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# Assessment of The Role of The Adipox Gene In the Development of Gallstone Disease in Patients with Obesity

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## Abstract

The article evaluates the significance of the ADIPOQ (T54G) genetic marker in the development of cholelithiasis in patients with obesity, the characteristics of the allelic and genotypic distribution of polymorphic changes in this gene, and their contribution to the risk of disease development. Analysis of the frequency of allelic and genotypic variants of the ADIPOQ (rs2241766) polymorphic locus, which encodes adiponectin, in the pathogenesis of gallstone disease development in patients with high body weight revealed a high prognostic significance of this polymorphism in the risk of developing this disease.

**Keywords:** Gallstone disease, choledocholithiasis, allele, genotype, hereditary risk.

## Introduction

The relevance of the problem. Across the world, gallstone disease (GKD) is considered one of the most common diseases of the biliary tract system. At the same time, according to the results of studies conducted by scientists, it is shown that this pathology occupies one of the leading positions among the

abdominal organs [9; 10; 15; 16]. According to data provided by the World Health Organization (WHO), clinical signs of gallstone disease are identified in 10-20% of cases among the adult population worldwide [1; 3;]. It has also been established that women suffer from this disease 2-3 times more often than men, which indicates that this condition is more related to hormonal factors [7]. According to a number of scientists, GSD remains one of the most pressing problems of modern medicine, especially due to its widespread prevalence among the population of economically developed countries and the steady increase in the number of cases. Therefore, early diagnosis of this disease and the implementation of preventive measures show that it has not only great medical but also important social significance. Therefore, in some sources, this pathology is also referred to figuratively as "prosperity disease" [8; 11; 14].

Therefore, the early detection of cholelithiasis in patients with obesity, the in-depth study of risk factors for its development, and the development of effective prevention and treatment strategies are among the priority tasks of modern medicine. Great attention is paid to studying the polymorphism of genes that regulate cholesterol metabolism and lipid metabolism. This is important and is of great scientific and practical interest. Especially in comorbid pathology [2; 12]. There is data showing a sufficiently clear correlation between gene mutations affecting inflammatory processes and the formation of gallstones [4, 5; 13]. This indicates the multifactorial nature of the genetic predisposition to GDM in obesity [6].

**Purpose of the research**. Evaluation of the significance of the T54G polymorphic locus of the ADIPOQ gene in the development of cholelithiasis in patients with obesity.

## Methods

A total of 233 subjects were selected as the object of the study. Specifically, the main group consisted of 123 patients (subgroup 1 consisted of 63 patients with obesity and GSD, subgroup 2 consisted of 60 patients with obesity and non-calculous cholecystitis) and the control group consisted of 110 "conditionally healthy" individuals who did not have these diseases in themselves or their close relatives at the time of the examination or in the anamnesis. Of the 123 patients who formed the main group, 58.5% (72) were women and 41.5% (51) were men.

During the formation of the study groups, the body mass index (BMI) indicators of the participants were first analyzed using the Quetelet index formula. According to the analysis results, grade 1 obesity with a BMI of 30–34.9 was recorded in 82 out of 123 patients in the main group, accounting for 66.7% of these patients. Of the 82 patients with grade 1 obesity, 51.2% (42 men, 10 (23.8%), and 32 women (76.2%) were patients in subgroup 1 with cholelithiasis, while 48.8% were patients in subgroup 2 with chronic non-calculous cholecystitis (40 men, 27 (67.5%), and 13 women (32.5%).

The proportion of patients in the main group with grade 2 obesity, with a BMI of 35–39.9, accounted for 30.9% of the total group (38 out of 128). The proportion of patients in the subgroups was equal (in the 1st subgroup - 19 (men - 5 (26.3%) and women - 14 (73.7%)); Subgroup 2 - 19 (men - 7 (36.8%) and women - 12 (63.2%)).

Patients with an BMI above 40 accounted for only 3 out of 128 during the study, with a share of 2.4%. 2 out of 3 patients were identified among male patients in subgroup 1. 1 female patient was recorded among the participants of the 2nd subgroup.

The average waist circumference values were 100.9±0.88 cm in subgroup 1 and 105.8±1.18 cm in subgroup 2.

The subject of the study was peripheral blood serum for general clinical studies, as well as molecular genetic studies. Molecular genetic analysis of ore samples was carried out in the departments of molecular medicine and cell technologies, as well as medical genetics of the Republican Specialized Scientific and Practical Medical Center of Hematology under the Ministry of Health of the Republic of Uzbekistan.

**Analysis of the results obtained**. The ADIPOQ (Adiponectin) gene encodes adiponectin, a biologically active hormone synthesized by adipose tissue in the human body. This gene is located in the 3q27 locus of chromosome 3 in the human body. The ADIPOQ gene plays an important role in the pathogenesis of metabolic processes, and the study of its genetic variants is of great scientific importance for the early prediction and prevention of obesity and related diseases [17].

The results obtained from the analysis of the T54G polymorphism of the ADIPOQ gene in accordance with the Hardy-Weinberg equilibrium showed that the proportion of the T allele was 0.85, and the frequency of the G allele was 0.15 among the patients of the main group. The proportion of observed genotypes among patients in the study group was as follows: T/T genotype – 0.72; Heterozygous T/G genotype - 0.27; The G/G genotype was -0.016. Furthermore, the proportion of theoretical or, in other words, expected genotypes was 0.77, 0.27, and 0.023, respectively.

Among the participants of the comparison group, the proportion of the T allele was 0.92, and the frequency of the G allele was 0.08. The frequency of observed genotypes among the reference group participants was 0.85 for the T/T genotype; The heterozygous T/G genotype was 0.16, but the G/G genotype was not recorded. Furthermore, the proportion of expected genotypes was 0.85, 0.14, and 0.006, respectively. Thus, according to the analysis of the Hardy-Weinberg equilibrium, statistically insignificant differences were noted between the observed and expected proportion of genotypes between patients in the main group and participants in the comparison group. These indicators indicate that the research results do not deviate from the IMF.

At the same time, the heterozygosity observed in the main group was 0.27, while the expected value was 0.26, and the inbreeding coefficient (D) was 0.05. In the control group, the Ho value was 0.15, and the He value was 0.14. The D indicator was 0.08. The results of the obtained statistical analysis show that the level of heterozygosity in both groups is close to the expected values, and genetic balance is maintained in these groups.

In accordance with the objectives of our study, as a result of studying the relationship between the T54G polymorphic locus of the ADIPOQ gene in the primary and reference groups and the development of cholelithiasis in patients with obesity, it was established that the T-positive allele variant of the studied locus plays a protective role in the pathogenesis of the aforementioned diseases (85.0% vs. 92.3%; $\chi2$=6.1; p=0.09; OR = 0.5; 95% CI: 0.26–0.86), it was observed that patients with high body weight with a negative allelic variant G have a relatively high risk of developing cholelithiasis, i.e., an inducing effect. That is, in patients with high BMI with this negative allelic variant, the probability of developing cholelithiasis increased by 2.1 times relative to the risk of patients without this allele (15.0% vs. 7.7%; $\chi2$=6.1; p=0.09; OR = 2.1; 95% CI: 1.16–3.84) (Table 1).

**Table 1**

**Characteristics of the distribution of alleles and genotypes of the T54G polymorphic locus of the ADIPOQ gene in the study and comparison groups.**

| Allele and genotype | Number of alleles and genotypes detected | | | | $\chi2$ | P | OR | 95%CI |
|---|---|---|---|---|---|---|---|---|
| | Main group n=123 | | Comparison group n=110 | | | | | |
| | n | % | n | % | | | | |
| T | 209 | 85.0 | 203 | 92.3 | 6.1 | 0.09 | 0.5 | 0.26 - 0.86 |
| G | 37 | 15.0 | 17 | 7.7 | 6.1 | 0.09 | 2.1 | 1.16 - 3.84 |
| T/T | 88 | 71.5 | 93 | 84.5 | 5.7 | 0.08 | 0.5 | 0.24 - 0.87 |
| T/G | 33 | 26.8 | 17 | 15.5 | 4.5 | 0.11 | 2.0 | 1.05 - 3.83 |

On the other hand, when studying the pathogenetic significance of the differences in the frequency of genotypic variants of the T54G polymorphic locus of the ADIPOQ gene between the main and conditionally healthy individuals, it was found that the positive T/T genotype reduces the risk of developing cholelithiasis in people with obesity (71.5% vs. 84.5%; $\chi2$=5.7; r=0.08 OR=0.5; 95%CI: 0.24–0.87), i.e., the presence of protective significance, the influence of heterozygous T/G genotypes on the risk of developing this disease, and the statistical significance of the correlation between heterozygous genotypes of the studied gene polymorphism and the development of the disease (26.8% vs. 15.5%; $\chi2$=4.5; r=0.11 OR=2.0; 95% CI: 1.05–3.83) (Table 1).

Molecular-genetic studies (T54G polymorphism of the ADIPOQ gene) among participants in subgroups 1 and 2, which constituted the main group, showed that as a result of statistical analysis, the positive T allele was detected in 85.7% of 63 patients with high BMI and cholelithiasis, of whom 14.3% had negative G allele expression (Table 2).

**Table 2.**

**Characteristics of the distribution of alleles and genotypes of the T54G polymorphic locus of the ADIPOQ gene in the main group of patients.**

| Allele and genotype | Number of alleles and genotypes detected | | | | χ2 | p | OR | 95%CI |
|---|---|---|---|---|---|---|---|---|
| | Patients with obesity and cholelithiasis n=63 | | Patients with obesity and cholecystitis without calculus n=60 | | | | | |
| | n | % | n | % | | | | |
| T | 108 | 85.7 | 101 | 84.2 | 0.1 | 0.84 | 1.1 | 0.56 - 2.27 |
| G | 18 | 14.3 | 19 | 15.8 | 0.1 | 0.84 | 0.9 | 0.44 - 1.78 |
| T/T | 47 | 74.6 | 41 | 68.3 | 0.6 | 0.63 | 1.4 | 0.62 - 2.98 |
| T/G | 14 | 22.2 | 19 | 31.7 | 1.4 | 0.45 | 0.6 | 0.28 - 1.38 |

Among the 60 subjects with obesity and non-calculous cholecystitis, the T-positive allele predominated, and the presence of this allele was noted in 82.4%. The remaining 15.8% of patients with the absence of this allele were carriers of the negative G allele. Statistical analysis of the results obtained within the framework of the study showed no significant differences in the frequency of alleles of the T54G polymorphism of the ADIPOQ gene between the studied patient subgroups (χ2=0.1; p=0.84; OR = 1.1; 95% CI: 0.56–2.27 and χ2=0.1; p=0.84; OR = 0.9; 95% CI: 0.44–1.78) (Table 2).

Heterozygous carriage of the T54G polymorphism of the ADIPOQ gene was observed in 14 out of 63 patients with obesity and cholelithiasis. In this group of patients, the total frequency of this heterozygous genotype was 22.2%, and the frequency of the homozygous T/T genotype of this genetic marker was 74.6% among patients with cholelithiasis. At the same time, in the remaining 2 (3.17%) patients with cholelithiasis, unlike the group of patients with obesity and non-calculous cholecystitis, the expression of the G/G negative genotype of this genetic locus was noted (Fig. 1).

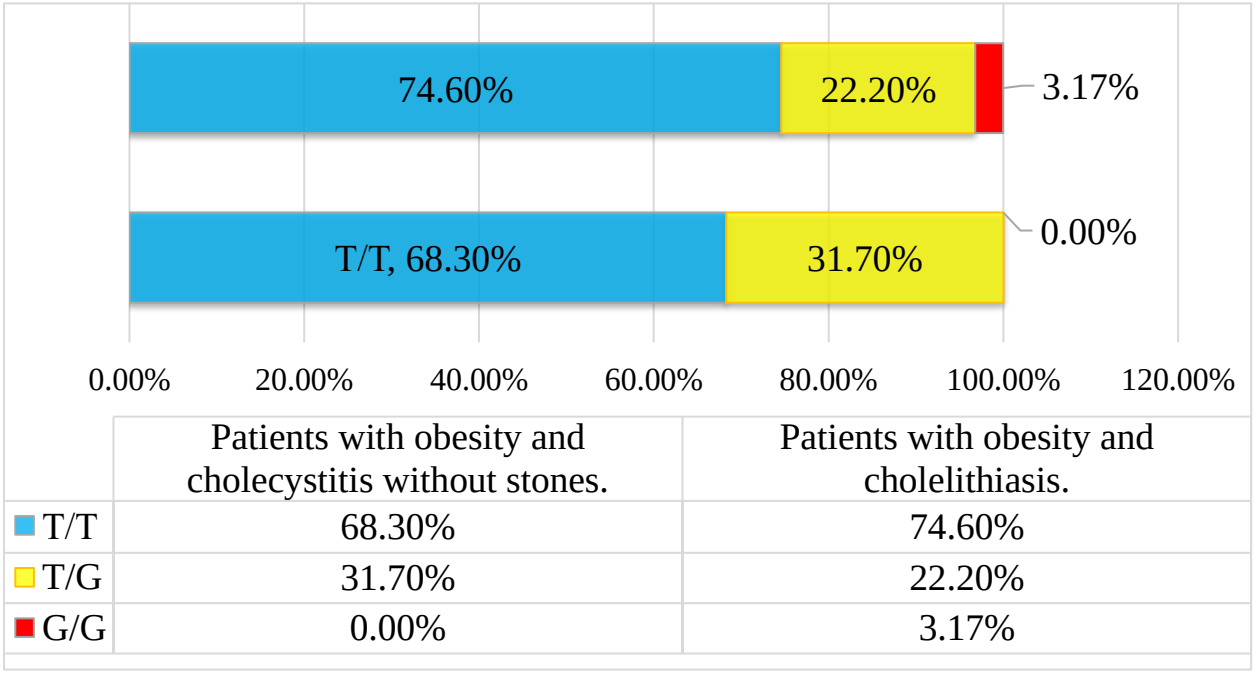


**Figure 1. Distribution of genotypes of the T54G polymorphism of the ADIPOQ gene among patients of the main group.**

Comparing the results obtained in the group of patients with obesity and non-calculous cholecystitis with data from the group of patients with high BMI and cholelithiasis, it was found that among patients with this disease, the T-positive allele of the ADIPOQ (T54G) gene was 84.2% and the G-negative allele was 15.8%, while the homogenous T/T and heterozygous T/G genotypes were 68.3% and 31.7%, respectively, which is close to the indicators of the 1st subgroup of patients with high BMI and cholelithiasis ($\chi2<3.84$, $p>0.05$) (Fig. 1).

**Table 3**

**Characteristics of the distribution of alleles and genotypes of the T54G polymorphic locus of the ADIPOQ gene in patients with high BMI and cholelithiasis and in the comparison group.**

| Allele and genotype | Number of alleles and genotypes detected | | | | χ2 | P | OR | 95%CI |
|---|---|---|---|---|---|---|---|---|
| | Patients with obesity and cholelithiasis n=63 | | Comparison group n=110 | | | | | |
| | n | % | n | % | | | | |
| T | 108 | 85.7 | 203 | 92.3 | 3.8 | 0.22 | 0.5 | 0.25 - 1 |
| G | 18 | 14.3 | 17 | 7.7 | 3.8 | 0.22 | 2.0 | 1 - 3.98 |
| T/T | 47 | 74.6 | 93 | 84.5 | 2.6 | 0.34 | 0.5 | 0.25 - 1.15 |
| T/G | 14 | 22.2 | 17 | 15.5 | 1.2 | 0.42 | 1.6 | 0.71 - 3.42 |

As noted in Table 3, a comparative analysis of the distribution of ADIPOQ (T54G) gene alleles across 63 DNA samples in patients with obesity and cholelithiasis revealed the presence of the positive T allele in 85.7% of cases and the negative G allele in 14.3% of cases, respectively. Among the participants in the reference group, the frequency of the aforementioned alleles was 92.3% and 7.7%, respectively. According to the results of statistical analysis, there is a strong tendency for the frequency of the negative G allele of the ADIPOQ (T54G) gene to be higher in the subgroup of patients with cholelithiasis compared to the comparison group, which means that the risk of developing cholelithiasis is 2.0 times higher in patients with a high body mass index ($\chi2=3.8$; $p=0.22$; OR = 2.0; 95% CI:1–3.98) (Table 3).

Among the examined groups, the positive homozygous T/T genotype of the ADIPOQ (T54G) gene was identified in 84.5% of cases versus 74.6%. Such indicators in the studied groups did not reach statistically significant values ($\chi2=2.6$; $p=0.34$; OR = 0.5; 95% CI: 0.25–1.15) (Fig. 2).

During the study, it was established that in the group of patients with cholelithiasis, the functionally heterozygous T/G genotypes of the ADIPOQ (T54G) gene increased insignificantly compared to the comparison samples, amounting to 22.2% versus 15.5%, respectively (Fig. 2). Despite insignificant differences in the odds ratio, a trend was observed where the risk of developing cholelithiasis among obese patients in the presence of this genotype was 1.6 times higher than in the conditionally healthy group ($\chi2=1.2$; $p=0.42$; OR = 1.6; 95% CI: 0.71–3.42) (Table 3).

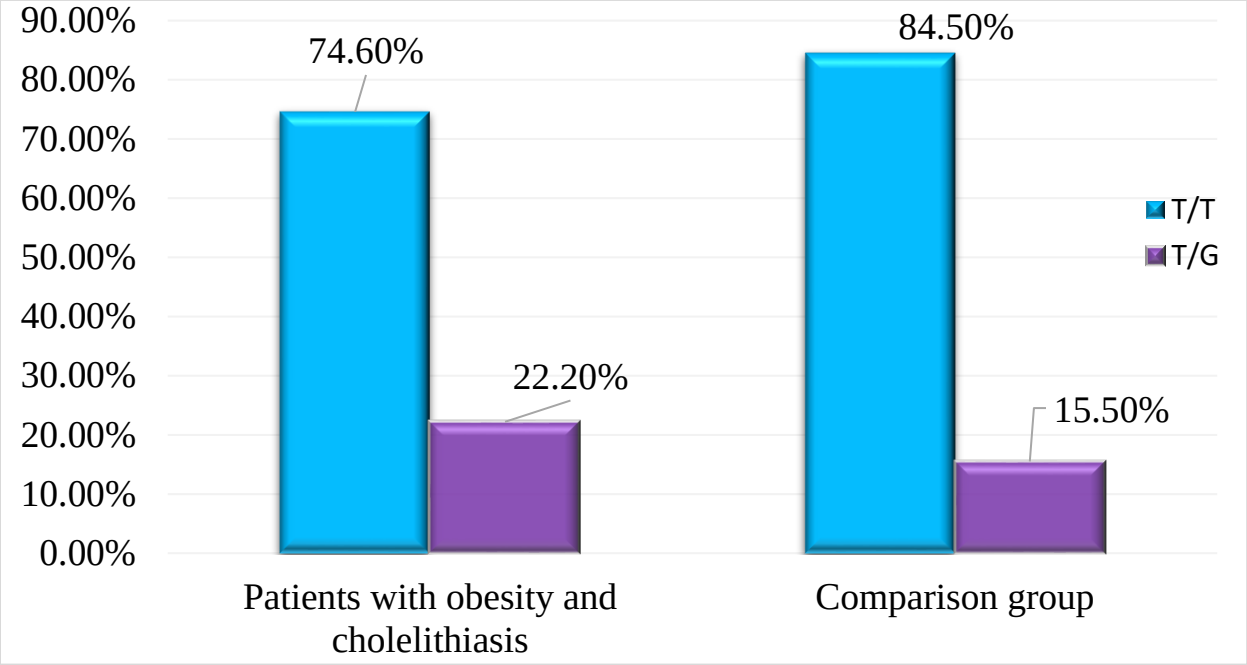


**Figure 2. Distribution of genotypes of the T54G polymorphism of the ADIPOQ gene among patients with high BMI and cholelithiasis and the comparison group.**

The results of the study showed that the risk of developing non-calculous cholecystitis in patients with the T-positive allele of the ADIPOQ gene polymorphism (T54G) is significantly lower compared to the control group (84.2% vs. 94.3%; $\chi2$=5.4; p=0.08; OR = 0.4; 95% CI: 0.22–0.88), on the contrary, it is substantiated that the relative risk of developing this pathology in patients with a G-negative allele is significantly 2.2 times higher compared to participants in the conditionally healthy group (15.8% vs. 7.7%; $\chi2$=5.4; p=0.08; OR = 2.2; 95% CI: 1.13–4.45) (Table 4).

As shown in Table 4, the heterozygosity (T/G) of the ADIPOQ (T54G) gene in patients with obesity and non-calculous cholecystitis was 31.7%, which was significantly higher by 2.5 times compared to the control group ($\chi2$=6.1; p=0.09; OR = 2.5; 95% CI: 1.21–5.3). It should be noted that in the 2nd subgroup of patients, the homozygous T/T genotype of the ADIPOQ (T54G) gene was significantly less frequent than in the comparison group (68.3% vs. 84.5%), indicating that this genotype possesses protective properties against the development of non-calculous cholecystitis in patients with high BMI ($\chi2$=6.1; p=0.09; OR = 0.4; 95% CI: 0.19–0.82) (Table 4).

**Table 4**

**Characteristics of the distribution of alleles and genotypes of the T54G polymorphic locus of the ADIPOQ gene in patients with high BMI and non-calculous cholecystitis and in the comparison group.**

| Allele and genotype | Number of alleles and genotypes detected | | | | $\chi2$ | P | OR | 95%CI |
|---|---|---|---|---|---|---|---|---|
| | Group of patients with obesity and non-calculous cholecystitis n=60. | | Comparison group n=110. | | | | | |
| | n | % | n | % | | | | |
| T | 101 | 84.2 | 203 | 92.3 | 5.4 | 0.08 | 0.4 | 0.22–0.88 |
| G | 19 | 15.8 | 17 | 7.7 | 5.4 | 0.08 | 2.2 | 1.13-4.45 |
| T/T | 41 | 68.3 | 93 | 84.5 | 6.1 | 0.09 | 0.4 | 0.19–0.82 |
| T/G | 19 | 31.7 | 17 | 15.5 | 6.1 | 0.09 | 2.5 | 1.21–5.3 |

Thus, our results are confirmed by Zhang X et al. (2018) [140; 382-390) revealed an association between the T54G polymorphism of the ADIPOQ gene and the risk of developing cholelithiasis in patients with obesity through metabolic risk.

## Conclusion

Thus, our results revealed an association between the T54G polymorphism of the ADIPOQ gene and the risk of developing cholelithiasis in obese patients through metabolic risk. The major allele T of the ADIPOQ (T54G) gene determinant (85.0% vs. 92.3%; $\chi2$=6.1; p=0.09; OR = 0.5; 95%CI: 0.26–0.86) and positive homozygous T/T genotype (71.5% vs. 84.5%; $\chi2$=5.7; r=0.08 OR=0.5; 95% CI: 0.24–0.87) among conditionally healthy subjects showed a significantly higher proportion compared to the main group, indicating its protective properties against the development of cholelithiasis; conversely, the recessive G allele (15.0% vs. 7.7%; $\chi2$=6.1; p=0.09; OR = 2.1; 95% CI: 1.16–3.84) and the heterozygous T/G genotype (26.8% vs. 15.5%; $\chi2$=4.5; r=0.11 OR=2.0; 95%CI:1.05–3.83) increases the risk of developing this disease up to 2.1 times.

One of the important tasks facing modern medicine is the early detection of the risk of gallstone disease development, its prevention, the timely implementation of personalized therapeutic and preventive measures, and a sharp reduction in the number of surgical interventions performed on patients. The identification of the T54G polymorphism of the ADIPOQ gene allows for an assessment of its significance in the development of cholelithiasis and the recurrence of postoperative cholelithiasis in obese patients, as well as the improvement of therapeutic and preventive measures taking into account hereditary risk factors.

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