amplification was carried out in GeneAmp 9700(Applied Biosystems). The PCR conditions were as follows: 95 ℃ for 5 min, and then 37 cycles of 94℃ for 30 s, 66℃ for 30 s, and 72 ℃ for 40 s and a final extension step of 72℃ for 5 minutes. Then PCR products were digested overnight at 65℃ with BstF5 I. Digested PCR products were subjected to horizontal electrophoresis in 1.5 % ethidium bromide-stained agarose gels in 1X TBE buffer at 120 V for 1 hr and were visualized using WiseDoc WGD-30 (DAIHAN, Korea). Interpretation of genotyping results was performed on the basis of different patterns of bands: CC genotype 200 and 133 bp, CG genotype - 333, 200 and 133 bp, GG genotype - 333 bp.

*Statistical analysis***.** The Hardy-Weinberg equilibrium was tested by a goodness-of-fit $\chi 2$ test to compare the observed genotype frequencies with the expected ones among the control subjects. Genotypic associations of SNPs were evaluated by Pearson's $\chi 2$ test and logistic regression analysis under additive, dominant and recessive models of inheritance, followed by risk assessment using odds ratio and 95% confidence of interval (CI) computation. All statistical analyses were performed by using STATA software version 12.0 for Windows (Stata Corporation, USA). A P value <0.05 (two-sided) was considered statistically significant.

Results. The result of genotyping revealed the following distribution of genotypes and alleles of the polymorphic marker c.276G>T (rs1501299) ADIPOQ gene: GG genotype was identified in 21 patients (22, 3%), GT genotype was identified in 53 patients (56, 4%) TT -20 (21, 3%) patients with authenticity $\chi 2=5,36$; p=0.006 (pic.1).

Analysis of the distribution of alleles among the patients, did not reveal a significant prevalence of carriers of the G allele compared to T-allele in patients with NAFLD Uzbek nationality: G allele – 50,5% (n=95), T allele – 49,5% (n=93), $\chi 2=3,56$; df=1, p=0,059.

At the same time, the results obtained in healthy individuals were as follows (n=49), the ratio of GG : GT : TT genotypes was 55.1% : 30.6% : 14.3% at $\chi 2=10.28$; df=2, p=0.0001, and the frequencies of G and T alleles were 70.4% (n=69) and 29.6% (n=29), respectively ($\chi 2=6.84$; df=1, p=0.001).



Picture 1. Distribution of frequencies of genotypes and alleles of + 276G>T polymorphism of the adiponectin gene in patients of Uzbek nationality and controls.

Comparative analysis of alleles in the two groups showed that the GG genotype and the G allele significantly predominated in the controls ($\chi 2=10.4$; df=1, p=0.001). The total distribution of genotype frequencies in the population corresponded to the theoretically expected Hardy-Weinberg calculation of genotype frequencies ($\chi 2=0.11$; p>0.05). (Table 1)

Table 1

Distribution of frequencies of genotypes and alleles 276G>T (rs1501299) of the ADIPOQ gene in the general population (n=143)

Genotypes/alleles	Observed frequencies	Expected frequencies	χ^2	P
GG	48	47,02	0,11	0,94
GT	68	69,95		
TT	27	26,02		
G allele	0,57	0,32		
T allelle	0,42	0,18		

It was revealed that the frequency of the minor allele in the Uzbek population as a whole is 42% and significantly exceeds the frequencies of the Vietnamese, British, Estonian, Swedish, European and American populations (24,9%, 25,1%, 28,2%, 28,5%, 28% and 30%, respectively).

Whilst the frequency of the minor allele in the Uzbek population is close to the frequencies of the Han (China), Yoruba (West Africa) and Africa as a whole (33%, 38% and 39%, respectively).
The distribution of allele and genotype frequencies in controls tends to deviate from the expected Hardy-Weinberg calculation of genotype frequencies, especially for the G/T and T/T genotypes ((χ2=3.45; p=0.06) (Table 2).

Table 2

The genotype distributions of the 276G>T (rs1501299) of the ADIPOQ polymorphisms in Hardy–Weinberg equilibrium (HWE) in control group (n=49; df=1)

Genotypes	**Controls**	**HWE**	χ^2	P
	n = 49			
G/G	0.551	0.496	3.45	0.06
G/T	0.306	0.417		
T/T	0.143	0.088		

Allele and genotype frequencies in patients with NAFLD corresponded to the theoretically expected Hardy-Weinberg calculation of genotype frequencies (Table 3).

Table 3

The genotype distributions of the 276G>T (rs1501299) of the ADIPOQ polymorphisms in Hardy–Weinberg equilibrium in patients (n=49; df=1)

Genotypes	**Controls**	**HWE**	χ^2	P
	n = 94			
G/G	0.223	0.255	1.53	0.22
G/T	0.564	0.500		
T/T	0.213	0.245		

A comparative analysis of the two groups (case/control) by a one-way analysis of variance (ANOVA) showed a significant difference in the genetic status of patients depending on the presence or absence of NAFLD (F=15.2; p=0.0001).

Table 4

Comparative analysis of the case/control groups depending on the genetic status

ANOVA						
Variation	*SS*	*Df*	*MS*	*F*	*P-value*	*F crit*
Between groups	11,03	1	11,03	15,23	0,00014	3,91
Within groups	102,16	141	0,72			
General	113,20	142				

These data were verified by The Kruskal-Wallis H test, and the Bonferroni correction was applied to them to exclude a false positive result (type 1 error). The Kruskal-Wallis test showed a value of H=11.2914 (p=0.0007), and the Bonferroni correction determined the minimum significance threshold for p = 0.005.

A comparative analysis of the general inheritance model revealed a significant difference in the distribution of genotype frequencies between NAFLD patients and healthy controls (Table 5). Moreover, there was a significant prevalence (56.4% vs. 30.6%) of the heterozygous (G/T) genotype at the marker locus 276G>T (rs1501299) of the ADIPOQ gene in NAFLD patients (p<0.001; OR=2.93; 95% CI1.41 – 6.09) and an insignificant (21.3% vs. 14.3%) prevalence of T/T genotype (OR=1.62; 95% CI 0.63 – 4.15).

Table 5

Comparative analysis of the frequency distribution of genotypes of the polymorphic marker 276G>T (rs1501299) of the ADIPOQ gene between NAFLD patients and healthy controls

Genotypes	Case	Controls	χ^2	p	*OR*	
	n = 94	n = 49			value	95% CI
G/G	0.223	0.551	15.63	0.0004	0.23	0.11 – 0.49
G/T	0.564	0.306			2.93	1.41 – 6.09
T/T	0.213	0.143			1.62	0.63 – 4.15

Thus, the accumulation of the GT-heterozygous state was revealed in patients with NAFLD of Uzbek nationality, while in healthy individuals the predominance of the GG homozygous genotype with a high frequency of the G-allele was revealed.

The study of genetic models and the ratio of the chances of developing NAFLD in carriers of a certain combination of alleles and genotypes showed that for the multiplicative model, a significant association of the T allele with the risk of developing NAFLD was revealed ($p<0.001$; OR=2.33; 95% CI1.39 – 3.92), in other words, the presence of the T allele increases the risk of developing NAFLD in persons of Uzbek nationality by 2.3 times. In the group of healthy individuals, there is a significant predominance of carriers of the G / G genotype in comparison with the group of patients ($\chi2=10.4$; df=1, $p=0.001$).

Discussion. Genetic studies of the rs266729 variant in the ADIPOQ promoter region have shown an association with obesity in several populations, including the Arab one [19]. At the same time, there are studies that indicate that there is no significant association of rs2241766 polymorphism with obesity, hypertension of NAFLD [20].

Inconsistency in the research results is also noted for the polymorphic marker locus rs266729. Thus, some studies have shown that the G allele of the rs266729 locus is a likely risk factor for the occurrence of diabetes mellitus 2 [9]. However, Li et al. found no significant association between the rs266729 polymorphism and metabolic syndrome [12]. The results obtained on the basis of a meta-analysis of a large number of studies in the Chinese population showed that the G allele of the polymorphic locus rs2241766 significantly increases the risk of metabolic syndrome [21]. Moreover, scientists agree that it is necessary to conduct a broader study involving large samples of representatives of different ethnic groups to identify the association between the polymorphisms rs2241766 and rs266729 of the ADIPOQ gene and the metabolic syndrome [21].

Ten case-control studies with a total of 2,672 subjects were conducted between Chinese and Indian population and revealed that the T variant of AdipoQ rs2241766 T>G polymorphism may be associated with an increased risk of NAFLD. There was also found a significant association between the G variant of AdipoQ rs1501299 G>T polymorphism and an increased risk of NAFLD. Country-stratified analysis indicated that a higher AdipoQ rs2241766 T>G polymorphism was closely related with an increased risk of NAFLD in Chinese and Indian populations (all Ps < 0.05); a similar result was observed in Chinese populations between AdipoQ rs2241766 T>G polymorphism and an increased risk of NAFLD (P < 0.05) [22].

It is remarkable to note that a significant association between variants in COL13A1, ADIPOQ, SAMM50, and PNPLA3, and risk of NAFLD/elevated transaminase levels in Mexican adults with an admixed ancestry [23]. Since then, some studies and a recent meta-analysis have replicated the association between the 276G>T (rs1501299) of the ADIPOQ gene polymorphism and NAFLD in several ethnic groups, but there is no report on the association between there factors in the Uzbek population.

Uzbek population is very interesting with regard to dietary habits, lifestyle and genetic structure. Historical, archaeological and genetic evidence indicated the “hybrid zone” scenario of origin of Uzbek nations, which postulates early occupation by western Caucasian peoples followed

by East Asian admixture [24,25]. This genetic admixture suggested that Uzbeks have the genetic affinity towards both Asians and Europeans.

In the present study, we identify the frequency of the minor allele in the Uzbek population as a whole is 42% and significantly exceeds the frequencies of the Vietnamese, British, Estonian, Swedish, European and American populations (24,9%, 25,1%, 28,2%, 28,5%, 28% and 30%, respectively). Whilst the frequency of the minor allele in the Uzbek population is close to the frequencies of the Han (China), Yoruba (West Africa) and Africa as a whole (33%, 38% and 39%, respectively).

Complex genetic diseases, such NAFLD are likely to be due to multiple, potentially interacting, genes and environmental factors and therefore are more challenging to study than the simple monogenic diseases. Presumably, many of these environmental and genetic risk factors are contextual, meaning that other factors, such as ethnic-specific genetic background, are likely to be key modifiers of these risk factors.

The results of the present study indicated that genetic effect of AdipoQ rs2241766 T>G and rs1501299 polymorphisms is so powerful that despite of potential existence of ethnic-specific genetic and environmental modifiers it still exerts significant impact on the development of NAFLD in a population with such historically mixed genetic background as Uzbeks. We confirm the reasonability of inclusion 276G>T (rs1501299) of the ADIPOQ test for identification of high risk groups for NAFLD in Uzbekistan.

In conclusion, the current study indicates that AdipoQ 1501299 G>T polymorphism may contribute to an increasing susceptibility to NAFLD. Furthermore, this research also suggests for future larger studies with stratified case-control population, and greater focus on the gene-environment interactions regarding NAFLD predispositon.

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