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DIAGNOSTIC SIGNIFICANCE OF MOLECULAR-GENETIC MARKERS IN THE DEVELOPMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE

Xamrayev A.A., Yuldasheva D.Kh., Shamsiyeva T.T., Haydarov D.B.

Tashkent Medical Academy,
Bukhara State Medical Institute. Uzbekistan

✓ ***Resume***

In this article, 98 patients with NAFLD and 70 healthy controls were selected to study the significance of the rs641738 polymorphism of the MBOAT7 gene in the pathogenesis of NAFLD. Our studies confirmed the presence of a positive statistically significant relationship between the rs641738 polymorphism of the MBOAT7 gene and JNAYoX, and this association is especially significant in patients with developed non-alcoholic steatohepatitis.

Key words: non-alcoholic fatty liver disease, hepatic steatosis, non-alcoholic steatohepatitis, rs641738 polymorphism of the MBOAT7 gene.

ЖИГАР НОАЛКОГОЛ ЁҒ ХАСТАЛИГИ РИВОЖЛАНИШИДА МОЛЕКУЛЯР-ГЕНЕТИК МАРКЁРЛАРНИНГ ДИАГНОСТИК АҲАМИЯТИ

Хамраев А.А., Юлдашева Д.Х., Шамсиева Т.Т., Хайдаров Д.Б.

Тошкент Тиббиёт Академияси,
Бухоро тиббиёт институти. Ўзбекистон.

✓ ***Резюме***

Ушбу мақолада 98 нафар MBOAT7 гени rs641738 полиморфизмини ЖНАЁХ патогенезидаги аҳамиятини ўрганиш мақсадида 98 та ЖНАЁХ билан касалланган беморлар ва 70 та ЖНАЁХга чалинмаган соғлом одамлар назорат гуруҳи сифатида танлаб олинган. Бизнинг тадқиқотимиз ёрдамида, MBOAT7 гени rs641738 полиморфизми ва ЖНАЁХ орасида мусбат статистик ишончли боғланиш мавжудлиги ва айниқса бу боғланиш ноалкогол стеатогепатит ривожланган беморларда сезиларлироқ намоён бўлиши тасдиқланди.

Калит сўзлар: Жигарнинг ноалкогол ёғ хасталиги, жигар стеатози, ноалкогол стеатогепатит, MBOAT7 гени rs641738 полиморфизми.

ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИХ МАРКЕРОВ В РАЗВИТИИ НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ

Хамраев А.А., Юлдашева Д.Х., Шамсиева Т.Т., Хайдаров Д.Б.

Ташкентская медицинская академия.
Бухарский государственный медицинский институт. Узбекистан.

✓ ***Резюме***

В этой статье для изучения значимости полиморфизма rs641738 гена MBOAT7 в патогенезе НАЖБП было отобрано 98 пациентов с НАЖБП и 70 здоровых лиц контрольной группы. С помощью наших исследований было подтверждено наличие положительной статистически достоверной связи между полиморфизмом rs641738 гена MBOAT7 и JNAYoX, причем эта ассоциация особенно значима у больных с развившимся неалкогольным стеатогепатитом.

Ключевые слова: неалкогольная жировая болезнь печени, стеатоз печени, неалкогольный стеатогепатит, полиморфизм rs641738 гена MBOAT7.

Relevance

Currently, the high growth rate of non-alcoholic fatty liver disease (NAFLD) is estimated by the tendency of the population to become obese. However, as the level of obesity increases, the severity of the disease also increases. NAFLD occurs with 30-100% obesity. In NAFLD, most patients (48-100%) are asymptomatic and are detected during general examinations. A non-progressive form of NAFLD - hepatic steatosis occurs in 40-78% of patients. When the disease progresses periodically, 12-40% of patients may develop non-alcoholic steatohepatitis after 8-13 years, and 15% of patients may develop liver cirrhosis and liver failure. 7% of patients with liver cirrhosis may develop hepatocellular carcinoma after 10 years [1,2,3,9,11,14,15].

It is known that NAFLD is a multifactorial disease. Younossi Z.M., one of the leading experts in the studied field. According to (2014), the importance of genetic factors in the development of NAFLD is scientifically based on insulin resistance and high body mass. The results of the research carried out in the last ten years show that the significant contribution of genetic factors in the progressive development of NAFLD has been revealed. Today, a number of scientific researches are being carried out in the world to study the genetic basis of NAFLD, to prevent its complications by developing early diagnosis and treatment methods. Scientific studies, the analysis of the studied literature show that in the development of NAFLD, it is necessary to carry out genetic tests in making an accurate diagnosis of the course of the disease. [4,9,10,11,12,13]. GCKR and polymorphism E P446L (rs1260326) and MBOAT7 (rs641738) are candidate genes for the accumulation of lipid fractions in the liver tissue in NAFLD and the development of more dangerous, aggressive forms of the disease [5,6,7,8,9]. Therefore, conducting research aimed at determining the distribution of these genes and polymorphism, alleles, genotypes, accumulation of lipid fractions in the liver, the origin and genetic dependence of dangerous forms of NAFLD is one of the urgent problems of hepatology.

The purpose of the study - Evaluation of the development of nonalcoholic fatty liver disease by molecular genetic markers.

Inspection materials and methods

The data of the results of clinical, laboratory and instrumental examination of 98 patients diagnosed with NAFLD were taken into the study. 53 (54%) of the patients were women, 45 (46%) were men, and their age ranged from 20 to 75 (average 49.2±4.2) years. Out of 98 patients with NAFLD, 67 (68.3%) stage of hepatic steatosis (JS) and 31 (31.6%) stage of steatohepatitis (SG) were included in the study. Of these, 45 (46%) were men and 53 (54%) were women, aged 20-75 (average age 49.2±4.2). The results of the examination were evaluated by a clinical reference card (questionnaire). Consent was obtained from the members of the ethical committee established under the auspices of the Bukhara Medical Institute to conduct the research. Criteria for inclusion in the study: patients with hepatic steatosis (JS) and steatohepatitis (SG) aged 20-75; persons who gave written consent to clinical and instrumental examinations. Exclusion criteria: alcohol or drug addiction, toxic, viral, autoimmune damage to the liver, patients with oncological disease, severe diseases (uncontrollable arterial hypertension, type 2 diabetes - decompensation stage, chronic heart failure III-IV functional class, myocardial infarction and stroke patients), pregnant women, breast-feeding women. To rule out alcoholic fatty liver disease, history (absence of periodic alcohol consumption) was collected and excluded using a specific CAGE questionnaire [4]. During the investigation, it was compared with 70 healthy individuals (age 20-65).

In the process of diagnosing patients, anamnesis data were collected, laboratory and ultrasound examinations were used. Ultrasonography of the hepatobiliary system was performed in 500 patients with risk factors for NAFLD: obesity, dyslipidemia, carbohydrate intolerance. As a result of liver ultrasound, steatosis and steatohepatitis were detected in 98 patients with NAFLD.

The following signs of liver steatosis were noted: liver enlargement, increased echogenicity, relatively decreased liver density compared to the spleen (liver-spleen index less than 1), decreased sound conductivity, poor visualization of the portal and hepatic veins. Ultrasound elastography was performed in 98 patients to rule out fibrosis in liver parenchyma. Gene and polymorphic markers were subjected to PTsR analysis as standards.

Result and discussion

According to the distribution of alleles in the main group, which included 98 patients with NAFLD from our study, the S wild-type allele was 64.8%, while the T minor allele was found in 35.2%. That is, compared to the indicators of the control group, the occurrence of S allele was observed 1.3 times less, while the occurrence of T allele increased 1.89 times. The distribution of genotypes in the MBOAT7 gene rs641738 polymorphism within the groups showed that in the main group, the wild homozygous S/S genotype was 41.8%, the S/T heterozygous genotype was 45.9%, and the T/T mutant homozygous genotype was 12.2%. . The obtained results showed that the performance of the control group was significantly different from that of the main group. That is, in the main group, it was found that the homozygous S/S genotype is 1.37 times less frequent, the S/T heterozygous genotype is 1.45 times less frequent, and the mutant T/T genotype is 4.21 times more frequent (see Figure 1).

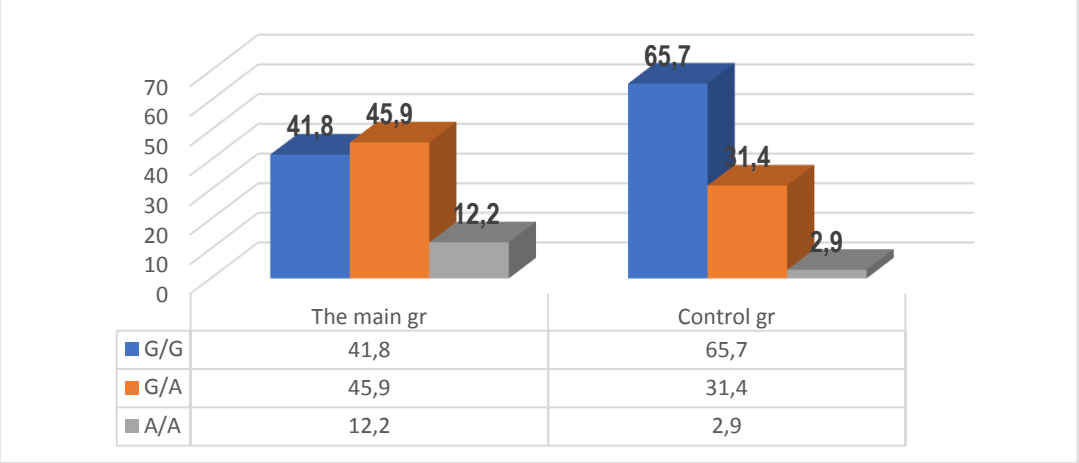

Figure 1. The distribution of the MBOAT7 gene rs641738 polymorphism in the main and control groups is presented in percentages.

When the results of the MBOAT7 gene rs641738 polymorphism were checked according to the Hardy-Weinberg law, it was found that the obtained results obeyed the Hardy-Weinberg law (3.84> χ2? 0.05<p), although there was a weak deviation. Normal homozygous – S/S and mutant homozygous genotypes T/T empirical test results are slightly higher than the expected results according to the Hardy-Weinberg law (0.418; 0.122 and 0.4115; 0.1215, respectively), the heterozygous genotype theoretically expected results, empirical prevailed with a slight difference from the determined results (respectively, 0.459 and 0.447) (see Table 1). In addition, in our study, the heterozygous genotype showed a positive result (D= 0.028) when the result obtained from the heterozygous genotype was checked using the D-quantity (D = (Ho - He)/He) in patients tested for the MBOAT7 gene rs641738 polymorphism (see Table 3). The compliance of the obtained results with the Hardy-Weinberg law indicates that the errors made during the research and during the selection of patients with NAFLD in the Uzbek population are minimal.

Table 1.

The MBOAT7 gene rs641738 polymorphism in the main group of patients was tested using the Hardy-Weinberg law (df=1)

Main group HWE				
Alleles	Percentage distribution			
C	64,8%			
T	35,2%			
Genotypes	Observable	Expected	χ^2	P-value
Genotype *C/C*	0,418	0,4115		
Genotype *C/T*	0,459	0,447		
Genotype *T/T*	0,122	0,1215		
Total	1,0	1,0	0,0041	0,9

Similarly, when the results of the control subjects were examined by the Hardy-Weinberg law, a weak deviation was found, but this result was not significant when re-examined by chi-square ($\chi 2<3.84$? $p>0.05$ with a significance threshold of 0.05). In our study, in the control group, the results obtained for the normal homozygous genotype and heterozygous genotype were less than the theoretically expected results (for C/C genotype and C/T genotypes, 0.657 and 0.663; 0.314 and 0.303, respectively), on the other hand, the observed result for the homozygous mutant genotype was expected. it was found to be slightly higher than the result (see Table 2). The result obtained from the heterozygous genotype was checked using the D-quantity and a positive result (D=0.036) similar to the main group was obtained (Table 3).

Table 2.

The control group was tested. The results obtained when the MBOAT7 gene rs641738 polymorphism was tested using the Hardy-Weinberg law (df=1).

Control group HWE				
Alleles	Percentage distribution			
C	81,4%			
T	18,6%			
Genotypes	Observable	Expected	χ^2	P-value
Genotype *C/C*	0,657	0,663		
Genotype *C/T*	0,314	0,303		
Genotype *T/T*	0,029	0,034		
Total	1,0	1,0	0,107	0,9

Table 3.

The difference between the empirical and expected theoretical results obtained in the main and control groups according to the heterozygous genotype

Groups	Observable	Expected	D*
Main group	0,459	0,447	0,027
Control group	0,314	0,303	0,036

*Formula *: $D=(H_{obs}-H_{exp})/H_{exp}$.*

Thus, the results of testing the MBOAT7 gene rs641738 polymorphism in patients with NAFLD revealed that the homozygous S/S and heterozygous S/T genotypes are rare, and the mutant T/T genotype is statistically significant.

Significance of MBOAT7 gene rs641738 polymorphism in NAFLD development. When the relationship between wild and mutant alleles of MBOAT7 gene rs641738 polymorphism and the origin of NAFLD was studied in the main and conditionally healthy group of people examined during the study, it was found that the wild S allele reduces the occurrence of the disease by 30% by having a protective effect in NAFLD origin (RR=0 .7; 95%CI: 0.611-0.862), and the mutant allele was found to have an initiating effect on the origin of NAFLD, and the relative risk was 1.38 (95%CI: 1.16-1.64). The obtained results were checked by $\chi 2$-square and p-value indicators and they were confirmed to be significant and reliable ($\chi 2=11.1$? $p<0.001$) (see Table 4).

Similarly, when studying the importance of genotype distribution of the studied polymorphism in the main and control group in NAFLD, it was found that the wild homozygous genotype - S/S has a strong protective value in the development of the disease (OR=0.375; 95%CI: 0.199-0.709) and the obtained results were confirmed as significant (ch2=7, 8; $p<0.01$). On the other hand, the mutant homozygous genotype - T/T was found to have an initiatory significance in the development of NAFLD (OR=4.74; 95%CI: 1.027-21.9) and it was found that the risk of disease occurrence increases 1.54 times (RR=1.54; 95%CI: 1.2–1.98). Also, the relationship between the mutant genotype and NAFLD was proved to be significant ($\chi 2=4.7$? $p<0.05$). Although the heterozygous genotype increased the risk of NAFLD development (RR=1.28; 95%CI: 0.997-1.643), its effect was confirmed to be unreliable in statistical analysis ($\chi 2>3.84$? $p>0.05$) (see Table 4) .

Thus, in the Uzbek nation, the main NAFLD pathogenesis is the T allele of the MBOAT7 gene rs641738 polymorphism (OR=2.38; 95% CI: 1.42-3.99) and the T/T genotype (OR=4.74; 95% CI 1.027-21.9) was found to be an important risk factor. In homozygous S/S genotype, on the contrary, we can see that there is a protective value against the development of pathology (OR=0.67; 95% CI: 0.199-0.709) (see Table 4).

Table 4.

rs641738	Main group n=98	%	Comparative group n=70	%	χ^2	*P*	*(Relative risk) RR*		*(Odds ratio)OR*	
							Value	95% CI	Value	95% CI
Alleles										
C	127	64,8	114	81,4	11,1	0,001	0,7	0,611-0,862	0,42	0,25-0,74
T	69	35,2	26	18,8			1,38	1,16-1,64	2,38	1,42-3,99
Genotypes										
C/C	41	41,8	46	65,7	7,8	0,006	0,67	0,514-0,872	0,375	0,199-0,709
C/T	45	45,9	22	31,4	3,5	0,06	1,28	0,997-1,643	1,8	0,975-3,521
T/T	12	12,2	2	2,9	4,7	0,03	1,54	1,2-1,98	4,74	1,027-21,9

Distribution of the MBOAT7 gene rs641738 polymorphism in the primary and control groups.

In addition, patients of the main group (98) were divided into two subgroups depending on the presence of steatohepatitis in addition to steatosis, based on the course of the disease and the results of instrumental examinations. In such a grouping of NAFLDs, we used the classification grouped by Matteoni and his colleagues in a simpler way. According to it, NAFLD is divided into 4 types, the first type - steatosis or simple fatty liver, the second type - steatohepatitis (inflammation process added to the process), the third type - steatonecrosis (multiple necrosis of liver cells added to the process) and the fourth type - steatonecrosis and Mallory hyaline or fibrosis process. is a joint manifestation.

The aim of this is to study the prevalence of alleles and genotypes of the MBOAT7 gene rs641738 polymorphism in small groups, and to determine the difference in OR and other statistical indicators compared to groups. In this way, it is possible to determine whether the studied gene polymorphism can induce the inflammatory process and other pathological processes in the liver in addition to liver hepatosis.

The first group was NAFLD, 67 patients with non-alcoholic steatosis were included, and the second group included 31 patients with non-alcoholic steatohepatitis. Then, in both groups, the percentage of allele distribution and the distribution of genotypes were checked based on the Hardy-Weinberg law. According to him, the results obtained from the first subgroup corresponded to the Hardy-Weinberg law, since there was no significant difference between the empirical results observed during the study and the theoretically expected results ($\chi 2 = 0.092$, P=0.95). That is, the observed homozygous wild-type and mutant homozygous genotypes were found to be less than the expected empirical results (C/C 0.433 and 0.441; T/T 0.130 and 0.133), which means that the homozygous genotypes are relatively deficient in the first group of patients, while the results of the heterozygous genotype are theoretical. were found to be superior to the expected results (C/T 0.464 and 0.446) (see Table 5).

Similarly, the results obtained from the group of patients with nonalcoholic steatohepatitis of the liver were also found to be in accordance with the Hardy-Weinberg law, and in this subgroup, unlike the subgroup of nonalcoholic steatosis, patients with the heterozygous genotype were less than the expected theoretical result (respectively, C/T 0.452 and 0.474) and the result of homozygous genotypes was found to be superior (respectively, C/C 0.387 and 0.376; T/T 0.161 and 0.15) (Table 6).

Table 5.

In the first subgroup, the results obtained when tested using the Hardy-Weinberg law (df=1)

HA steatosis HWE				
Alleles	Percentage distribution			
C	66,4%			
T	33,6%			
Genotypes	Observable	Expected	χ^2	P-value
Genotype *C/C*	0,433	0,441		
Genotype *C/T*	0,464	0,446		
Genotype *T/T*	0,103	0,113		
Total	1,0	1,0	0,092	0,95

Table 6.

In the second subgroup, the results obtained when tested using the Hardy-Weinberg law (df=1)

HA steatohepatitis HWE				
Alleles	Percentage distribution			
C	61,3%			
T	38,7%			
Genotypes	Observable	Expected	χ^2	P-value
Genotype C/C	0,387	0,376		
Genotype C/T	0,452	0,474		
Genotype T/T	0,161	0,15		
Total	1,0	1,0	0,07	0,96

Among the first subgroup, when the association between the MBOAT7 gene rs641738 polymorphism and non-oncological steatosis was examined, the wild-type - S allele was found in 66.4% of patients, and the mutant - T allele was found in 33.6% of patients. Using these results, when examining the importance of different allelic genes in the pathogenesis of the disease, it was found that the wild allele plays a protective role in the pathogenesis of the disease (odds ratio - 0.45; 95%CI: 0.258-0.787), while the mutant allele increases the risk of developing the disease (OR=2 .21; 95%CI: 2.21 1.27-3.869). And the association between these alleles and the disease was statistically significant and reliable ($\chi2 = 8$; P=0.005) (see Table 7).

When the distribution of the MBOAT7 gene rs641738 polymorphism by genotype was studied in the first subgroup, it was found that the wild S/S genotype met with a significant difference in the control group (65.7% and 43.3%). At the same time, it was proved that the wild homozygous genotype plays a protective role in the pathogenesis of non-ecological steatosis (OR=0.4 95%CI: 0.2-0.79; $\chi2 = 6.95$ p=0.009). On the other hand, although the percentage of homozygous mutant and heterozygous genotypes was found to be more common in the first subgroup compared to the control group (respectively, 10.3% and 46.4%, while in the control group these indicators were 2.9% and 31.4%) found them to have a disease-inducing effect (OR=1.88; 95%CI: 0.936-3.771 for the heterozygous genotype, OR=3.97; 95%CI: 0.793-19.832), but the statistical reliability of these results was not confirmed ($\chi2 < 3$ .84; P>0.05) (see Table 7).

On the other hand, in the second subgroup, when the results of the distribution of wild and mutant alleles of the MBOAT7 gene rs641738 polymorphism were examined, it became clear that the percentage of mutant allele prevalence was found to be twice as high in the group of patients with non-alcoholic steatohepatitis as compared to the control group (38.7% and 18.8%), and the prevalence of the wild-type allele was 81.4% in the control group (61.3% in the nonalcoholic steatohepatitis group). In this context, by examining alleles for their pathogenetic significance, the mutant allele increased the incidence of the disease by 1.92 (95%CI: 1.29-2.861) times relative risk and 2.78 (95%CI: 1.424-5.386) times by odds ratio. inducing effect was confirmed, while the wild - S allele was found to have

a strong protective value in the origin of the disease (OR=0,36; 95%CI: 0,196-0,702). At the same time, the mentioned results were confirmed to be statistically significant ($\chi 2 = 9.4$ p=0.003).

Table 7.

Distribution of the MBOAT7 gene rs641738 polymorphism in the subgroup with non-oncological steatosis and the control group.

rs641738	HA steatosis group n=67	%	Comparative group n=70	%	χ^2	*P*	*(Relative risk) RR*		*(Extimolar ratio) OR*	
							Value	95% CI	Қиймат	95% CI
Alleles										
C	89	66,4	114	81,4	8,0	0,005	0,7	0,547-0,875	0,45	0,258-0,787
T	45	33,6	26	18,8			1,45	1,142-1,83	2,21	1,27-3,869
Genotypes										
C/C	29	43,3	46	65,7	6,95	0,009	0,63	0,446-0,893	0,4	0,2-0,79
C/T	31	46,4	22	31,4	3,18	0,075	1,36	0,976-1,90	1,88	0,936-3,771
T/T	7	10,3	2	2,9	3,21	0,074	1,66	1,118-2,463	3,97	0,793-19,832

Conclusion

Thus, on the basis of the conducted research, it can be concluded that MBOAT7 gene polymorphism rs641738 mutant homozygous - T/T form is caused by various metabolic disturbances in cells, in particular, disruption of the synthesis of phospholipids that are part of the cell membrane from arachidonic cyst, its increase inside the cell and prostaglandins, which are many inflammatory factors and the inflammatory process can be induced by the formation of leukotrienes, and at the same time, it can cause fat accumulation and inflammation in hepatocytes as a result of decreasing the lipolytic processes inside the cell and increasing the lipogenesis process. With the help of our research, it was confirmed that there is a positive statistically reliable association between the MBOAT7 gene rs641738 polymorphism and NAFLD, and that this association is especially significant in patients with developed non-alcoholic steatohepatitis.

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