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A Study of ABCG2 Versus SLC2A9 in the Treatment of Gout

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Abstract: Describe the symptoms of gout, the number of deaths caused by gout, and the impact of gout in various countries, and analyze its pathogenic mechanisms. Treatment with two uric acid transporters, ABCG2 and SLC2A9, is used as drugs, from tracing the origin of ABCG2 and SLC2A9 to understanding their nomenclature and studying their chemical properties and then to the relationship between ABCG2 and SLC2A9 and gout, as well as the comparison of the mechanism of action of ABCG2 and SLC2A9. As a common disease with unclear pathogenic mechanisms, gout has limited drugs for treatment and large side effects; ABCG2 and SLC2A9 have obvious effects on gout by controlling the uric acid content in the body with almost no side effects.

Keywords: Gout, ABCG2, SLC2A9.

1. Introduction

The symptoms of gout [3] are sudden severe pain in one or more joints, which usually starts suddenly at night, and there will also be redness, swelling, increased skin temperature, and red, purple, tense and shiny skin on the joint surface. Gout is diagnosed by laboratory tests (blood uric acid levels and synovial fluid tests) and imaging tests (X-rays, ultrasounds, and CT).

First of all, the attack of gout disease can affect joint redness, swelling, heart pain, local immobility, and difficulty walking, and cause the patient unbearable pain. If gouty nephropathy is caused, it will cause kidney stones and decreased kidney function, and in severe cases, it can lead to kidney failure and uremia. Gout can also cause heart problems, which can cause cardiac insufficiency and even cardiac arrest. Gout has become the fourth killer of Chinese residents after cardiovascular and cerebrovascular diseases, cancer, and diabetes [11].

With the change in lifestyle and dietary habits around the world, the incidence of gout has increased year by year and has become a growing public health problem. Gout not only affects the quality of life of patients [6]. It can also result in severe complications such as joint deformity and renal insufficiency. At home and abroad, the medical community's understanding of gout has undergone a long and deepening process [4].

Gout is a metabolic arthropathy caused by purine metabolism disorders. The specific pathogenesis of gout is not clear, but it can generally be classified as primary gout and secondary gout. The primary is usually due to genetic factors, like people with a family history of gout, will have a high chance of gout; if there is also an abnormality of congenital kidney function uric acid transporter, it may lead to gout. Secondary factors include excessive alcohol consumption (which can cause metabolic disorders, resulting in the inability of the body to excrete uric acid normally, so the risk of gout is greatly increased), and the intake of a high-purine diet [15] (when the metabolism of uric acid exceeds

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the metabolic capacity of the kidneys, uric acid may accumulate in the body, which may induce gout for a long time) [8]. The specific pathogenesis of gout is complex, but it is due to the imbalance of purine metabolism in the body and the insufficient metabolism of uric acid. Hyperuricemia is the most crucial biochemical foundation of gout. Under the natural environment, human tissues contain purine substances, and uric acid will be produced after the purine in the body and the food eaten is decomposed. When there is too much uric acid in the body, uric acid crystals will accumulate in the body fluids, tissues, and joints in the body, thus causing gout.

There are many treatments for gout. According to the above summary of the pathogenic mechanism, there are generally the following treatments. In the acute phase of gout, anti-inflammatory and analgesic therapy is usually given. For example, non-steroidal anti-inflammatory (NSAIDs), colchicine, and glucocorticoids. However, these drugs have certain side effects. Adverse effects on the gastrointestinal tract and kidneys can also affect the blood system. Uric acid-lowering therapy is generally used during interictal and chronic phases. Allopurinol, febuxostat, benzbromarone, or probenecid are used. If necessary, surgery to remove tophi and orthopedic deformed joints may be an option. There is also a way of TCM treatment. According to a large number of traditional Chinese medicine classics, "turbidity and stasis" is a disease pathogenesis element throughout the gout disease, and the use of dampness and turbidity drugs and dampness and stasis drugs can be considered in clinical treatment. There are also non-drug treatments, such as adjusting your diet: maintaining a low-purine diet, controlling your total calorie intake, and increasing your water intake. Lifestyle changes are also possible. Develop good habits such as moderate exercise, quitting smoking, limiting alcohol consumption, and controlling weight.

Treatment also varies for different age groups. Gout in the elderly is characterized by multiple joint involvement and many comorbidities, but symptoms are atypical. When they have gout, the typical symptoms, such as joint pain, redness, and swelling, are not as obvious as those of young people. The pain is milder and may only manifest as local dull pain and soreness. Gout in the elderly is more likely to affect multiple joints, such as hands, feet, knee joints, and other parts at the same time. They also usually suffer from multiple underlying diseases, such as hypertension, diabetes, coronary heart disease, etc. The treatment of gout during pregnancy and lactation is very limited in terms of drug selection and treatment methods. There are also some difficulties in monitoring the condition. There are also some potential effects on the fetus and baby. If a pregnant woman uses inappropriate drugs during pregnancy, it may lead to adverse consequences such as fetal malformations, growth retardation, premature birth, and miscarriage. If a pregnant woman's gout is severe, pain and inflammation may cause the pregnant woman's body to increase the stress response, affecting the environment in which the fetus grows. Long-term pain and discomfort may also affect the woman's mood and sleep, which in turn can have an indirect effect on fetal development. The effects on the baby are mainly due to the delivery of the drug through breast milk. In terms of nutritional availability, lactating women restrict their diet because of gout, which affects the quality and production of milk, and physical discomfort and pain can also affect the frequency and quality of breastfeeding.

2. Description of chemical information of drugs

ABCG2 and SLC2A9 are two kinds of uric acid transporters. Transporters are a huge group of membrane proteins that intervene in the commute of chemicals inside and outside the biofilm as well as signals. The lipid bilayer forms a hydrophobic barrier around the organelle or cell, isolating it from its surroundings. While there are some small molecules that can be crossed directly, most hydrophilic compounds, such as amino acids, sugars, ions, drugs, etc., require the help of specific transporters to cross the hydrophobic barrier. Thus, transporters play important roles in nutrient absorption,

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metabolite release, and signal transduction in many cellular activities. So, as the name suggests, uric acid transporters are transporters that affect renal urate reabsorption.

The ABCG2 protein belongs to the ATP-binding cassette transporter (ABC transporter) and is included in the G subfamily of the ABC gene, which was first cloned from drug-resistant breast cancer cells in 1998. It is a gene that encodes a breast cancer resistance protein, so it is also known as the breast cancer resistance protein (BCRP) gene, which uses the energy produced by the hydrolysis of ATP to transport a variety of different substrates from intracellular to extracellular. The structure of ABCG2 protein includes 6 transmembrane helical domains and an amino-terminal intracellular nucleic acid-binding domain, which can only function by forming homodimers, heterodimers, or multimers with other heme transporters. SLC2A9 originates in the kidney. SLC2A9 gene-encoded protein SLC2A9 is expressed in renal proximal tubular epithelial cells and is primarily responsible for urate reabsorption. This gene belongs to the solute carrier family 2, a member of the facilitating glucose transporter family, and is therefore also known as Glut9.

The chemical properties of transporters mainly include specificity, saturation, selectivity, and participation in passive or active transport. Firstly, specificity refers to the fact that different substances require different transporters for transport, which means that the kind and number of transporters on the cell membrane will change according to the function of the cell and the substance that needs to be transported. The second is saturation; when a specific transporter on the cell membrane reaches saturation, the rate at which the cell absorbs the substance no longer increases with the increase in the consistency difference between the two sides of the membrane. This means that the transporter has a limit beyond which the rate at which the cell can absorb the substance no longer increases. The third is selectivity, where transporters allow only molecules or ions that are compatible with their binding site to pass through, and this selectivity guarantees that the cell can selectively permit certain substances to get through the cell membrane. While carrier proteins undergo a change in their own conformation with each transport, channel proteins allow only molecules or ions that are appropriate for the diameter, size, and charge of their own channels to pass through without binding to the channel proteins. Finally, there is the involvement in passive transport or active transport, where transporters can be involved in passive transport (facilitated diffusion) or active transport (transport pump). Although the membrane transport proteins involved in facilitated diffusion have no enzymatic activity, they have the characteristics of enzyme catalysis, while active transport involves the process of transporting substances by cells using energy inverse concentration gradients. This is also what ABCG2 and SLC2A9 have in common.

ABC transporters' basic structure of their peptide chains is arranged in the order of N-terminus-MSD1-MBD1-MSD2-NBD2-C-terminus, and the trans-membrane domain contains 12 α-helices related to ATP binding. SLC2A9 has two main transcripts: GLUT9L and GLUT9S. GLUT9L is a long isomer with 540 amino acids, while GLUT9S is a short isomer with 512 amino acids[2]. Since the N-terminus of GLUT9L is longer than that of GLUT9S, these two isoforms are expressed in different domains of the cell membrane.

3. Conclusion

Dysfunction of ABCG2 protein expression or dysfunction can lead to decreased uric acid excretion, which can lead to an increase in blood uric acid levels in the body, which can lead to gout. For the first time in genome-wide (GWAS) studies, SNPs have been identified in genes encoding ABCG2 protein that is associated with blood uric acid levels and gout pathogenesis, and SNP mutations at the gene level may lead to reduced function at the level of ABCG2 protein. The most common SNPs of ABCG2 gene are C421A, which is caused by a base mutation at position 421 of exon 5, which leads to the mutation of glutamine at position 141 to lysine (Q141K), and the two most significant missense mutation sites (SNPs) are rs2231142 and SNP rs2725220, which can reduce the transport rate of uric

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acid by 53%. SLC2A9 plays a vital role in maintaining uric acid balance in the body. Its loss-of-function mutations cause hereditary hyperuricemia, manifested by hypouricemia, kidney failure associated with kidney stones, and a tendency to increase acute renal failure during strenuous exercise. In addition, the study of SLC2A9 is of great significance for comprehending the development of hyperuricemia and gout, especially in the process of renal excretion of uric acid, and the variation of the SLC2A9 gene is closely related to the development of these diseases.

The drug development course has many difficulties. Initially, the identify and ascertainment of drug targets. Target validation using in vitro assays or animal models is not necessarily applicable to human disease. In addition, it is hard to deduce a causal relationship between changeable danger elements and illness on account of observational data alone. Another challenge is conducting clinic tests. Especially in the early absence of symptoms, the only way to ascertain the result of the drug being tested is to monitor the perennial trend of urine albumin-to-creatine ratio or estimated glomerular filtration rate (eGFR), so we can observe changes by keeping watch on standing trends in urine albumin-to-creatine ratio. Therefore, drug target validation before starting clinical research is the crux to improving the success rate of drug invention. Target validation in view of traditional genetics has proven to be one of the potential methods.

In the study, we adopted a drug-target MR approach to appraise promising drug targets that may protect kidney function by lowering urate-reducing effects. Linear and logistic regression methods are used for continuous and binary outcome variables severally. The causal relationship between exposure and consequence was estimated by the Wald ratio method. The data for this paper is a publicly available data set on potential drug targets for chronic kidney disease in Japan. (https://www.mrbase.org/). rs16890979 on SLC2A9 is the loss-of-function variant involved in uric acid transport capacity, while rs2231142 on ABCG2 is the loss-of-function variant of uric acid transport capacity. And SLC2A9, the 4 SNPs in the locus have high LD (R=>0.8) among each other. Thus, the effect of the missense variant (rs16890979) on the functional alteration of Glut9 will be reflected in the other three IV-exposure panels of SNPs using the SLC2A9 locus. The intronic version rs2199936 in ABCG2 is associated with this gene "changes in lipoprotein-associated phospholipase A2 activity after statin therapy," but no causal relationship was detected when this SNP was used as an IV. We found that there was a coincident negative correlation between genetically augmented serum UA levels and eGFR only when the genetic instrument was selected from the SLC2A9 gene coding locus. To accord with MR hypotheses, we ensure that there is a strong association between each IV and exposure from a statistical and biological perspective. It is worth mentioning that the effect of rs16890979 on the UA transport capacity of SLC2A9 has been directly illustrated by biological experiments. To estimate the non-horizontal pleiotropy hypothesis, we determined that there were no data showing an association between the selected IVs and any trait other than the displays of interest, at least in the IEU GWAS database. The results of the positive/negative control study also sustain the effectiveness of our method. From a genetic point of view, a large number of GWAS have distinguished the main loci associated with UA levels in SLC2A9, and loss-of-function mutations in SLC2A9 have been shown to cause hypouricemia. Demonstrating that loss-of-function variants in ABCG2 lead to decreased intestinal UA excretion, suggesting elevated UA levels in gut cell-specific Slc2a9 knockout mice[9].

The benefits of uric acid protein in the treatment of hyperuricemia are mainly reflected in three aspects. Highly effective, urate-lowering proteins can specifically bind uric acid and increase the efficiency of uric acid clearance. It can accurately capture the uric acid molecules in the blood and quickly convert them into a form that is easier to excrete from the body, thereby effectively reducing blood uric acid levels. Compared with some traditional medicines, its effect is more direct, and the effect is more significant. With high safety, uric acid protein is a relatively natural therapeutic substance, and in general, it has fewer side effects on the human body. It is not like some chemically

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synthesized drugs, which may cause gastrointestinal discomfort, liver and kidney function harm, and other side effects. While reducing uric acid, it plays a certain protective role in other organs of the body and reduces other health risks caused by treatment. long-term stability. Uric acid protein can continue to function in the body to maintain the stability of uric acid levels. Unlike some transient treatments, frequent interventions are required. It can provide patients with longer-lasting uric acid control, which can help to manage hyperuricemia in the long term.

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