EVALUATION OF THE INFLUENCE OF APEX1 (RS2307486) GENE VARIANTS ON THE EFFICACY OF THE TREATMENT IN WOMEN WITH GOUT

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Abstract: *This scientific study aimed to evaluate the effect of polymorphisms in the APEX1 (rs2307486) on the effectiveness of hypouricemic therapy in women with gout. The study included 102 female and 100 male patients diagnosed with gout in 2021–2025. The patients were prescribed allopurinol and febuxostat, and their effectiveness was assessed across different genotypes of the above genes. According to the results of the study, patients with the G/G genotype of the APEX1 gene had a low response to allopurinol, and only febuxostat was effective. In patients with the T/T genotype, both drugs were almost equally effective. These results indicate that polymorphisms of the APEX1 gene are important pharmacogenetic biomarkers in determining the individual effectiveness of hypouricemic therapy. The selection of drugs and their doses based on a personalized approach increases therapeutic efficacy, eliminates resistance, and improves quality of life.*

Keywords: *gout, women, hypouricemic therapy, APEX1, gene polymorphism, pharmacogenetics, febuxostat, allopurinol, genotype, personalized medicine, quality of life.*

Introduction. The effectiveness of gout treatment is influenced by various individual factors, including genetic factors. Polymorphisms of the APEX1 (rs2307486) have been found to be important in assessing the effectiveness of hypouricemic therapy (allopurinol and febuxostat) in women. Patients with certain genotypic forms of APEX1 may have a poor response to hypouricemic therapy, may have high uric acid titers, and may have a longer duration of inflammation. In such situations, increasing the dose or using alternative drugs such as febuxostat may be effective. In such cases, combined or high-dose hypouricemic therapy may be necessary. By developing personalized hypouricemic therapy regimens taking into account the genotypic composition, it is possible to increase the effectiveness of treatment, reduce the development of drug resistance, and reduce the risk of complications.

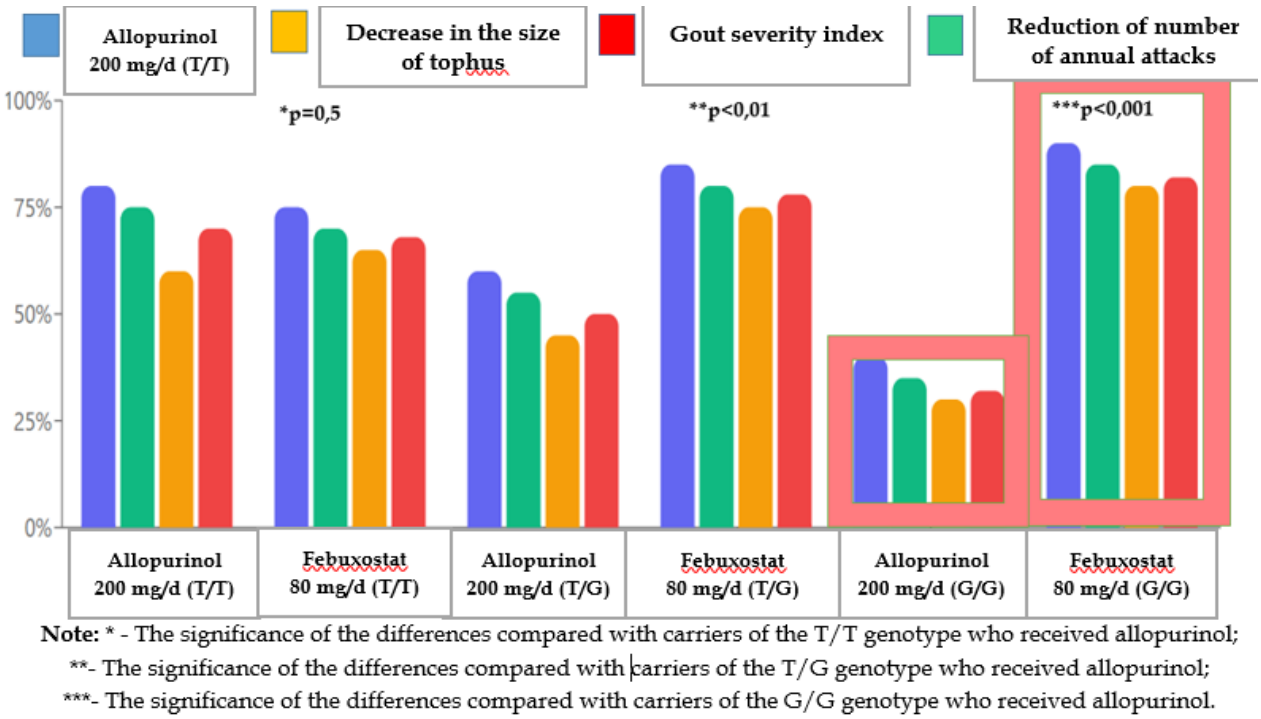
In conclusion, an individual approach based on gene polymorphisms in the hypouricemic treatment of gout in women plays an important role in altering the effectiveness of therapy.

Objective: to assess the significance of the APEX1 (rs2307486) gene polymorphisms in the effectiveness of hypouricemic treatment of gout in women.

Material and methods. The scientific research study (meeting the EULAR/ACR criteria, 2015) included 102 women and 100 men aged 18 to 75 years (mean age 46.5±1.4

years), who had applied for outpatient treatment to the Arthrological Intensive Outpatient Diagnostic Consultative (IADC) Department of the Multidisciplinary Clinic of the Tashkent Medical Academy (TMA) during 2021-2025 and were receiving inpatient treatment in the departments of cardiorheumatology, rheumatology, general therapy, and traumatology-orthopedics. Women with gout formed group I, and men formed group II. The control group included 20 practically healthy women who were age-matched to the patients in the main group and did not reveal pathological changes in clinical, laboratory, and instrumental examinations. The efficacy of hypouricemic drugs such as allopurinol and febuxostat in patients with gout was assessed depending on various genotypic variants of the APEX1 gene polymorphisms. Pharmacogenetic analyses were conducted to determine the relationship between genetic factors and response to treatment. Molecular genetic studies were conducted at the Inter-Institutional Research Laboratory (IRL) of the Tashkent Medical Academy. Venous blood for genetic analysis was taken on an empty stomach in the morning under sterile conditions. DNA isolated from peripheral blood leukocytes served as the research material. The DNA-Express Blood (LLC NPF Litekh, Russia) reagent kit was used to perform genetic tests. The APEX1 and URAT1 genes were tested by polymerase chain reaction (PCR) using a reagent kit provided by the Russian scientific and manufacturing company Litekh. DNA PCR was performed on a DT-96 PCR amplifier (LLC NPO "DNA-Technology", Russia). DNA amplification was performed by initial denaturation at 95 °C for 3 minutes, followed by 40 cycles of denaturation at 95 °C for 15 seconds, followed by annealing and elongation at 63 °C for 40 seconds.

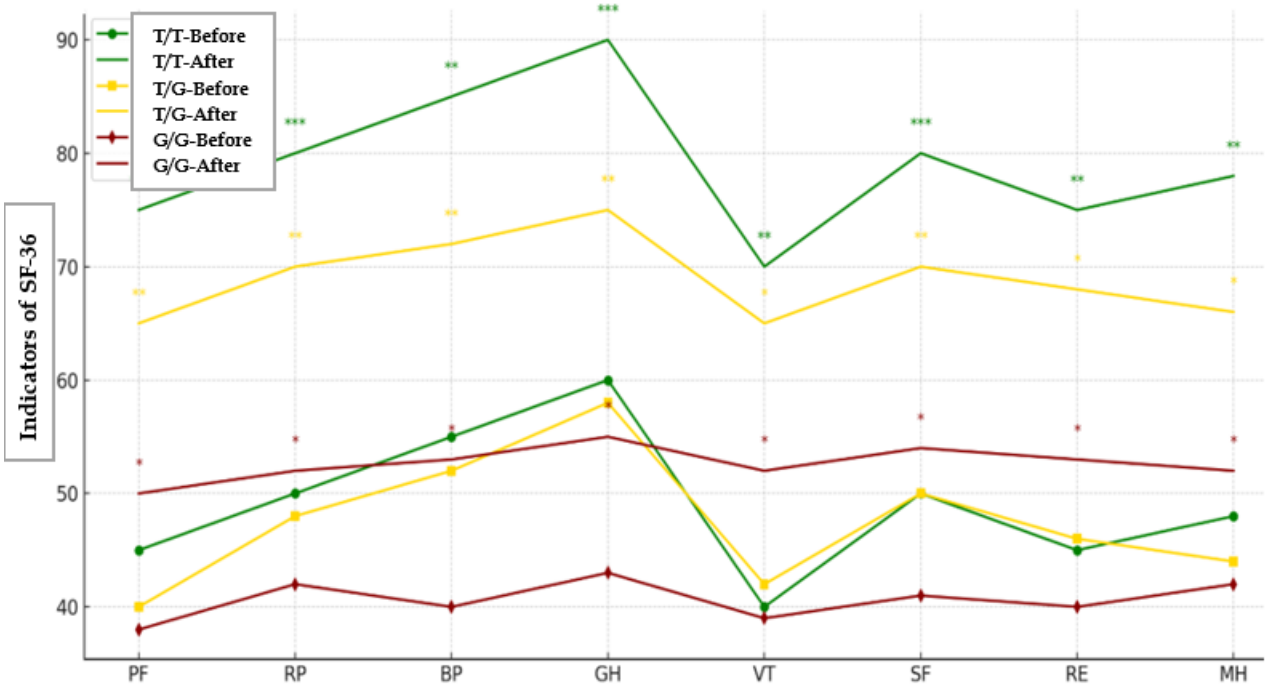
Results: The diagram in figure 1 below compares the efficacy of hypouricemic therapy with allopurinol and febuxostat in gout patients with the APEX1 (rs2307486) polymorphism in four clinical parameters across genotypes (T/T, T/G, G/G). In this study, the level of uric acid in the blood, the reduction/disappearance of tophi volume, the gout severity index, and the reduction in the number of annual attacks were studied against the background of hypouremic therapy recommended for patients with these genotypes. The effectiveness of allopurinol and febuxostat prescribed to patients with the homozygous T/T genotype of the APEX1 (rs2307486) gene was similar, with all indicators improving by ~70–80%. However, it was noted that $p = 0.5$, which did not have statistical significance. In this case, both drugs provided the same benefit in patients with the T/T genotype. Patients with the T/G genotype had significantly higher reductions in uric acid, disappearance of tophi, and reduction in the number of annual attacks against the background of febuxostat treatment. In contrast, the efficacy of allopurinol treatment was significantly lower than that of febuxostat ($p<0.01$). In the heterozygous state, febuxostat was superior to allopurinol. In the G/G genotype, the efficacy of allopurinol treatment was very low, especially in terms of uric acid levels and the number of annual attacks. When febuxostat was used instead, all parameters improved significantly (~80–90%; ($p<0.01$)). In the G/G homozygous mutation, only febuxostat was effective, and allopurinol was almost useless.



Note: * - The significance of the differences compared with carriers of the T/T genotype who received allopurinol;
**- The significance of the differences compared with carriers of the T/G genotype who received allopurinol;
***- The significance of the differences compared with carriers of the G/G genotype who received allopurinol.

Figure 1. Dynamics of the main clinical indicators against the background of hypouremic therapy in different variants of the APEX1 (rs2307486) genotype

Indeed, it was found that the response to hypouricemic therapy in gout patients with the APEX1 (rs2307486) polymorphism depends on the genotype. In patients with the T/T genotype, the efficacy of allopurinol and febuxostat is similar, in the T/G heterozygote state, febuxostat is more effective, and in the G/G mutated homozygote, allopurinol is ineffective, only febuxostat showed a high efficacy. These results provide an important basis for a pharmacogenetically adequate approach to personalized treatment and indicate the need to take into account the APEX1 (rs2307486) genotype when planning successful therapy.



Note: PF – physical activity; RP – role of physical problems in limiting life activities; BP – pain scale; GH – general health; VT – life capacity scale; SF – social activity scale; RE – importance of emotional problems in limiting life activities; MH – mental health.

P – reliable difference compared to the values of the compared group.

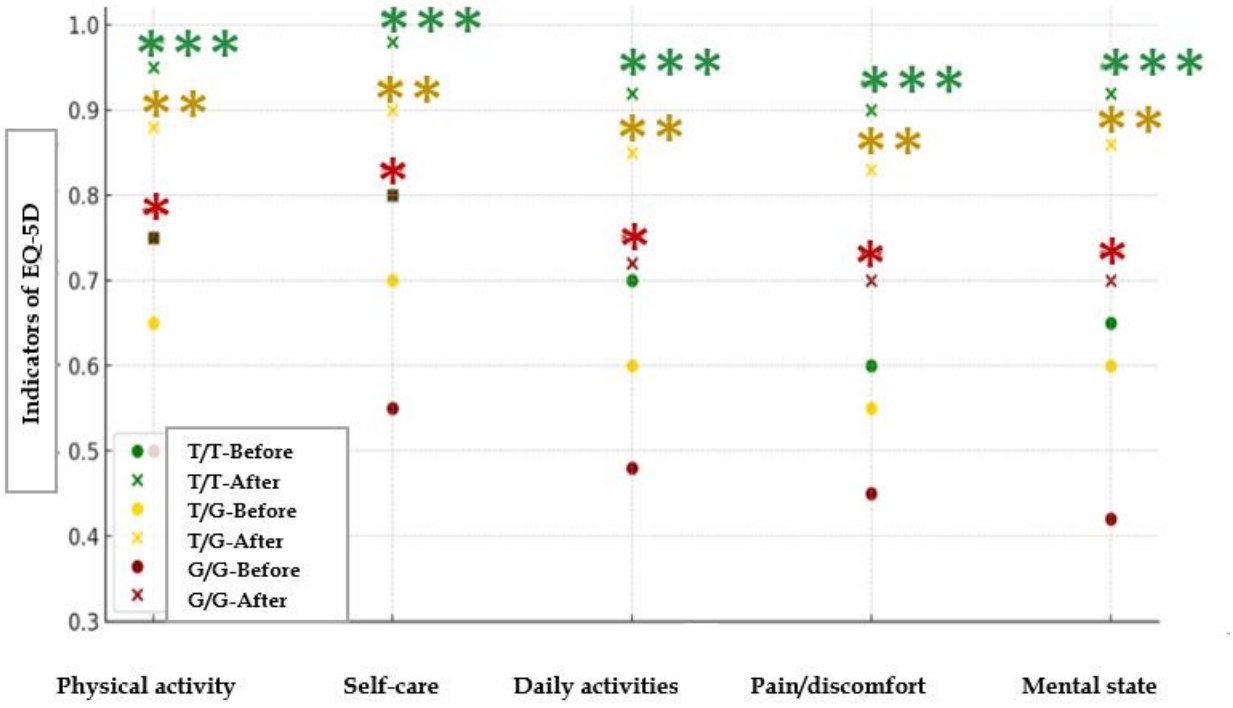
Note: *-p<0.5 – significance of differences compared to pre-treatment indicators;

**-p<0.01 – significance of differences compared to pre-treatment indicators;

***-p<0.001 – significance of differences compared to pre-treatment indicators;

Figure 2. Dynamics of SF-36 quality of life indicators against the background of hypouremic therapy in different variants of the APEX1 (rs2307486) genotype

The bar graph in figure 2 above presents a comparative analysis of the indicators of the overall quality of life on the SF-36 scale before and after treatment for different genotypes of the APEX1 (rs2307486) gene (T/T, T/G, G/G) detected in gout patients. In the graph, in the T/T genotype (green line), a significant improvement was observed in all SF-36 domains after treatment. Some indicators (VT, SF, PF) approached 90 points, which indicates a very high quality of life ($p<0.001$). In the T/G genotype (yellow line), moderate positive dynamics were observed in all indicators. Statistically significant differences were noted in some indicators ($p<0.01$). Thus, patients with the T/G heterozygous mutant genotype also respond positively to hypouremic therapy, but the effectiveness of treatment is lower than that of the T/T genotype. Patients with the G/G genotype (red line) retained significantly lower levels of quality of life indicators after treatment. No clinically or statistically significant improvement was observed in all domains. Thus, the effectiveness of treatment in the G/G genotype is lower than in patients with other genotypes, which indicates the presence of this genetic resistance in them.



Note: *-p<0.05; **-p<0.02; ***-p<0.01 – significance of differences compared to pre-treatment indicators;

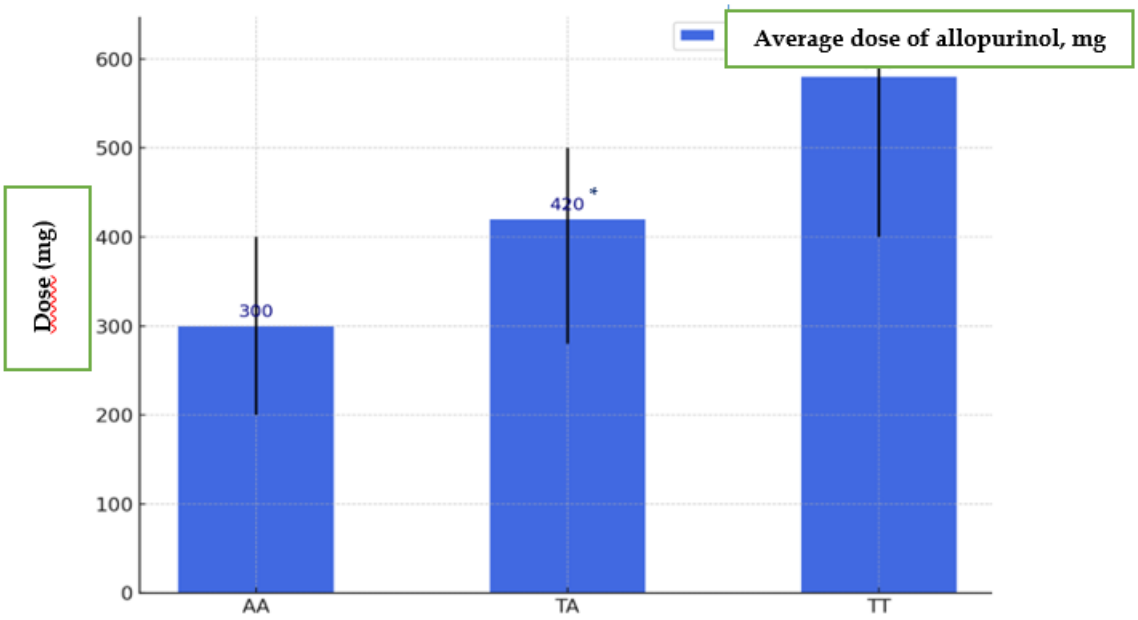
Figure 3. Dynamics of quality of life indicators according to the EQ-5D scale in different variants of the APEX1 (rs2307486) genotype against the background of hypouremic therapy

The graph in figure 3 shows changes in the 5 main components of the quality of life index (EQ-5D scale, range 0–1) before and after treatment in patients with gout according to different genotypes of the APEX1 (rs2307486) gene (T/T, T/G, G/G). Against the background of hypouremic therapy, statistically positive dynamics were noted in physical activity, self-care, daily activities, pain/discomfort, and mental state ($p<0.05$; $p<0.02$;$p<0.01$). In patients with the T/T genotype (green), the differences in efficacy before and after treatment were very significant, all indicators approached ~0.9. After treatment, the quality of life almost approached the norm. Highly reliable differences ($p<0.05$) were observed in all components. Hypouricemic therapy significantly improved the quality of life in patients with the T/T genotype. As a result of treatment, moderate positive dynamics were noted in patients with the T/G genotype (yellow), the indicators were around ~0.75–0.8. Improvement in mental state and daily activities was obvious, but relatively less positive dynamics were observed in physical activity and pain. In the heterozygous state (T/G), it can be concluded that the treatment effect was moderate, but stable. In patients with the G/G genotype (red), the indicators remained around 0.5–0.6, that is, the clinical improvement was slightly lower than in patients with the previous two genotypes. No significant improvement was observed in all components. Thus, in patients with the G/G

genotype, resistance to treatment and no significant positive shift in quality of life were noted.

In conclusion, it can be said that the analysis of quality of life indicators assessed by the EQ-5D scale shows that the APEX1 (rs2307486) polymorphism accurately determines the effectiveness of treatment and functional status in patients with gout. In the T/T genotype, a significant difference in the quality of life index was noted for all components, and almost complete rehabilitation was achieved after hypouricemic therapy. In patients with the T/G genotype, the improvement was moderate, while in patients with the G/G genotype, the therapeutic effect was low, and quality of life indicators were less close to clinical norms.

The diagram in figure 4 below compares the average daily dose of allopurinol (mg) for different genotypes (A/A, T/A, T/T) of the URAT1 (rs11231825) gene. This analysis was aimed at identifying the most appropriate dose for patients based on a pharmacogenetic approach. Patients with the A/A genotype responded effectively with a low dose of allopurinol (300 mg) - since this genotype does not have any mutations, the standard dose was sufficient.



Note: *-p<0.5 – significance of differences relative to AA genotype indicators;
**-p<0.01 – significance of differences relative to TA genotype indicators;
$-p<0.001 – significance of differences relative to AA genotype indicators;

Figure 4. Average Clinically Used Doses of Allopurinol (mg) by URAT1 (rs11231825) Genotypic Variants

In the T/A genotype, the average dose was 420 mg. This is a heterozygous mutation, requiring a higher dose to achieve full effect ($p < 0.01$). Patients with the T/T genotype received up to 580 mg of allopurinol, indicating resistance to allopurinol in the homozygous mutation state ($p < 0.001$).

Conclusions

1. The APEX1 (rs2307486) gene polymorphism is an important pharmacogenetic marker affecting the effectiveness of hypouricemic therapy in women with gout. While patients with the T/T genotype responded highly and almost equally to allopurinol and febuxostat, only febuxostat was effective in patients with the G/G genotype.
2. The T/T genotype showed a high response to febuxostat in APEX1 gene, therefore, febuxostat can be recommended as a first-line drug for patients with this genotype.
3. Assessments using the SF-36 and EQ-5D quality of life scales showed that the effectiveness of treatment was different depending on the APEX1 genotypes. While quality of life indicators were consistently increased in patients with the T/T genotype, they remained lower in patients with the G/G and T/T genotypes.
4. The development of personalized hypouricemic therapy regimens taking into account genetic polymorphisms allows optimizing treatment effectiveness, reducing drug resistance and improving the quality of life of patients.
5. The introduction of pharmacogenetic screening into clinical practice for women with gout, especially the analysis of the APEX1 gene, has important clinical and practical significance in determining individual therapy tactics and prognosis.

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