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FEATURES OF THE CLINICAL COURSE AND EFFICIENCY OF HYPOURICEMIC THERAPY OF GOUT IN FEMALE DEPENDING ON GENE POLYMORPHISM

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Abstract

The article presents modern data on the influence of the most common polymorphisms APEX1 T444G and ABCG2 C421A RS2231142 of genes encoding proteins that are involved in the renal urate transport system and, thus, associated with the level of uric acid or gout. Characterization of polymorphisms APEX1 T444G and ABCG2 C421A RS2231142 of genes: V253I, Q126X, Q141K was carried out. It was determined that the GCA and GTC haplotypes of the Q126X and Q141K polymorphisms can be predictors of gout. The interrelation of APEX1 T444G and ABCG2 C421A RS2231142 gene polymorphisms with the presence of hyperuricemia depending on gender, components of metabolic syndrome, and response to allopurinol was analyzed. Most genes associated with MK or gout in a genome-wide association study encode proteins that are involved in the renal urate transport system, for example, APEX1 T444G (solute carrier family 2, member 9) and ABCG2 C421A RS2231142 (ATP-binding cassette, family G) are well-known genes for urate transporters responsible for their reabsorption and excretion [13, 14, 27]. Thus, the determination of polymorphism - APEX1 T444G and ABCG2 C421A RS2231142 genes can help in diagnosing the risk of developing gout and optimizing the schemes of uricosuric therapy in patients with refractory gout.

Keywords: *hyperuricaemia, gout, ABCG2 C421A RS2231142, APEX1 T444G, gene polymorphism.*

Gout is a systemic disease characterized by the deposition of sodium monourate crystals in various tissues and developing in connection with this inflammation in individuals with hyperuricemia (HU) caused by external environmental and / or genetic factors [4]. In this regard, the study of the role of genetic factors in understanding the pathogenesis of HU and gout is of particular relevance. The

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famous Hungarian scientist Egon Orowan explained this by the structural similarity of the uric acid molecule with methylated purines, such as, for example, caffeine, being an excellent stimulant for working on the higher cortical functions of the brain. Gout can be divided into primary and secondary gout. Primary gout is a hereditary disease, an example of which is Gierke's disease, which is characterized by a defect in glucose-6-phosphatase, as a result of which it is accompanied by excessive formation of ribose-5-phosphate. Secondary gout is a polyetiologic disease, with metabolic disorders at the molecular level against the background of various organ pathologies. It is worth noting that an isolated increase in uric acid levels is not yet gout, although it is a key component of it. An example of this phenomenon is the multiple increase in uric acid in various types of leukemia, which is not accompanied by the development of gout. It is necessary to understand that for the development of the disease, it is necessary to create certain conditions, as well as, possibly, the presence of genetic prerequisites. Arthritis of gouty nature is a direct manifestation of impaired utilization of purine nucleotides, which is accompanied by hyperuricemia. The nucleotides adenosine and guanosine, through a series of transformations and transformations, come to the formation of hypoxanthine and xanthine, respectively, which, under the action of the xanthine oxidase enzyme, are converted into uric acid. Such a chain of transformations of uric acid is characteristic only for primates and humans, all other mammals have another enzyme - uricase, which converts uric acid into allantoin, which, unlike uric acid, is better soluble in an aqueous medium. Knowledge of this chain of transformations makes it possible to explain not only the cause of the disease, but also to determine the goals of the influence of drug therapy. The excretion of uric acid is mainly carried out by the kidneys, by the secretion of molecules from the cubic epithelium of the proximal tubules, and also by the intestine. Accordingly, a persistent increase in uric acid levels is a consequence of either an increased production and supply of purines, or a decrease in the excretion of uric acid. In the pathogenesis of gout, three key stages are distinguished: the accumulation of uric acid compounds in the body, then these compounds begin to be deposited in various organs and tissues, and everything ends with the emergence of acute attacks of inflammation at the site of the lesion, with the formation of gouty granulomas and tofuses. In 2000, WHO proposed diagnostic criteria for gout, divided into 3 groups: The presence of characteristic crystalline urates in the joint fluid. Presence of tofuses (proven) that contain crystalline urates confirmed by chemical or polarizing microscopy. The presence of at least 6 of 12 signs: more than one acute attack of arthritis in history; maximum joint inflammation in the first day; monoarticular nature of arthritis; hyperemia of the skin over the affected joint; swelling or pain localized in the first metatarsophalangeal joint; unilateral damage to the joints of the arch of the foot; nodular formations resembling tophus; hyperuricemia; unilateral lesion of the I metatarsophalangeal joint; asymmetric swelling of the affected joint; detection on radiographs of subcortical cysts without erosion; lack of flora in the joint fluid. Hyperuricemia, defined as serum uric acid concentration in excess of its solubility limit (approximately 6.8 mg / dL), is considered a general biochemical abnormality that reflects extracellular fluid overload with urate. The American College of Rheumatology in 2012 recommended that the goal should be to achieve serum uric acid levels <6 mg / dL in all patients with gout or <5 mg / dL for patients with tophi [2]. The distribution of gout is uneven throughout the world, with the prevalence being highest in the Pacific. Developed countries tend to have a more severe course

of gout than developing countries, and their incidence continues to rise steadily. Certain ethnic groups are particularly susceptible to gout, supporting the importance of genetic predisposition [3]. The very phenomenon of hyperuricemia is detected in 4–12% of the population, while 0.1% of the population of Russia suffers from gout. In the USA and Europe, about 2% of residents suffer from gout; among men aged 55–65 years, 4–6% suffer from gout; this prevalence of the disease among women occurs on average 10–15 years later than in men [5]. V. Bhole et al. studied the incidence of gout in 2476 women and 1951 men. For the period taken for analysis, the risk of developing gout in men was only 3.7 times higher. According to the results of the largest national study NHANES, the prevalence of gout among adult women in the United States increased to 2%, and the total number of women suffering from gout in the United States was 2.2 million [1]. But, nevertheless, to this day, gout is considered a male disease, and most publications and large-center studies are based on the incidence of men. Even Hippocrates wrote that the disease is typical for men and does not occur in eunuchs and women before menopause. Indeed, those rare cases of gout in women almost 100% of cases precede menopause. There is no consensus and complete scientific justification for this phenomenon. The most truthful explanation is the protective force of the estrogenic background, because this hormone exerts its influence directly on the cell nucleus, activating or blocking certain groups of genes, which once again confirms the genetic predisposition to the development of gout. To date, Taiwanese scientists have proven the relationship between the ABCG2 C421A RS2231142 gene and the increase in uric acid, which leads to the occurrence of gout. This is associated with dysregulation of the inflammatory process through increased release of IL-8 from the endothelial cell. Previously, only the influence of this gene on the urate load of the kidneys and intestines was proved, but today it has been added to this that, against the background of hyperuricemia, the activation of endothelial cells leads to an excessive release of IL-8, which will start the processes of activation of neutrophils, phagocytosis and a complete immune response of the body, which eventually lead to an exacerbation of gout. For example, the rs9999470 polymorphisms, which regulate the function of another gene, APEX1 T444G, showed an additive significant association with gout in patients with the rs2231142 polymorphism of the TT genotype. APEX1 T444G encodes the glucose transported transporter GLUT9, which links the more severe course of gout in the presence of diabetes mellitus. Several studies have shown that renal hypouricemia was caused by a dysfunction in the APEX1 T444G gene through its decreased urate reabsorption in the proximal renal tubule. A combination of mutations in both ABCG2 C421A RS2231142 and APEX1 T444G genes cause an additive interaction effect in the onset of gout [6]. According to the Russian Research Institute of Rheumatology named after V.A.Nasonova, gout in women is more severe than in men, which may contribute to an increase in cardiovascular risk. If in men the presence of gout only insignificantly (1.1 times) increases the risk of developing myocardial infarction, both for any of its outcomes and for fatal, then in women, gout increases this risk by almost 1.4 times. The correlation between gout and cardiovascular risk is explained by the fact that in gout, the immune response is provided by the interaction of sodium monourate with Toll-like receptors, which is the trigger for the release of pro-inflammatory cytokines, such as 1β-IL, 6-IL, 8-IL, TNF-α, which in turn have a high proatherogenic potential. In addition, a high content of uric acid leads to the release of myeloperoxidase by neutrophils, which in turn is capable of activating xanthine oxidase

with the development of oxidative stress, which is also an atherogenic factor and a predictor of endothelial dysfunction [7]. Recently, the chronic course of gout, as a systemic inflammation, has been attributed to the risk of atrial fibrillation [10]. Also, the disease in women is characterized by the rapid development of chronic arthritis and the formation of subcutaneous tophi, to a greater extent it is characteristic of small joints of the hands and feet, the involvement of a greater number of joints, an increase in the duration of arthritis attacks, and frequent cases of inflammation of the joints of the upper extremities. Women with gout are more often diagnosed with type 2 diabetes, CKD, higher cholesterol levels, they are more likely to take diuretics, which together complicates the course of gout [9]. Based on the foregoing, it is necessary to conclude that gout is a disease with a complex etiopathogenesis.

The literature provides evidence of the influence of genetic aspects in the regulation of synthesis and excretion of MK in experiment and clinic [8]. In a genome-wide association study, 2015 (GWASs) -6 urate transporters were identified that affect serum MC levels by regulating the processes of urate reabsorption and excretion [11]. One of the most studied is the ABCG2 C421A RS2231142 ATP-binding cassette transporter gene located at the MIM138900 locus on chromosome 4q22, encoding a protein responsible for breast cancer resistance (Breast Cancer Resistance Protein - BCRP). BCRP is simultaneously a transporter of urates and various derivatives of purines, xenobiotics, porphyrins, preventing their accumulation in erythrocytes, and, according to a number of researchers, is associated with the transport of allopurinol and the response to it [15].

Structure and polymorphism of the APEX1 T444G gene.

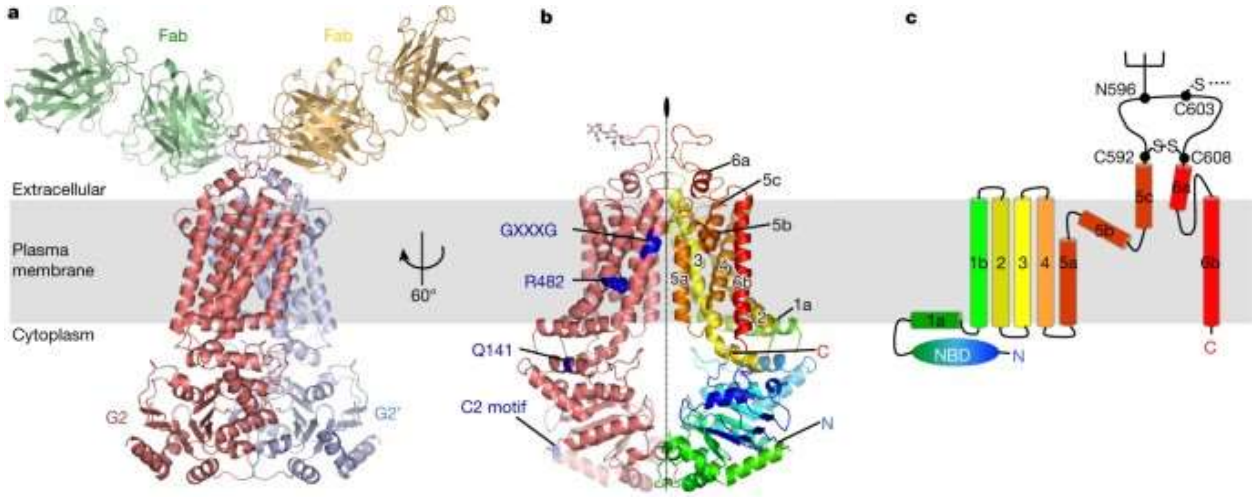
The APEX1 T444G gene is located on the short arm of chromosome 4 at the 6.1 position; it encodes the glucose and fructose transporter GLUT9, which is also a highly specific urate transporter in the cells of the proximal renal tubules, directly affecting the reabsorption of MK [13].

The GLUT-9 transporter is expressed on hepatocytes, chondrocytes, intestinal cells, leukocytes, and renal epithelial cells [12], but its function in chondrocytes and leukocytes is unknown. GLUT-9 exists in two isoforms: 9a (located on the basolateral membrane, transports urates from the cells of the proximal tubules) and 9b (on the apical membrane, transports urates into the cells of the proximal tubules), can be partially inhibited by uricosuric agents (probenecid, benzbromarone), losartan [14]. Rule A.D. et al. [16] identified 63 single nucleotide substitution polymorphisms (SNPs) in Caucasians and 53 SNPs in African Americans. The most statistically significant were rs11723439 and rs13113918. According to other scientists, the most significant polymorphisms associated with hyperuricemia and severe gout are rs16890979 in the European population and rs3733591 in the Chinese and Japanese populations [19] rs16890979 is located in the 8th exon of the gene, leading to the replacement of the amino acid valine with isoleucine in 253 position [18] is associated with creatinine level and glomerular filtration rate, which can explain the role of MC in the onset of chronic kidney disease [17]. According to Parsa A. et al. [20] each copy of the minor Ile allele of the Val253Ile polymorphism is associated with a significant decrease in MK levels (up to 0.44 mg / dL) and systolic blood pressure by 1.5–2.2 mm Hg. In the study of the influence of the rs11722228 APEX1 T444G gene, the minor T allele is associated with hyperuricemia, mainly in women of the Chinese population [21]. Brandstatter A. et al. [22], after examining 4 polymorphisms APEX1 T444G (rs6855911,

rs7442295, rs6449213, rs12510549), concluded that each copy of the minor allele reduced the MK level by an average of 0.3 mg / dL, a stronger relationship between these SNPs and the MK level was found in women. No connection was found between polymorphisms, including rs16890979, with components of metabolic syndrome, type 2 diabetes mellitus, triglyceride levels, and urine albumin-creatinine ratio [25]. Thus, well-known risk factors for hyperuricemia are not associated with APEX1 T444G gene polymorphisms [24], although many studies have found a strong relationship between the level of MC and cardiovascular risk factors [23].

The structure of the ABCG2 C421A RS2231142 gene.

The ABCG2 C421A RS2231142 gene of the ATP-binding cassette transporter (ABC) of the G family, localized at the MIM138900 locus on chromosome 4q22, encodes the Breast cancer resistance protein (BCRP), which is also a transporter of urates and various purine derivatives , xenobiotics, porphyrins, preventing their accumulation in erythrocytes, and is also associated with the transport of allopurinol and the response to it. This protein has one ATP-binding domain at the end of NH2 and one COOH-terminal of transmembrane segments [26]. ABCG2 C421A RS2231142 is expressed in the greatest amount in the placenta, heart, ovaries and kidneys (on the apical membrane of the proximal renal tubules), lower levels - in the liver, colon and small intestine, and the brain. In tumor cell lines, ABCG2 C421A RS2231142 expression is found in the mammary gland, colon, stomach, myeloma, sarcoma [20] (pic.1 a,b,c).



Picture 1. The structure of the ABCG2 gene

Polymorphism of the ABCG2 C421A RS2231142 gene.

Sequencing of the ABCG2 C421A RS2231142 gene revealed more than 80 different variations in natural sequences [28], some of which lead to functional changes in proteins. SNP rs2231142 in the 5th exon of the ABCG2 C421A RS2231142 gene has been studied in many studies. This variant occurs with a low frequency in persons of African American (2-5%), European (11-14%), Spanish (10%), Middle Eastern (13%) origin, with a high frequency in Chinese (35%) and Japanese (35%) [29]. The rs2231142 variant results in the replacement of the amino acid glutamine with lysine (Q141K), having a strong relationship with the level of MK and gout in individuals of black and white races [30]. By

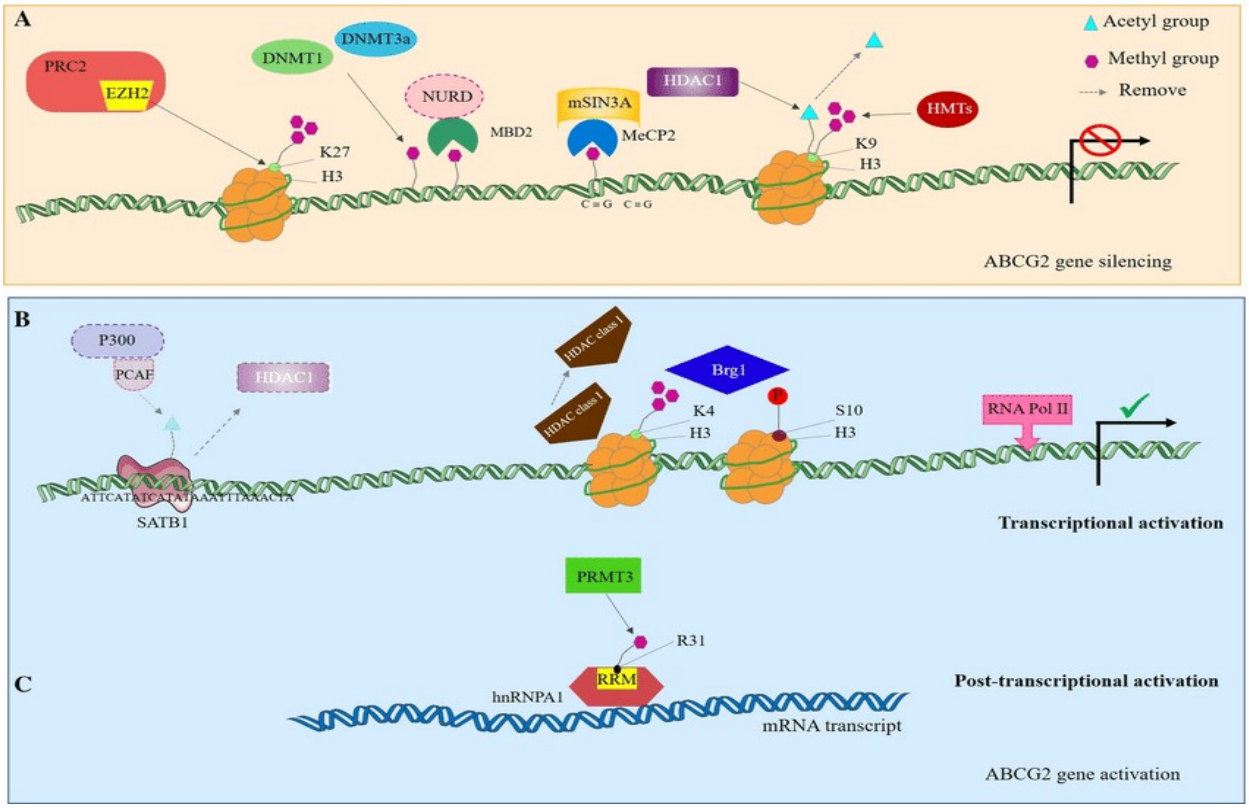
decreasing ATP activity, the rs2231142 polymorphism is associated with a 53% decrease in BCRP transport function [11]. An additional copy of the minor T allele is associated with an increase in serum urate of approximately 0.3 mg / dL per copy among individuals of the European population. In addition, the T allele is associated with a higher degree of hyperuricemia in men [31], whereas rs16890979 APEX1 T444G was associated with a higher level of MC in women [25].

Matsuo H. et al. [6] showed that Q126X rs72552713 (Gln126Ter), a polymorphism of the 4th exon of the ABCG2 C421A RS2231142 gene, increases the risk of gout in the Japanese population (odds index 5.9) to a greater extent than the Q141K variant of rs2231142 (Gln141Lys). 10% of all patients with gout studied had a combination of genotypes Q126X and Q141K, which resulted in a 75% decrease in ABCG2 C421A RS2231142 function compared to patients who were homozygous for the major C allele in both variants. Among the alleles of these polymorphisms, the 141K allele is associated with low levels of ABCG2 C421A RS2231142 expression and decreases ATP-dependent urate transport compared to the wild-type gene [32], the 126X T allele impairs ABCG2 C421A RS2231142 expression, reducing its transport activity. The 12M allele of the ABCG2 C421A RS2231142 gene produces a protein with a significantly lower ability to transport some drugs [27]. Zhou D. et al. [38] analyzed the allelic frequencies of three SNPs (Q141K, V12M, and Q126X), which showed that the minor A allele Q141K was found on 49.6% of chromosomes in patients with gout compared with 30.9% of chromosomes in the control group; and the minor T allele Q126X was found on 4.7% of the chromosomes of patients with gout versus 1.7% of the chromosomes of the control group. 141K and 126X were associated with an increased risk of gout, while the frequency of the minor A allele V12M was significantly reduced in patients with gout (18.3%) compared with controls (29%) [9].

Analysis of SNP haplotypes (V12M, Q126X and Q141K) showed that GCA and GTC haplotypes are more often present in patients with gout than in the control group and can be considered as risk haplotypes for gout (odds ratio 2.3 and 2.71, respectively) [13]. Wen S.S. et al. [10] concluded that the Q141K variant (rs2231142) can directly modulate BCRP-mediated transport of allopurinol and oxypurinol. To determine the mechanism by which ABCG2 C421A RS2231142 is associated with the response to allopurinol, cells were transfected with the rs2231142 (Q141K) variant, as a result of which they accumulated significantly more allopurinol and oxypurinol, decreasing BCRP expression on the plasma membrane. Allele K BCRP - Q141K was associated with a smaller decrease in the level of MK during treatment with allopurinol, although acting as a secretory transporter in the kidneys and intestines, it should have led to a decrease in excretion and higher levels of the drug in plasma, and therefore to a greater decrease in MK. Since plasma levels of allopurinol have not been measured, the exact mechanism by which the Q141K variant induces a decreased response to allopurinol cannot be determined. It is possible that allopurinol and oxypurinol, in addition to inhibiting xanthine oxidase, can act as a uricosuric drug, increasing renal excretion of MK, since mice with experimental hyperuricemia treated with allopurinol have an increased fractional excretion of MK [1]. In addition, studies by Anzai N. et al. [22] demonstrate that oxypurinol is a potent inhibitor of APEX1 T444G, which leads to a decrease in MK reabsorption and an increase in its renal excretion. According to the findings of Wen S.S. et al. [29] none of the known MK transporters are associated with the response

to allopurinol, suggesting a key role for BCRP in drug transport. Alopurinol, a purine analog that is metabolized to oxypurinol, remains the most commonly used and first-line drug for lowering urate levels. Both components inhibit xanthine oxidase [4]. Only 42% of patients taking allopurinol reach the recommended MC levels (less than 6 mg / dL or 0.36 mmol / L). 21% of patients taking 300 mg / day of allopurinol achieve optimal MC levels [5]. The safety of using allopurinol at doses over 300 mg / day has not been studied; there is a need for dose adjustment in the elderly and in the presence of impaired renal function [18].

Since ABCG2 C421A RS2231142 dysfunction is the main cause of gout in 80% of patients with gout, ABCG2 C421A RS2231142 studies will provide a new approach to the prevention and treatment of hyperuricemia [27] (pic.2).



Picture 2. The epigenetic regulation of the ABCG2 gene

APEX1 T444G and ABCG2 C421A RS2231142 gene polymorphism as a prognosis for the development of gout

The key for patients with hyperuricemia is to prevent the development of gout and, if present, to reduce the risk of future outbreaks of gout and the development of complications such as damage to teeth and / or joints. However, the serum urate level is not the only factor that reliably predicts the progression of gout. Risk stratification, including genetic testing, will allow for more targeted patient decisions regarding the administration of urate-lowering therapy after (or even earlier) the first gout outbreak. In a genomic study, it was revealed that the variance of variants of the APEX1 T444G gene locus is most strongly associated with hyperuricemia, while the variability of ABCG2 C421A

RS2231142 is more closely associated with the development of gout, influencing other checkpoints in pathogenesis, such as the formation of crystals and / or the inflammatory response to their deposition.

Personalization of urate-lowering therapy

ABCG2 C421A RS2231142 is the only gene currently known that is associated with the efficacy of allopurinol, the most widely used urate-lowering drug. Another drug of the same group, febuxostat, which acts by inhibiting xanthine oxidase, has not yet been involved in genetic studies.

The URAT1 transport protein, encoded by the SLC22A12 gene, mediates the reabsorption of uric acid at the apical membrane of the proximal renal tubules. Its inhibitors - uricosurics probenecid (benzbromarone) and leunurad - normalize urate excretion. There is some evidence that probenecid (benzbromarone) has no pharmacological effect in patients with renal hypouricemia and functional mutations in URAT1. Thus, genetic data gains importance for the choice of individual pharmacotherapy.

Predicting side effects of pharmacotherapy

The identification of the genetic marker HLA-B * 5801 as a major risk factor for intolerance to allopurinol was a major step forward in the safe administration of this drug. Tests for HLA-B * 5801 in high-risk groups along with screening have led to a decrease in the prevalence of this life-threatening complication.

Another example of genetic testing with a potential risk assessment of adverse effects of urate-lowering therapy is the testing of cytochrome metabolite proteins CYP 2C9, CYP 2C9 * 2 and CYP 2C9 * 3. CYP 2C9 * 3 homozygotes have a significantly longer half-life of benzbromarone than other CYP 2C9 genotypes, which may increase the risk of benzbromarone-induced hepatotoxicity.

Genetic testing will also help with anti-inflammatory drug selection, as the CYP 2C9 gene is associated with the metabolism of many non-steroidal anti-inflammatory drugs, including celecoxib, diclofenac, ibuprofen, naproxen, and piroxicam.

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