ORIGINAL INVESTIGATIONS

Association of the Q141K polymorphism of the *ABCG2* gene with the effectiveness of urate-lowering therapy in patients with gout (a pilot study)

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Achieving the target serum uric acid (UA) level is a priority in the treatment of gout.

Objective: *to study the relationship of the ABCG2 gene polymorphism (rs2231142) with the efficacy of allopurinol and febuxostat in patients with gout.*

Patients and methods. *The study included 82 patients with gout over 18 years of age with serum UA level >360 μmol/L who did not take urate-lowering therapy.*

All patients were prescribed allopurinol 100 mg daily, followed by its titration until the target UA level was reached (<360 μmol/L or <300 μmol/L in patients with chronic tofus gout), up to a maximum of 900 mg/day, in patients with glomerular filtration rate <60 ml/min/1.73 m^2 – up to 300 mg/day. Patients who did not reach the target UA level when using allopurinol were prescribed febuxostat 80 mg/day, which, if necessary, was increased to 120 mg/day. Monitoring of each patient was continued until the target serum UA level was reached.

All patients underwent genotyping of the C>A polymorphism (rs2231142) of the ABCG2 gene. We compared the probability of achieving the target UA level, the mean values of a decrease in the serum UA level, and the mean doses of urate-lowering drugs in patients with different genotypes (CC, CA, AA) of the ABCG2 gene.

Results and discussion. *The target UA level in 45 (55%) of 82 patients was defined as <300 μmol/L, in the remaining 37 – as <360 μmol/L. In 26 patients, the dose of allopurinol did not exceed 300 mg/day. In 28 (34%) patients treated with allopurinol, the target UA level was achieved, in the remaining 54 (66%) patients, allopurinol was substituted by febuxostat, and in 22 (41%) of them the UA level decreased and was below the target.*

The CC genotype of the ABCG2 gene was detected in 51 (62%) patients, the CA genotype in 30 (37%) and the minor genotype AA in 1 (1%). The probability of achieving the target UA level during therapy with allopurinol in carriers of homozygous CC genotype and genotypes CA or AA did not differ: 17 (33%) and 11 (35%) cases, respectively, but patients with CA and AA genotypes required a significantly higher dose of allopurinol (365±102 mg/day) than patients with the CC genotype (290±85 mg/day), p=0.002. Of the 54 patients who took febuxostat and did not reach the target UA level, 30 (56%) had the CC genotype and 24 (44%) had the CA genotype, the probability of reaching the target UA level was also comparable (p=0.22).

Conclusion. *The probability of reaching the target serum UA level in patients with gout taking allopurinol is not associated with the C>A polymorphism of the ABCG2 gene, but the presence of CA and AA genotypes is identified with a higher dose of the drug. The C>A (rs2231142) polymorphism of the ABCG2 gene does not affect the ability to achieve the goal of therapy when using febuxostat in patients with allopurinol ineffectiveness.*

Key words: *gout; gene ABCG2; allopurinol; febuxostat; uric acid; target level.*

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Achievement of the target uric acid (UA) level in the serum is a priority task in the treatment of gout and a condition for complete control over the disease [1, 2]. The solution of this problem became possible in most patients with gout after the introduction of xanthine oxidase inhibitors – allopurinol, and febuxostat – into clinical practice. These drugs are mostly used in patients with gout to maintain normouricemia. However, the limitations associated with allopurinol usage in patients with reduced kidney function, adverse drug reactions, poor drug tolerance and medical errors do not allow achieving the target serum level of UA in 100% of patients with gout [3–5]. In addition, in a large group of patients, including those with normal renal function, it is not possible to achieve the goal of treatment even with the use of allopurinol and febuxostat in maximum possible doses [6]. Allopurinol is justifiably the first-line treatment for gout and is prescribed to most patients [7, 8]. However, there are a some potential mechanisms responsible for insufficient effectiveness: malabsorption and reduced conversion of allopurinol to its active metabolite oxypurinol, increased renal excretion of oxypurinol and abnormalities in the structure or function of xanthine oxidase, as a result of which oxypurinol becomes less effective [9]. Moreover, we cannot exclude the relationship of genetic factors with the

response to allopurinol. In 2015 C.C. Wen et al. [10] showed an association between the A (141K) allele of the Q141K (C>A) rs2231142 polymorphism of the *ABCG2* gene (ATP-binding cassette transporter G2) and a weak response to allopurinol. It was previously found that a decrease in the activity of *ABCG2* increases both bioavailability of drugs (due to a decrease in their outflow into the intestine), and the serum level of UA (due to a decrease in the excretion of urate into the intestinal lumen) [11]. For febuxostat, such an association was not found, moreover, there is evidence that it can inhibit ABCG2 in the intestine, thereby improving intestinal absorption of drugs [12]. However, there are insufficient data on the effect of ABCG2 gene polymorphism on predicting the effectiveness of xanthine oxidase inhibitors in clinical practice.

The aim of the research was to study the association between the ABCG2 gene polymorphism (rs2231142) and the efficacy of allopurinol and febuxostat administered in maximum warrantable doses and strictly in accordance with the national guidelines for the treatment of gout [13].

Patients and methods. The prospective study included 82 patients with gout examined at V.A. Nasonova Research Institute of Rheumatology (Moscow) in 2020 who met the inclusion criteria.

Inclusion criteria: patients of both sexes over 18 years old with an established diagnosis of gout according to the classification criteria ACR / EULAR (American College of Rheumatology / European Alliance of Associations for Rheumatology) 2015, not receiving urate-lowering drugs; serum UA level >360 μmol / L; signed informed consent form.

Exclusion criteria: presence of contraindications listed in the instructions for the use of febuxostat [14] and allopurinol [15]; uncontrolled arterial hypertension (AH), chronic heart failure (CHF) ⩾ III stage according to NYHA, ischemic heart disease (coronary artery disease, angina pectoris, postinfarction cardiosclerosis, painless myocardial ischemia, ischemic cardiomyopathy), heart surgery (coronary artery bypass grafting, endovascular surgery and other), ischemic stroke; transient ischemic attack; glomerular filtration rate (GFR) <30 ml/min (CKD-EPI); an increase of the level of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2 norms; diabetes mellitus, serum glycated hemoglobin level >7%; the presence of somatic or mental diseases that impede the procedure implementation; taking urate-lowering drugs others than prescribed in the study; taking diuretics.

When urate-lowering therapy was initiated, allopurinol was used at a starting dose of 100 mg per day. Further, the dose was increased by 100 mg per day every 2–3 weeks until the target UA level was reached (<360 μmol/L or <300 μmol/L in patients with chronic tophus gout). The maximum dose was 900 mg per day, and with GFR <60 ml/min/1.73 m^2 – 300 mg per day.

Patients were monitored until the target serum UA level was reached (<360 μmol/L or <300 μmol/L in patients with chronic tophus gout), i.e. at least 2 weeks of continuous use of allopurinol or febuxostat. After screening and enrollment, patients underwent routine examinations by a doctor every 2 weeks until the target serum UA level or the maximum daily dose of allopurinol was reached.

Venous blood samples were taken from all patients for genotyping of the C>A (rs2231142) polymorphism of the ABCG2 gene. Genotyping was performed by real-time polymerase chain reaction using original sequence-specific primers and samples labeled with various fluorescent labels (NPK "Syntol"). Automatic registration and interpretation of the results was carried out on an innovative detecting amplifier DT-96 (DNA-Technology LLC). Genotyping was carried out according to the manufacturer's instructions.

During the visits to the doctor, mandatory laboratory tests were performed, including the determination of serum levels of UA, ALT, AST, creatinine, glucose, and glycated hemoglobin (in patients with diabetes).

We compared the probability of achieving the target UA level, the mean values of a decrease in the serum UA level, and the mean doses of urate-lowering drugs in patients with different genotypes (CC, CA, AA) of the *ABCG2* gene.

The research was approved by the local ethics committee of V.A. Nasonova Research Institute of Rheumatology. All patients signed informed consent to participate in the study.

Statistical analysis was carried out using the Statistica 12.0 software package (StatSoft / Inc., USA) descriptive statistics, as well as the SPSS v.17.0 statistical software. The results are presented as mean values and standard deviations (M ± _) for quantitative traits with a normal distribution, in other cases – as a median and interquartile range (Me [25-th; 75-th percentile]). Methods of descriptive statistics were applied; the Mann–Whitney test was used to compare two independent groups by quantitative criteria. Accordance of the observed distributions of genotype frequencies to the theoretically expected ones according to the Hardy–Weinberg equation in the group of patients was assessed using the Pearson χ^2 independence criterion. Differences in the distribution of genotypes between groups were assessed by the value of the χ^2 criterion. Differences were considered statistically significant at $p < 0.05$.

Results. The clinical characteristics of patients with gout included in the study are shown in Table. 1.

As can be seen from the data presented, the median duration of the disease was 10 years, almost half of the patients (44%) had subcutaneous tophi. In one third of patients, allopurinol administration in high doses was limited by a low GFR. In 45 (55%) of 82 patients the target UA level was defined as <300 μmol/L and in the remaining 37 – as <360 μmol/L.

At baseline, all patients received allopurinol, and 28 (34%) of them achieved the target UA level. In the remaining 54 (66%) patients, allopurinol was replaced with febuxostat. On the background of febuxostat therapy, in 22 (41%) of them, the serum UA level decreased – its value was below the target. Thus, in 50 (61%) out of 82 patients taking xanthine oxidase inhibitors (allopurinol and febuxostat), the target UA level was achieved.

In the examined group of patients, there were no differences in the frequency of genotypes of the *ABCG2* gene when analyzed according to the Hardy–Weinberg law (p>0.05). The study of the rs2231142 polymorphism of the ABCG2 gene showed that the homozygous CC genotype was present in 51 (62%) patients, the heterozygous CA genotype – in 30 (37%) and the «mutant» minor AA genotype – in 1 (1%).

Patients with different genotypes of the *ABCG2* gene were found to have comparable serum UA levels both at baseline (p=0.50) and after 6 months of therapy (p=0.35; see Table 2). At the same time, the probability of achieving the target UA level in carriers of homozygous CC genotype, and CA and AA genotypes who took allopurinol did not differ, but patients with CA and AA genotypes required a significantly higher dose of the drug (p=0.002; see Table 2).

Thirty (56%) of 54 patients taking febuxostat had the CC genotype, and 24 (44%) had the CA genotype. Both groups of patients with different genotypes of the *ABCG2* gene had comparable serum UA levels at baseline (p=0.83) and after the study completion (p=0.17). The genotype of the ABCG2 gene did not affect the number of patients requiring the maximum dose of febuxostat (see Table 2).

The target level of UA was reached by 27 (52.9%) out of 51 patients with the CC genotype, and 23 out of 31 patients with at least one allele A (genotypes CA and AA), (74.2%; χ^2=3,6, p=0.06).

Discussion. In the updated EULAR guidelines and the national guidelines for the treatment of gout, it is proposed to maintain a serum UA level less than 360 μmol/L in all patients, and less than 300 μmol/L in patients with severe gout [1, 13]. Individual dose variability and treatment efficacy depend on many factors: baseline serum UA level, renal function, body weight, use of diuretics and, finally, polymorphic variants of the ABCG2 gene (rs2231142) encoding urate transporters in the kidneys, liver, intestines and associated with allopurinol efficacy [16–18].

Nevertheless, the choice of such study design, with titration of the dose of urate-lowering drugs based on real need, as well as exclusion from the study of patients with severe renal failure and those taking diuretics, made it possible to minimize the likelihood of errors in evaluating the results. Preliminary data based on the results of a survey of a relatively small cohort of patients showed that the minor A allele of the *ABCG2* gene (rs2231142, Q141K, CSA), which predetermines ineffectiveness of allopurinol, is found very rarely – in only 1% of cases, which fully coincides with the data of N. N. Kushnarenko [19]. It can be assumed that the frequency of polymorphic variants of the *ABCG2* rs2231142 gene has ethnic and population characteristics. For example, in a population of one of the regions of China, the frequency of CC genotypes was 44.4%, CA – 44.8%, and AA – 11.8%, that is, the AA genotype was detected 10 times more often than in our data [20]. In the Taiwan population, the distribution of genotypes was 46.1; 44.8 and 9.1%, respectively [21]. However, if we consider patients carrying at least one A allele (CA or AA), since both of them are associated with a higher level of uricemia [20, 21], then the differences will not be so significant. Although persons with the A allele have a higher baseline serum UA level, this is not the cause of a poor response to allopurinol, as evidenced by a large study that included a total of 4446 patients treated with allopurinol [22]. It turned out that the probability of reaching the target UA level (<6 mg/dL or 360 μmol/L) was minimal in patients with the AA genotype, intermediate – with the CA genotype, and the greatest – with the CC genotype of the *ABCG2* gene. The association of the A allele of the *ABCG2* gene with a lower probability of the response to allopurinol persisted even after correcting the data for the initial blood serum UA level, gender, and allopurinol dose. It should be noted that there were no differences between the groups in the average doses of allopurinol, and the doses themselves were low (about 200 mg/day). Thus, the necessary dose titration of the drug was not carried out, which is indirectly confirmed by the authors of the study, concluding that the problem of ineffectiveness of allopurinol may be solved by using its large doses.

In our work, the average doses of allopurinol were generally higher than in the study by D.J. Brackman et al. [22], which affected the identification of the differences between patients with

Table 1. Characteristics of patients with gout (n = 82)

Characteristics	Value
General characteristics	
Age, years, M±σ	51.7±11.1
Gender (men/women), n (%)	75(92)/7(8)
BMI, кг/м^2, M±σ	30.8±6.4
Laboratory data (serum level)	
UA, μmol/L, M±σ	533.1±87.5
Creatinine, μmol/L, M±σ	96.5±20.6
AST, unit/L, Me [25-th; 75-th percentile]	22.1 [17.6; 26]
ALT, unit/L, Me [25-th; 75-th percentile]	24.4 [19; 33.2]
CPK unit/L, Me [25-th; 75-th percentile]	101.2 [82; 136.4]
Glucose, mmol/L, M±σ	5.8±1.3
GFR, ml/min/1.73m^2, M±σ	79.3±20
Clinical data	
Duration of the disease, years, Me [25-th; 75-th percentile]	10 [5.5; 15.8]
The number of affected joints in anamnesis, Me [25-th; 75-th percentile]	6 [4; 9]
Frequency of arthritis attacks per year, n (%), Me [25-th; 75-th percentile]	6 [6; 17]
The presence of tophuses, n (%)	36 (44)
Accompanying diseases	
Diabetes mellitus, n (%)	10 (12)
Arterial hypertension, n (%)	40 (49)
Obesity (BMI >30 kg/m^2), n (%)	34 (41)
CKD stage III and more (GFR <60 ml/min/1.73 m^2), n (%)	26 (32)

Table 2. Influence of different genotypes of the *ABCG2* gene (rs2231142) on the probability of reaching the target UA level when taking allopurinol and febuxostat

Index	Genotype CC	Genotypes CA and AA	p
Allopurinol, n (%)	51 (62)	31 (38)	
Initial serum UA level, μmol/L, M±σ	529.8±88.6	543.3±83.5	0.50
Serum UA level after 6 months of observation, μmol/L, M±σ	343.8±89.6	363.2±91.9	0.35
Δ UA, μmol/l, Me [25-th; 75-th percentile]	195 [103; 287]	202 [167; 317]	0.42
Patients who achieved the target serum UA level, n (%)	17 (33)	11 (35)	0.84
Average dose of the drug in patients who have reached the target UA level, mg / day, M ± σ	290±85	365±102	0.002*
Febuxostat, n (%)	30 (56)	24 (44)	0,25
Initial serum UA level, μmol/L, M±σ	537.4±92.9	542.6±86.6	0.83
Serum UA level after 6 months of observation, μmol/L, M±σ	324±107.7	285.6±88.4	0.17
Δ UA, μmol/l, Me [25-th; 75-th percentile]	206 [121; 297]	256 [182; 327]	0.22
Patients who achieved the target UA level, n (%)	10 (33)	12 (50)	0.22
Patients who achieved the target UA level during therapy with febuxostat at a maximum dose of 120 mg/day, n (%)	4 (40)	7 (64)	0.28

*Differences are statistically significant (p<0.05).

CA and AA genotypes, who required the administration of higher doses of the drug than carriers of the CC genotype. It is interesting that the initial mean serum UA level in the CA genotype, although expectedly higher than in the CC genotype, did not reach statistical significance.

The results of this research are consistent with the data obtained in the work of N.N. Kushnarenko et al. [19]: the frequency of determining the CC genotype was 62% and 73.7%, and the CA genotype – 37% and 25%, respectively. These authors analyzed the likelihood of achieving the target UA level depending on the genotypes of the *ABCG2* gene; however, their study had a number of differences from ours and limitations: the initial serum UA level in patients with the CC genotype was significantly lower than in patients with the CA genotype; the work was retrospective; titration of the dose of allopurinol was carried out not up to the maximum allowed doses, but only up to 300 mg/day and only in some patients (60%), which probably predetermined the differences in the results.

Although the average doses of allopurinol in patients with the CA genotype were 1.5 times higher than in carriers of the CC genotype (178.5±69.9 and 119.9±57.4 mg/day, respectively; p=0.03), as in our study (the dose required to achieve the target UA level was 1.26 times higher in patients with the CA genotype), no dependence of the achievement of target serum UA levels on the *ABCG2* gene genotype was found. At the same time, all patients with the CA genotype who took allopurinol noted its insufficient effect or its complete absence [19].

The mechanism by which polymorphism (rs2231142) of the *ABCG2* gene may affect the effectiveness of allopurinol therapy remains unclear. It is assumed that the A (141K) allele of the *ABCG2* gene is associated with a decreased conversion of allopurinol to its active metabolite oxypurinol or an increased level of elimination of oxypurinol by the kidneys. It was noted that an increase in the concentration of oxypurinol with an increase in the dose of allopurinol by 100 mg and a decrease in the serum UA level in patients with the AA genotype were more significant than in carriers of the CC genotype of the *ABCG2* gene [23].

It is important to clarify that other genes, for example *GREM2* and *GLUT 9* [22], may also be involved in the response to allopurinol, but their contribution to the genesis of the ineffectiveness of allopurinol requires more detailed study.

According to our data, the Q141K (rs2231142) polymorphism of the *ABCG2* gene does not affect the achievement of the therapy goal when using febuxostat in patients with allopurinol ineffectiveness. Previously, the absence of an association of the Q141K polymorphism of the *ABCG2* gene with the response to febuxostat, including after adjustment for age, gender, BMI and duration of drug administration, was shown in the study by L.K. Stamp et al. [24], who followed 226 patients taking febuxostat at a dose of 80 mg/day.

Conclusion. Thus, the results of our study are comparable with the data of other works, indicating the effect of the rs2231142 polymorphism of the *ABCG2* gene on the effectiveness of allopurinol. Nevertheless, the main conclusion of the study is the possibility of achieving the target serum UA level in patients with gout even in the case of the heterozygous *ABCG2* genotype, although this requires a large dose of the drug. In addition, the rare detection of the AA genotype in our cohort of gout patients suggests that total genotyping of the rs2231142 polymorphism of the *ABCG2* gene before starting allopurinol therapy is inappropriate. However, the present work was carried out on a small group of patients, and further studies are needed to finally answer the question of the relationship between the (rs2231142) polymorphism of the *ABCG2* gene and the effectiveness of urate-lowering therapy in patients with gout.

REFERENCES

1. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis.* 2017 Jan;76(1):29-42. doi: 10.1136/annrheumdis-2016-209707. Epub 2016 Jul 25.
2. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Care Res (Hoboken).* 2020 Jun; 72(6):744-60. doi: 10.1002/acr.24180. Epub 2020 May 11.
3. So AK. Why better treatment of gout is needed. *Clin Exp Rheumatol.* 2016 Jul-Aug; 34(4 Suppl 98):63-5. Epub 2016 Jul 20.
4. Yeap SS, Gun SC. Gout: why is this curable disease so seldom cured? *Ann Rheum Dis.* 2013 May;72(5):e5. doi: 10.1136/annrheumdis-2012-203161. Epub 2013 Jan 17.
5. Doherty M, Jansen TL, Nuki G, et al. Gout: why is this curable disease so seldom cured? *Ann Rheum Dis.* 2012 Nov;71(11): 1765-70. doi: 10.1136/annrheumdis-2012-201687. Epub 2012 Aug 3.
6. Чикина МН, Елисеев МС, Желябина ОВ. Практическое применение национальных клинических рекомендаций по лечению подагры (предварительные данные). Современная ревматология. 2020; 14(2):97-103.
[Chikina MN, Eliseev MS, Zhelyabina OV. Practical application of national clinical guidelines for the management of gout (preliminary data). *Sovremennaya revmatologiya = Modern Rheumatology Journal.* 2020;14(2): 97-103. (In Russ.)]. doi: 10.14412/1996-7012-2020-2-97-103.
7. Елисеев МС. Комментарии к обновленным рекомендациям Американской коллегии ревматологов по лечению подагры. Уратснижающие препараты (часть 1). Современная ревматология. 2020;14(3): 117-24.
[Eliseev MS. Commentaries on the updated American College of Rheumatology guidelines for the management of gout. Urate-lowering drugs (Part 1). *Sovremennaya revmatologiya = Modern Rheumatology Journal.* 2020;14(3):117-24. (In Russ.)]. doi: 10.14412/1996-7012-2020-3-117-124.
8. Елисеев МС. Обновленные рекомендации EULAR по лечению подагры. Комментарии к некоторым позициям. Научно-практическая ревматология. 2017;55(6):600-9.
[Eliseev MS. Updated EULAR recommendations for the treatment of gout. Comments on some positions. *Nauchno-prakticheskaya revmatologiya.* 2017;55(6):600-9. (In Russ.)].
9. Stamp LK, Merriman TR, Barclay ML, et al. Impaired response or insufficient dosage? Examining the potential causes of «inadequate response» to allopurinol in the treatment of gout. *Semin Arthritis Rheum.* 2014 Oct;44(2):170-4. doi: 10.1016/j.semarthrit.2014.05.007. Epub 2014 May 9.
10. Wen CC, Yee SW, Liang X, et al. Genome-wide association study identifies ABCG2 (BCRP) as an allopurinol transporter and a determinant of drug response. *Clin Pharmacol Ther.* 2015 May;97(5):518-25. doi: 10.1002/cpt.89. Epub 2015 Apr 6.
11. Ichida K, Matsuo H, Takada T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. *Nat Commun.* 2012 Apr 3;3:764. doi: 10.1038/ncomms1756.
12. Miyata H, Takada T, Toyoda Y, et al. Identification of Febuxostat as a New Strong ABCG2 Inhibitor: Potential Applications and Risks in Clinical Situations. *Front Pharmacol.* 2016 Dec 27;7:518. doi: 10.3389/fphar.2016.00518. eCollection 2016.
13. Подагра. Клинические рекомендации Министерства здравоохранения Российской Федерации.
[Gout. Clinical guidelines of the Ministry of Health of the Russian Federation]. http://cr.rosminzdrav.ru/#!/recomend/174.
14. https://grls.rosminzdrav.ru/grls.aspx?s=фебуксостат&m=mnn.
15. https://grls.rosminzdrav.ru/grls.aspx?s=аллопуринол&m=mnn.
16. Wright DFB, Dalbeth N, Phipps-Green AJ, et al. The impact of diuretic use and ABCG2 genotype on the predictive performance of a published allopurinol dosing tool. *Br J Clin Pharmacol.* 2018 May;84(5):937-43. doi: 10.1111/bcp.13516.
17. Wright DF, Duffull SB, Merriman TR, et al. Predicting allopurinol response in patients with gout. *Br J Clin Pharmacol.* 2016 Feb;81(2):277-89. doi: 10.1111/bcp.12799.
18. Wallace MC, Roberts RL, Nanavati P, et al. Association between ABCG2 rs2231142 and poor response to allopurinol: replication and meta-analysis. *Rheumatology (Oxford).* 2018 Apr 1;57(4):656-60. doi: 10.1093/rheumatology/kex467.
19. Кушнаренко НН, Мишко МЮ, Медведева ТА, Витковский ЮА. Полиморфизм гена abcg2 у больных подагрой в Забайкальском крае. Комплексные проблемы сердечно-сосудистых заболеваний. 2019;8(2):77-86.
[Kushnarenko NN, Mishko MYu, Medvedeva TA, Vitkovskii YuA. Polymorphism of the adrb2 gene in patients with gout in the Trans-Baikal Territory. *Kompleksnye problemy serdechno-sosudistykh zabolevanii.* 2019;8(2): 77-86. (In Russ.)].
20. Yang X, Xiao Y, Liu K, et al. Prevalence of hyperuricemia among the Chinese population of the southeast coastal region and association with single nucleotide polymorphisms in urate anion exchanger genes: SLC22A12, ABCG2 and SLC2A9. *Mol Med Rep.* 2018 Sep;18(3):3050-8. doi: 10.3892/mmr.2018.9290.
21. Cheng ST, Wu S, Su CW, et al. Association of ABCG2 rs2231142-A allele and serum uric acid levels in male and obese individuals in a Han Taiwanese population. *J Formos Med Assoc.* 2017 Jan;116(1):18-23. doi: 10.1016/j.jfma.2015.12.002.
22. Brackman DJ, Yee SW, Enogieru OJ, et al. Genome-Wide Association and Functional Studies Reveal Novel Pharmacological Mechanisms for Allopurinol. *Clin Pharmacol Ther.* 2019 Sep; 106(3):623-31. doi: 10.1002/cpt.1439.
23. Stamp LK, Chapman PT, Barclay M, et al. Relationships Between Allopurinol Dose, Oxypurinol Concentration and Urate-Lowering Response-In Search of a Minimum Effective Oxypurinol Concentration. *Clin Transl Sci.* 2020 Jan;13(1):110-5. doi: 10.1111/cts.12686.
24. Stamp LK, Topless R, Miner JN, et al. No association between ATP-binding cassette transporter G2 rs2231142 (Q141K) and urate-lowering response to febuxostat. *Rheumatology (Oxford).* 2019 Mar 1;58(3):547-8. doi: 10.1093/rheumatology/key423.

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Conflict of Interest Statement

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