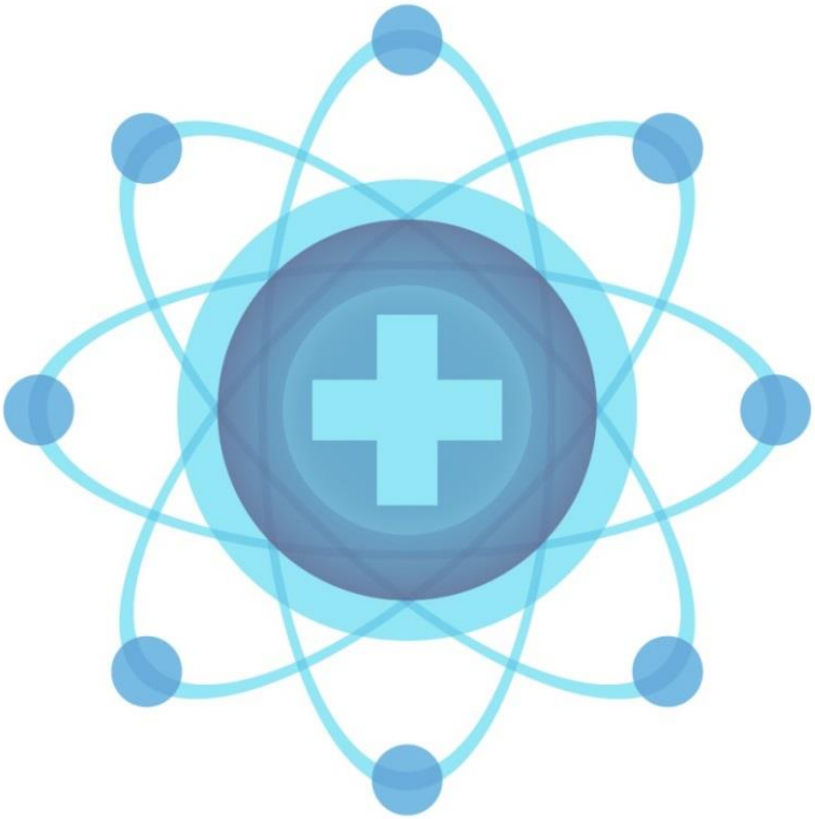

INTERNATIONAL MEDICAL SCIENTIFIC JOURNAL

ART OF MEDICINE

Art of Medicine *Volume-3*
International Medical Scientific Journal *Issue-1*
Founder and Publisher **North American Academic Publishing Platforms**
Internet address: http://artofmedicineimsj.us
E-mail: info@artofmedicineimsj.us
11931 Barlow Pl Philadelphia, PA 19116, USA +1 (929) 266-0862

Available at https://www.bookwire.com/
ISBN: 978-0-578-26510-0

Molecular genetic association of simultan pathologies gallstone disease and metabolic syndrome

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Abstract. The prevalence of the disease increases with age and is accompanied by metabolic disorders: GD is detected in persons with diabetes mellitus (DM) 45-50%, overweight - in 40-60%, with high-grade obesity - up to 70% of cases [2]. At the same time, individuals with MS reveal various pathological changes in the gastrointestinal and biliary tract, although the role of gastroenterological diseases in the development of MS has not yet been fully studied [3]. The development of GD and MS remains controversial, despite the well-studied mechanism. These two diseases share several risk factors in common, including age, gender, overweight, and impaired lipid and glucose metabolism. Purpose of the study. Studying the role of rs1042713 and rs1042714 polymorphisms of the ADRB2 gene in the pathogenesis of the nosological combination of simultaneous pathologies gallstone disease and metabolic syndrome. The analysis of associations of polymorphisms rs1042713 and rs1042714 of the ADRB2 gene was carried out using a case-control model. The main group consisted of 118 patients living in the Khorezm region. Among 118 patients, women accounted for 66.1% (78 patients) and 33.9% - men (40 patients) aged 19 to 80 years. All examined patients were divided into 3 subgroups: Subgroup - A 58 patient with GD in combination with obesity, subgroup - B 27 patient with GD with a combination of DM and 33 patient with GD without MS in subgroup B. Genomic DNA preparations were used as a material for the control sample (n = 120), conditionally healthy unrelated donors of Uzbek nationality and had no history of GD and MS. Our results allow us to conclude that the homozygous Glu/Glu genotype plays an important role in the pathogenesis of simultaneous pathologies of gallstone disease and metabolic syndrome. The risk of developing gallstones with MS in the presence of this genotypic variant of the ADRB2 gene can significantly increase by more than 3.5 times. The homozygous Gln/Gln genotype indicates a protective effect in the formation of GD with a combination of MS. The rs 1042713 polymorphism of the ADRB2 gene does not allow the use of this locus as a genetic marker for predicting the risk of MS in patients with GD

Keywords: simultan, gallstone disease, metabolic syndrome, polymorphism, gene, allele, genotype, pathogenesis, obesity

Introduction. Currently, there is a steady trend towards an increase in the number of patients simultan pathologies with gallstone disease (GD) and metabolic syndrome (MS). MS and GD are widespread in the world: 15-25% are patients with MS, 10-15% - patients with GD, and in both cases there is a tendency towards rejuvenation and a progressive increase in the number of patients. The proportion of gallstones in the general structure of diseases of the digestive system is constantly growing [1, 5]. The prevalence of the disease increases with age and is accompanied by metabolic disorders: GD is detected in persons with diabetes mellitus (DM) 45-

50%, overweight - in 40-60%, with high-grade obesity - up to 70% of cases [2]. At the same time, individuals with MS reveal various pathological changes in the gastrointestinal and biliary tract, although the role of gastroenterological diseases in the development of MS has not yet been fully studied [3]. At the same time, the main components of MS are also modifiable risk factors for GD (overweight, hyperlipidemia, hyperglycemia, etc.) [4], therefore their timely detection and correction are the most important modern measures for the treatment and prevention of GD. This is all the more important because there are convincing data that MS is not only a risk factor for the manifestation of GD, but also its complicated course [5]. The development of GD and MS remains controversial, despite the well-studied mechanism. These two diseases share several risk factors in common, including age, gender, overweight, and impaired lipid and glucose metabolism [6]. In the pathogenesis, the development of GD and MS plays an important role in the violation of lipid metabolism [7]. Lipid metabolism disorders are primarily characterized by an increase in cholesterol and triglyceride levels in the blood. The primary cause of lipid metabolism disorders is hereditary - genetic factor [8]. Single or multiple mutations of genes associated with lipid metabolism contribute to the disruption of lipid metabolism in the body. One of these genes is ADRB2. The β2-adrenergic receptor (ADRB2) is involved in lipid mobilization as the main lipolytic receptor in human fat cells, and genetic variation of this receptor gene can theoretically reduce lipolysis and predispose to MS and GD [9, 10]. The ADRB2 gene is located in the 5q31-32 chromosomal region and to date there are more than 200 polymorphic variants, of which the most studied variant are Arg16Gly (rs1042713) and Gln27Glu (rs1042714) [11, 12, 13]. However, the results of associative studies are quite contradictory.

Purpose of the study. Studying the role of rs1042713 and rs1042714 polymorphisms of the ADRB2 gene in the pathogenesis of the nosological combination of simultaneous pathologies gallstone disease and metabolic syndrome.

Material and methods. The materials of our research work were carried out at the Base of the Department of Faculty and Hospital Surgery of the Urgench Branch of the Tashkent Medical Academy in the surgical departments of the Khorezm Regional Multidisciplinary Medical Center based on clinical analysis and the results of diagnostics of patients with GD with MS and GD without metabolic disorders. Molecular genetic studies were carried out in the Department of Molecular Medicine and Cell Technologies of the Republican Specialized Scientific and Practical Medical Center of Hematology. The analysis of associations of polymorphisms rs1042713 and rs1042714 of the ADRB2 gene was carried out using a case-control model. The main group consisted of 118 patients living in the Khorezm region. Among 118 patients, women accounted for 66.1% (78 patients) and 33.9% - men (40 patients) aged 19 to 80 years. All examined patients were divided into 3 subgroups: Subgroup - A 58 patient with GD in combination with obesity, subgroup - B 27 patient with GD with a combination of DM and 33 patient with GD without MS in subgroup B. Genomic DNA preparations were used as a material for the control sample (n = 120), conditionally healthy unrelated donors of Uzbek nationality and had no history of GD and MS.

Results and discussion. To elucidate the role of polymorphic loci Arg16Gly (rs1042713) and Gln27Glu (rs1042714) of the ADRB2 gene in the formation of susceptibility to GD and MS, a comparative analysis of the distributions of the frequency of occurrence of alleles and genotypes between subgroups of patients with a control sample. In both groups, the actual distribution of the genotypes of the rs1042713 and rs1042714 gene polymorphisms corresponded to those expected at Hardy-Weinberg equilibrium (HWE).

Diagram 1 and 2 shows the frequencies of occurrence of genotypes and alleles of the Arg16Gly polymorphic locus. The distribution frequency of the Arg and Gly alleles in patients was 58.9% and 41.1%, the control group was 55.4% and 44.6%, respectively. The study of the distribution of genotypes showed that the dominant genotype in the studied groups of patients and controls was the heterozygous genotype Arg/Gly, the frequency of which was 50.0% and 50.8%, respectively. When statistically processing the data, the criteria $\chi 2 < 3.84$; $P > 0.05$; OR=1.0; 95% CI 0.58-1.61, which indicates the impossibility of this genotype in relation to the formation of gallstone disease and MS. The distribution of homozygous Arg/Arg and unfavorable Gly/Gly genotypes in the studied groups of patients was recorded -33.9% and 16.1%, respectively, in the control group 30.0% and 19.2%, respectively ($\chi 2 < 3.84$; $P > 0.05$; OR<1.0; 95% CI 0.69-1.58). The frequencies of alleles and genotypes revealed by us in the control group corresponded to the data obtained in the studies of European, Japanese and Russian scientists. For example, the frequency of occurrence of Arg16 is from 51.4 to 64.6% in Europeans and from 71.4 to 85.6% in East Asians [14].

It is interesting to note that there was no clear relationship between the risk of developing GD with MS and the distribution of predisposing genotypic variants of the rs1402713 polymorphism of the ADRB2 gene, which does not allow the use of this locus as a genetic marker for predicting the risk of developing this combination (P> 0.05).

Diagram №1

Prevalence of ADRB2 gene rs1042713 polymorphism alleles in baseline and control group samples

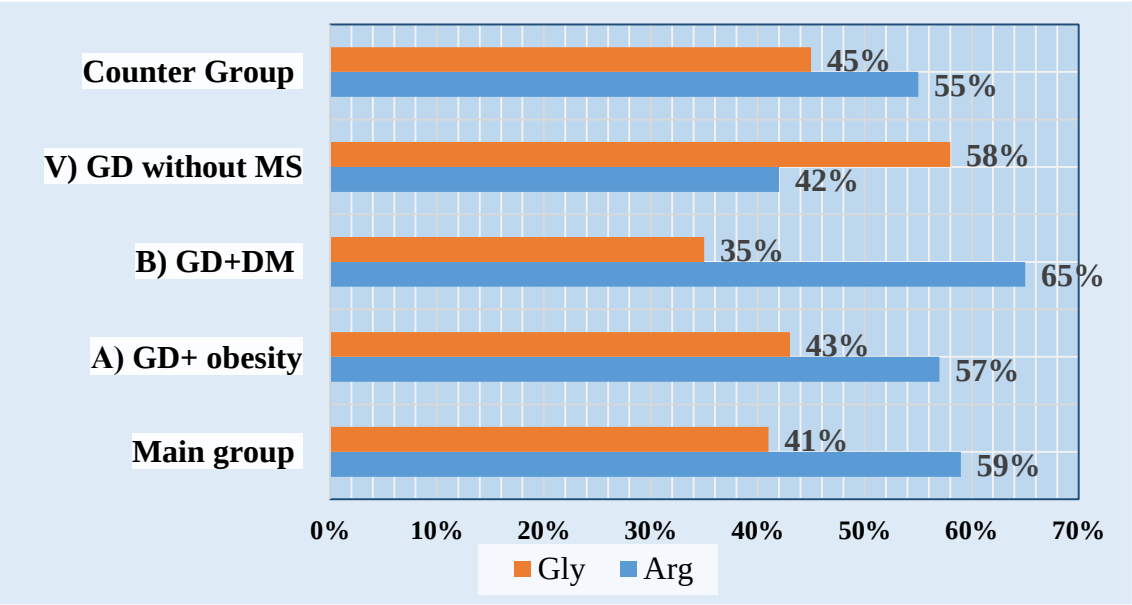


Diagram №2

Prevalence of ADRB2 gene rs1042713 polymorphism genotypes in baseline and control group samples

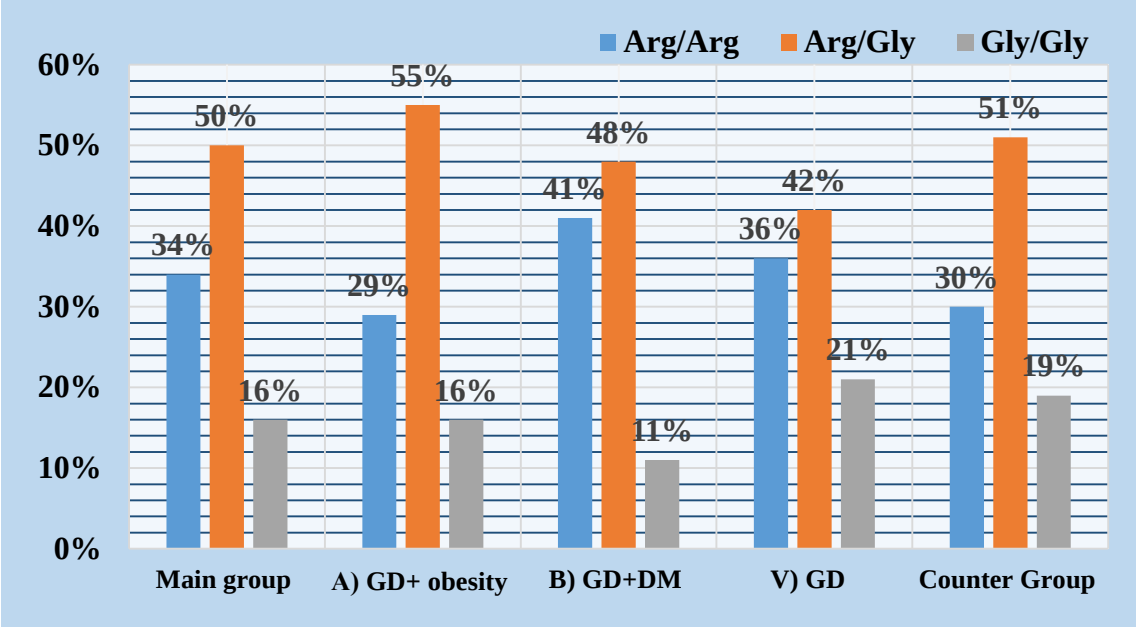


Diagram 3 and 4 shows the frequencies of the genotypes and alleles of the Gln27Glu polymorphic locus of the ADRB2 gene in the studied groups. In the studied groups of patients and controls, the proportion of 27Gln and 27Glu alleles was 35.2% and 34.8% versus 73.7% and 26.3%, respectively. The frequency of the 27Gln allele is slightly higher than the frequency of the 27Glu allele and is comparable to the average values for Europe (56.0%). This allele is more common in Africans (82.5%), Chinese (87.8%), and Japanese (92.0%) [11]. Statistical processing, despite insignificant differences, revealed a noticeable trend towards an increase in the frequency of the unfavorable 27Glu allele (with high odds ratios) and a decrease in the dominant, wild 27Gln allele in patients with GD with a combination of MS compared to conventionally healthy donors. The calculated odds ratio showed that the chance of detecting the unfavorable functional allele 27Glu in patients increased 1.5 times compared to the control group ($\chi 2=4.0$; P=0.04; OR=1.5; 95% CI: 1.01–2.216).

The frequencies of Gln/Gln, Gln/Glu and Glu/Glu of the rs1402714 genotypes of the ADRB2 gene in the studied groups of patients with gallstone disease with a combination of MS and control were: 44.1%, 42.4% and 13.6% versus 52.5%, 42.5% and 5.0%, respectively. As can be seen, the frequency of the homozygous Gln/Gln genotype among patients was lower than in the control group (44.1% versus 52.5%, respectively, with $\chi 2=1.7$; P=0.2; OR=0.7; 95% CI: 0.427-1.187). A tendency to an increase in the amount of homozygous Gln/Gln in the control sample was revealed, which indicates a possible protective effect of this genotype in relation to the formation of GD with a combination of MS. The distribution of the heterozygous Gln/Glu genotype in the studied groups of patients was recorded - 42.4% and in the control group - 42.5% ($\chi 2<3.84$; P=0.9; OR=1.0; 95% CI 0.594-1.663).

There was also a tendency to an increase in the proportion of carriers of the unfavorable Glu/Glu genotype among patients compared with the control group (13.6% versus 5.0%, respectively). According to the odds ratio, the risk of developing GD with a combination of MS in the presence of this genotype increases 3 times ($\chi 2$=5.2; P=0.02; OR=3.0; 95% CI: 1.124-7.925).

Diagram №3

Prevalence of ADRB2 gene rs1042714 polymorphism alleles in baseline and control group samples

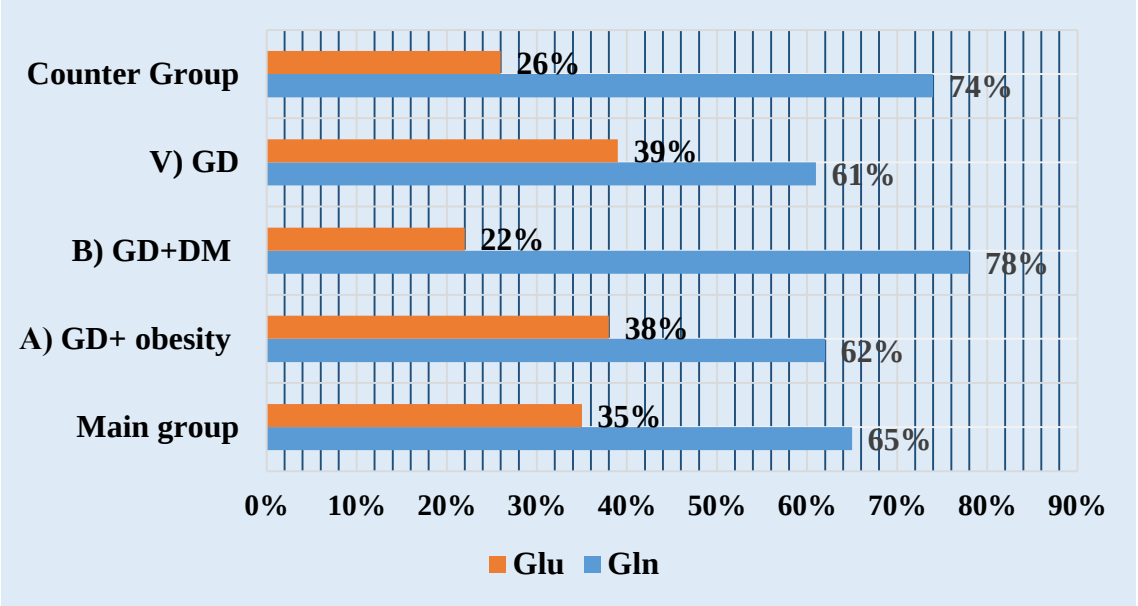
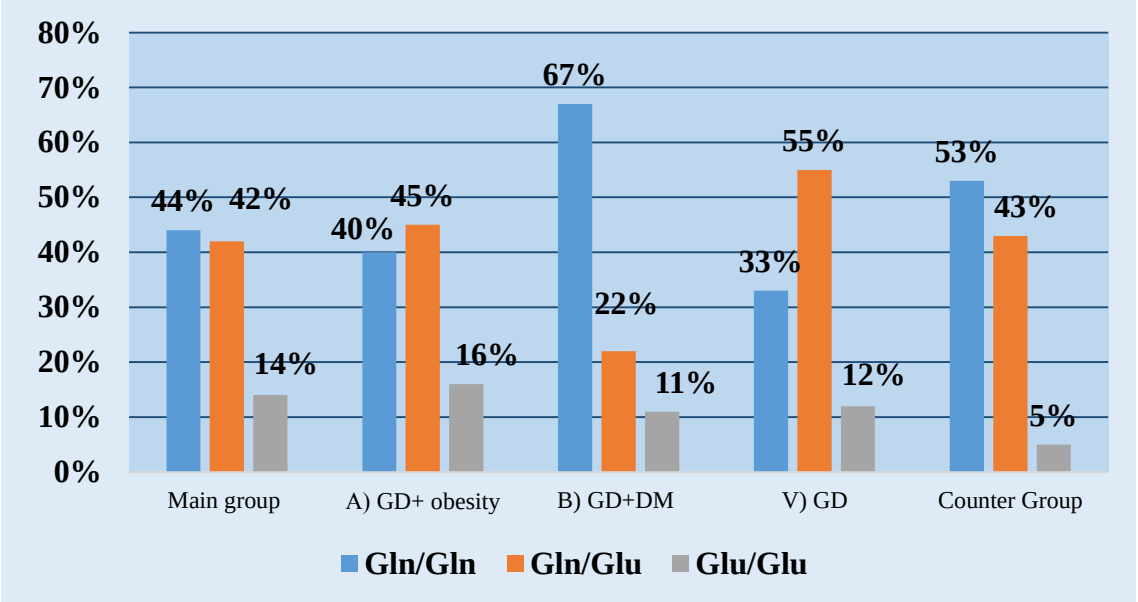


Diagram №3

Prevalence of ADRB2 gene rs1042714 polymorphism genotypes in baseline and control group samples



There was a significant difference in the frequency of distribution of the unfavorable Glu allele and the minor Glu/Glu genotype between the subgroups of obese patients and the control sample. According to the odds ratio, the risk of

developing obesity with the carriage of the Glu/Glu genotype significantly increases by more than 3.5 times (χ^2=5.6; P=0.02; OR=3.5; 95% CI 1.78-10.34).

Thus, our results clarify a significant relationship between Gln27Glu polymorphism and an increased risk of gallstones and MS. Interestingly, the increased risk of gallstones and MS is associated only with the Gln27Glu ADRB2 polymorphism, not the Arg16Gly polymorphism, but the researchers found a significant association in Japanese women. Swedish women have Large et all. (2012) found obesity was associated with rs1042714 but not rs1042713. For rs1042714 Lin et all. (2011) found that polymorphism is more common in overweight people, while Ehrenborg found that it is associated only with mild to moderately elevated BMI [13].

Conclusion: Our results allow us to conclude that the homozygous Glu/Glu genotype plays an important role in the pathogenesis of simultaneous pathologies of gallstone disease and metabolic syndrome. The risk of developing gallstones with MS in the presence of this genotypic variant of the ADRB2 gene can significantly increase by more than 3.5 times. The homozygous Gln/Gln genotype indicates a protective effect in the formation of GD with a combination of MS.

The rs 1042713 polymorphism of the ADRB2 gene does not allow the use of this locus as a genetic marker for predicting the risk of MS in patients with GD.

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