Susceptibility genes of hyperuricemia and gout

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Abstract
Gout is a chronic metabolic disease that seriously affects human health. It is also a major challenge facing the world, which has brought a heavy burden to patients and society. Hyperuricemia (HUA) is the most important risk factor for gout. In recent years, with the improvement of living standards and the change of dietary habits, the incidence of gout in the world has increased dramatically, and gradually tends to be younger. An increasing number of studies have shown that gene mutations may play an important role in the development of HUA and gout. Therefore, we reviewed the existing literature and summarized the susceptibility genes and research status of HUA and gout, in order to provide reference for the early diagnosis, individualized treatment and the development of new targeted drugs of HUA and gout.

Keywords: Hyperuricemia, Gout, Susceptibility gene, Single nucleotide polymorphism, Serum uric acid

Introduction
Gout is a common disease caused by purine metabolism disorder, which is primarily caused by the accumulation of uric acid (UA) crystals in joints and other tissues. It is typically characterized by recurrent episodes of acute inflammatory arthritis, and the metatarsophalangeal joint of the big toe is the most vulnerable part [1]. The occurrence of gout is often significantly correlated with the increase of serum uric acid (SUA) levels. In most mammals, UA is oxidized by uricase to a more water-soluble allantoin, which is excreted from the kidney (Fig. 1). However, in the process of human evolution, due to the silent mutation of the gene encoding uricase, UA becomes the final product of purine metabolism in humans, and its concentration is 3 to 10 times that of other mammals [2]. When the concentration of SUA in human exceeds 420 μmol/L (male) or 360 μmol/L (female) was defined as HUA. HUA plays a crucial role in the occurrence and development of gout. It has been reported that about a quarter of patients with HUA will develop gout [3]. Chronic gout can lead to lifelong disability. Moreover, studies have shown that the heritability of SUA is about 73% [4], which suggests that HUA and gout are largely determined by genetic factors. Therefore, it is significant to explore HUA and gout from the perspective of genetic variation.

UA is mainly produced by the liver, two-thirds of which is excreted via the kidney and one-third via the intestine [5]. Among them, HPRT and PRS1 are the most important enzymes involved in liver UA production (Fig. 1); while GLUT9, ABCG2 and OATs, etc. are the main transporters involved in the reabsorption and excretion of UA in the kidney and intestine (Fig. 2). Studies have shown that HPRT and PRPS1 gene mutations seem to be the main cause of primary gout [6]; SLC22A11 gene mutation is associated with RUE (renal underexcretion) gout [7]; ABCG2 seems to be one of the reasons for the genetic heterogeneity of ROL (renal overload) and RUE gout [8]. It can be seen that any abnormality of enzymes or transporters involved in UA metabolism and their upstream genes will affect SUA levels. Consequently, this paper reviews the genes involved in HUA and gout mainly from...
Fig. 1  Uric acid metabolism diagram. The solid line represents one-step reaction and the dotted line represents multi-step reaction, the blue part is mainly found in most mammals except humans.

Fig. 2  UA transport proteins on the membrane of renal tubular epithelial cells. In the red square frame are transport proteins involved in UA reabsorption. In the blue square frame are transport proteins involved in UA excretion.
three aspects (Table 1): UA production, UA reabsorption and UA excretion.

Genes related to UA production

**HPRT**

*HPRT* gene is located on human chromosome X (Xq26.2-q26.3), with a total length of 44 kb, including 9 exons and 8 introns, encoding hypoxanthine guanine phosphoribosyltransferase (HPRT) [9]. As shown in Fig. 1, HPRT is the most important enzyme in the purine salvage pathway, which catalyzes the synthesis of hypoxanthine into hypoxanthine nucleotides and the conversion of guanine into guanine nucleotides. Its activity is regulated by the synergistic effect of guanine and IMP [28]. *HPRT* gene mutation can cause HPRT enzyme activity defect, then it will lead to the surplus of its substrates hypoxanthine and guanine, and these surplus purines will be converted into UA under the action of xanthine oxidase (XO) (Fig. 1), resulting in the increase of UA levels in the body [29], and finally cause gout. Clinically, the disease caused by *HPRT* deficiency belongs to X-linked genetic disease, which mainly affects men [30], and the severity of the disease is positively correlated with the degree of enzyme deficiency [31]. Moreover, diseases caused by *HPRT* gene mutations can be divided into three types according to the degree of enzyme deficiency: the most serious one is Lesch-Nyhan syndrome (LND) with enzyme activity less than 1.5%, mainly manifested in HUA, abnormal development of nervous system, involuntary movement, and self-injurious behavior; however, 1.5–2% of patients with enzyme activity showed HUA with neurological dysfunction; in addition, Keesey-seegmiller syndrome with enzyme activity of 8%—60% only shows HUA related symptoms [31]. Recently, studies have found that *HPRT* pathogenic mutants c.103G > A (p.V35M) [12], c.277-281delATTGC, c.299 (exon 3) T > A, c.468-470delGAT and loss (exon: 6) 84 bp are related to family juvenile gout. [6]. The interaction between *HPRT* gene mutants and β-amyloid precursor protein (APP) gene regulate the epigenetics of LND by affecting alternative APP pre-mRNA splicing [32]. The increase of SUA caused by *HPRT* deficiency is regulated by GLUT9 single nucleotide polymorphism (SNP) [5]. P53 up-regulates the expression of *HPRT* [33]; miR-181a down-regulates the expression of *HPRT* [34]. It can be seen that *HPRT* pathogenic mutants are significantly associated with familial juvenile gout. Therefore, it is particularly important to detect *HPRT* gene in these patients.

**PRPS1**

*PRPS1* gene is located on human chromosome X (Xq22.3), encoding phosphoribosyl pyrophosphate

| Table 1 Susceptibility Genes of HUA and Gout |
|---------------------------------------------|
| **Classification** | **Gene name** | **Gene product** | **Location (human)** | **Tissue distribution** | **Refs** |
| Production | *HPRT1* | HPRT1 | Xq26.2-q26.3 | Multi-tissue expression | NCBI, [9] |
| Production | *PRPS1* | PRPS1 | Xq22.3 | Multi-tissue expression | NCBI, [10] |
| Production | *ALDH16A1* | ALDH16A1 | 19q13.33 | High expression in kidney | NCBI, [11] |
| Reabsorption | *SLC22A11* | OAT4 | 11q13.1 | Kidney | NCBI, [12, 13] |
| Reabsorption | *SLC22A12* | URAT1 | 11q13.1 | Kidney | NCBI, [13] |
| Reabsorption | *SLC22A13* | OAT10 | 3p22.2 | Kidney | NCBI, [14] |
| Reabsorption | *SLC2A9* | GLUT9 | 4p16.1 | Liver and kidney | NCBI, [15] |
| Excretion | *ABCG2* | BCRP | 4q22.1 | Kidney and other tissues | NCBI, [16] |
| Excretion | *ABCC4* | MRP4 | 13q32.1 | Kidney and other tissues | NCBI, [17] |
| Excretion | *SLC22A6* | OAT1 | 11q12.3 | Kidney and other tissues | NCBI, [13, 18] |
| Excretion | *SLC22A8* | OAT3 | 11q12.3 | Kidney and other tissues | NCBI, [13, 18] |
| Excretion | *SLC17A1* | NPT1 | 6p22.2 | Kidney and other tissues | NCBI, [12] |
| Excretion | *SLC17A3* | NPT4 | 6p22.2 | Kidney and other tissues | NCBI, [12, 19] |
| Excretion | *SLC17A4* | NPT5 | 6p22.2 | Kidney and other tissues | NCBI, [12, 20] |
| Excretion | *SLC2A12* | GLUT12 | 6q23.2 | Kidney and other tissues | NCBI, [21] |
| Other | *PDZK1* | Various scaffold proteins | 1q21.1 | Liver, kidney and other tissues | NCBI, [22] |
| Other | *GCKR* | GKR | 2p23.3 | Liver | NCBI |
| Other | *PKD2* | Polycytin-2 | 4q22.1 | Multi-tissue expression | NCBI, [23, 24] |
| Other | *SLC16A9* | MCT9 | 10q21.2 | Kidneys and other tissues | NCBI, [12] |
| Other | *CARMIL1* | CARMIL1 | 6p22.2 | Kidney and other epithelial tissues | NCBI, [25] |
| Other | *SCGN* | Secretagogin | 6p22.2 | Neuroendocrine tissue and pancreas | NCBI, [12] |
| Other | *UMOD* | THP | 16p12.3 | The major secretory protein in urine | NCBI, [26, 27] |
synthase 1 (PRS1), which is involved in human nucleotide synthesis via catalyzing the synthesis of phosphoribosyl pyrophosphate (PRPP) by adenosine triphosphate (ATP) and 5-phosphoribosyl (R-5P) (Fig. 1) [10]. PRPS1 is transcriptionally regulated by miR-p376 [35], whose accelerated transcription will lead to the superactivity of PRS1 and eventually cause the increase of UA synthesis [36]. In general, pathogenic mutants of PRPS1 cause hereditary gout, Arts syndrome, Charcot-Marie-Tooth neuropathy type 5 (CMTX5) and X-linked deafness 1 (DFNX1), and mainly affect men [37]. Recently, Zikanova et al. [38] found a new mutation of PRPS1: c.520 G > A (p.G174R) leads to PRS1 hyperactivity, then resulting in severe HUA. In addition, Yang et al. [36] also found another missense mutation of PRPS1: c.521(exon)G > T, p. (Gly-174Val) is associated with HUA and gout. However, studies have found that PRPS1 missense mutant c.359G > T (p.Gly120Val) causes a rare adult-onset cerebellar ataxia in female [37], and PRPS1 mutant c.82 G > C causes optic atrophy and deafness [39]. It can be seen that only the mutations that cause the superactivity of PRPS1 will increase the synthesis of UA. Therefore, the possibility of PRPS1 gene mutation cannot be ruled out when SUA levels is normal. Furthermore, the detection of PRPS1 activity is great significance for the early diagnosis of HUA and gout. PRPS1 may be a potential target for the treatment of HUA and gout in the future. Because this gene mutation is more likely to occur in early-onset gout, thus, young patients with simple HUA should be screened for PRPS1 mutation.

**ALDH1A1**

ALDH1A1 gene is located on human chromosome 19q13.3 and consists of 17 exons, encoding acetaldehyde dehydrogenase 16 family A1 (ALDH16A1) [11]. It is highly expressed in kidney [40] and catalyzes a variety of aldehyde reactions [11]. Leask et al. found that ALDH16A1 rs150414818 (Pro476Arg) mutation disrupted the interaction between ALDH16A1 and HPRT, thereby affecting purine metabolism, resulting in elevated UA [41]. In mice, knockdown of ALDH16A1 resulted in decreased SLC17A3 expression and increased SLC16A9 and ABCC4 expression [41]. Therefore, ALDH16A1 may be involved in the regulation of SUA via interacting with other UA transporters.

**Genes related to UA reabsorption**

**Solute carrier family 22 (SLC22A)**

SLC22A11 SLC22A11 gene is located on chromosome 11q13.1, encoding organic anion transporter 4 (OAT4) and is expressed in the apical membrane of renal proximal tubular epithelial cells. OAT4 is an asymmetric UA transporter with 53% homology with URAT1 [12]. It reabsorbs UA in the form of exchange between organic anions and dicarboxylate (Fig. 2) [12, 13]. The expression of OAT4 is regulated by PDZK1, NHERF1 and protein kinase C [13, 42]. IL-23 down-regulates OAT4 mRNA expression [43]. In addition, the inhibition of Wnt signaling pathway down-regulates the expression of OAT1, OAT3 and OAT4 [42]. GWAS have revealed that SLC22A11 rs17300741 was associated with SUA levels, while rs2078267, rs2186571, rs17299124 and rs17300741 were associated with gout [44]. Among them, rs17300741 is dramatically associated with RUE gout in Japanese population [7], but whether this association exists in other regions has not been confirmed.

SLC22A12 SLC22A12 gene is located on chromosome 11q13.1 and encodes urate transporter 1 (URAT1), which is expressed in the apical membrane of renal tubular epithelial cells. URAT1 is a high affinity UA transporter, which absorbs UA from raw urine and plays an important role in maintaining human UA homeostasis. Like OAT4, URAT1 is also an asymmetric UA transporter [13], which participates in the reabsorption of UA through monocarboxylate exchange (Fig. 2). SLC22A12 gene dysfunctional mutations cause URAT1 dysfunction, then leading to hereditary renal hypouricemia type 1 (RHUC1), which is characterized by decreased SUA levels and increased UA excretion [45]. Epidemiological investigation showed that 90% of hypouricemia (SUA ≤ 2.0 mg/dl) was caused by nonfunctional URAT1 mutations [46]. The rare variant of SLC22A12 gene is considered to have strong ethnic specificity [47]. SLC22A12 rs559946 is associated with a higher risk of gout in the Han population; rs3825017 is associated with gout risk in Czech population; rs75786299, rs7929627 and rs3825017 are associated with HUA in Korean population [37]; rs11231825 (p.H142H) is related to gout susceptibility in Vietnamese population [48]. SLC22A12 rs121907892 (p.142H) is related to EA gout in Vietnamese population [49, 50]. Sakiyama et al. [50] proved that these two variants were protective factor for HUA and gout. Consistent with previous studies, Pavelova et al. also found that SLC22A12 gene variant rs3825017 (p.N82N) increased the risk of gout [51]. However, Toyoda et al. [53] found that dysfunctional mutations of SLC22A12 gene have prominent anti-gout effect. Even in the presence of ABCG2 pathogenic mutations, these mutations still have a protective effect on gout. In addition, they found that the protective effect of SLC22A12 on gout exceeded the pathogenic effect of ABCG2 on gout. Meta-analysis showed that SLC22A12 rs3825016 and rs3825018 are risk factors for gout and HUA, while rs475688 is a protective factor for HUA [52]. It can be seen that the vast
majority of SLC22A12 gene mutations inhibit the function of URAT1 and reduce the risk of gout. In addition, 27-Hydroxycholesterol (a metabolite of cholesterol) can activate SLC22A12 gene promoter via estrogen response elements (EREs), and then up-regulate the expression of SLC22A12 [53].

SLC22A13  SLC22A13 gene is located on chromosome 3p21.3, which encodes organic anion transporter 10 (OAT10). It is expressed in the apical membrane of proximal tubular epithelial cells [14]. In vitro analysis showed that OAT10 is a low affinity UA transporter, which has 44% homology with OAT1 and is mainly involved in the reabsorption of UA (Fig. 2) [54]. Insulin can selectively activate its UA transport function [55]. Bahn et al. [54] found that the expression of SLC22A13 in chickens was gender dependent, and the female was higher than the male. However, this gender dependent expression does not seem to exist in humans, because the SUA levels of men is higher than women. Recent studies have also shown that dysfunctional missense mutation of SLC22A13 gene reduced SUA levels and the risk of gout. Meta-analysis displayed that rs117371763 (R377C) variant of SLC22A13 gene has significant anti-gout effect [56]. It is certain that SLC22A13, like SLC22A12, can provide effective targets for the treatment of gout.

SLC2A9  SLC2A9 gene is located on chromosome 4p16.1 and has 13 exons, encoding glucose transporter 9 (GLUT9) with strong UA transport capacity, which is mainly expressed in liver and kidney [15]. Human GLUT9 has two subtypes: GLUT9L and GLUT9S. In proximal tubular epithelial cells, GLUT9L expressed in the basolateral membrane is the only UA efflux transporter [57](Fig. 2); GLUT9S expressed in the apical membrane regulates the reabsorption of UA together with URAT1 [58] (Fig. 2). Therefore, the loss of GLUT9 function will completely inhibit the outflow of UA, thus blocking the reabsorption of UA by the apical membrane UA transporter. It is well known that SLC2A9 gene mutation causes hereditary renal hypouricemia type 2 (RHUC2), which is characterized by severe hypouricemia and easy to be complicated with acute renal failure and renal calculi. Windpessl M et al. found that SLC2A9 gene mutation is a cause of RHUC2 in Austrian native families, especially homozygotes will have severe hypouricemia, and carriers have a higher risk of acute renal injury (AKI) [59]. Moreover, the CC genotype of SLC2A9 SNP rs1172228 in gout patients is significantly associated with renal calculi in Malaysian population [60]. However, consistent with previous results, two variants of SLC2A9 gene (p.V282I:rs16890979 and c.1002 + 78A > G:rs6823877) may be protective factors of gout [51]. Moreover, SLC2A9 SNP rs6293298 attenuates the risk of HUA [61]. In addition, SLC2A9 SNPs affect gout caused by HPRT deficiency and the therapeutic response of allopurinol [5]. Meta-analysis showed that SNP rs16890979, rs1014290 and rs12510549 of SLC2A9 could prevent gout. Among them, rs16890979 was associated with lower gout risk in Caucasians and Asians, rs1014290 was associated with lower gout risk in Asians, and rs12510549 was associated with lower gout risk in Caucasians [62]. SLC2A9 rs3733591 (Arg265His) variant increases the risk of gout [45]. SLC2A9 rs 737267, rs649213 and rs1014290 are associated with gout in the UK, German and Croatian populations, respectively [45]. SLC2A9 rs3775948G and rs13129697G alleles reduce the risk of HUA [63]. Therefore, SLC2A9 SNPs may have a protective effect on gout, but its severe hypouricemia and its complications may endanger the lives of patients. Non-additive genetic interaction between SLC2A9 and insulin related genes also affects SUA [55]. Moreover, this effect is most obvious in women, which is consistent with the greater effect of SLC2A9 on UA in women. Insulin promotes the activity of various UA transporters via activating MAPK p38, MAPK p44/42 and Akt pathways [55]. E4 promoter- binding protein 4 (E4BP4) gene directly binds P2 promoter to down-regulate the expression of SLC2A9 in mouse liver [64].

Genes related to UA excretion  
**ABCG2**  ATP-binding cassette (ABC) transporters belong to the transmembrane protein family and are divided into seven subfamilies: A-G. At present, it is known that there are five members of ABCG subfamily: ABCG1, ABCG2, ABCG4, ABCG5 and ABCG8 [16]. Among them, the ABCG2 gene is located in chromosome 4q22.1, which consists of 16 exons and 15 introns, encoding ABC transporter G2(ABCG2), also known as breast cancer resistance protein (BCRP). ABCG2 is an ATP dependent exogenous transporter, which mediates the excretion of UA (Fig. 2) [65, 66]. Therefore, ABCG2 dysfunction will increase the risk of HUA and gout. Progesterone response factor down-regulates the expression of ABCG2, while estrogen response element up-regulates its expression [67]. GWAS showed that the genetic variation of ABCG2 seems to be one of the reasons for the genetic heterogeneity of ROL and RUE gout [8]. Its pathogenic mutants are considered to be the strongest genetic risk factor for RUE gout and HUA [68]. Among them, rs2231142 (Q141K) variant reduces its allele expression in the kidney and block the excretion of intestinal UA [41]. Furthermore, rs2231142 has gene dose effect on gout [61]. In Xenopus oocytes, insulin could up-regulate
tubular epithelial cells [76]. MRP4 is an ATP depend-
[75]. It is mainly expressed in the basolateral membrane
[17] and encodes multidrug resistance protein 4 (MRP4)
[76]. MRP4 is associated with gout susceptibility in Vietnamese popula-
tion [70]; rs72552713 is expression of ABCG2 [68].

ABCG2 and rs200894058 (S572R) could down-regulate the
expression of mutants Q141K and Q126X can be used to evaluate
ABCG2 activity [73]. The association of A1CF variation
and BAZ1B variation with HUA and gout has also been
centered recently. Intriguingly, these two new variants
appear to be associated with ABCG2 dysfunctional vari-
ants. In other words, when ABCG2 dysfunctional vari-
and A1CF variation exist at the same time, A1CF
variation is significantly correlated with gout, but in the absence of ABCG2 variation, the correlation between
A1CF variation and gout is no longer significant. How-
ever, the BAZ1B variation has a significant correlation
with gout with or without ABCG2 dysfunctional vari-
ation [74]. It can be seen that ABCG2 gene variants and
their SNPs are not only risk factors for HUA and gout,
but also increase the risk of HUA and gout via interacting
with other gene variants.

**ABCC4**

*ABCC* is the largest subfamily of ABC Family with 9 mem-
bers. *ABCC4* gene is located on chromosome13q32.1
[17] and encodes multidrug resistance protein 4 (MRP4)
[75]. It is mainly expressed in the basolateral membrane
of hepatocytes and apical membrane of proximal renal
tubular epithelial cells [76]. MRP4 is an ATP dependent
unidirectional efflux pump, which can participate in the
excretion of UA in proximal tubules in coordina-
tion with BCRP [77] (Fig. 2). miR-124a and miR-506
down-regulate the expression of *ABCC4* [78]. In poultry,
knockdown of *ABCC4* in proximal tubules reduced UA
secretion by 80% [77]. It can be seen that ABCG2 is the
key transporter of UA excretion in poultry kidney. After-
wards, Tanner et al. [79] repeated sequencing of *ABCC4*
in patients with HUA in New Zealand Māori and Pacific,
identified a common variant SNP rs4148500 and a rare
variant P1036L that were significantly associated with
HUA and gout. They also found that the transport activ-
ity of MRP4 seemed to be affected by elevated UA levels,
because the UA transport activity of MRP4 in individuals
with P1036L mutation decreased by 30% compared with
normal controls. Obviously, ABCC4 plays a key role in
maintaining UA homeostasis.

**SLC22A6 and SLC22A8**

Human SLC22A6 and SLC22A8 genes are located on
chromosome 11q12.3. The former encodes organic anion
transporter 1 (OAT1) and the latter encodes organic anion
transporter 3 (OAT3). In the kidney, immunohis-
tochemistry showed that both OAT1 and OAT3 were
located in the basolateral membrane of proximal tubular
epithelial cells [13, 18]. OAT1 and OAT3 not only show
overlapping substrate specificity, but also share transpor-
tation mode and driving force. They are famous multi-
specific drug transporters [80]. The expression of OAT1
and OAT3 are regulated by protein kinase A and C [42].
Inhibition of Wnt signaling pathway down-regulates the
expression of OAT1 and OAT3 [42]. Hepatocyte nuclear
factor 1-α significantly up-regulates the expression of
OAT1 in mouse kidney [81]. Estrogen receptor-α (ER-α)
directly induces the transcriptional expression of OAT1
[82]. cAMP-response element(CRE) regulates the consti-
tutive expression of human SLC22A8 gene [83]. Previous
studies have shown that UA is the endogenous substrate
of OATs [18]. OAT1 and OAT3 participate in the excre-
tion of UA through UA/dicarboxylate exchanger [84]
(Fig. 2). Existing studies have shown that the expression
of OAT1 and OAT3 is decreased in HUA. Recently, it was
found that alcohol-soluble extract increases the expres-
sion of OAT1 in mouse kidney [85]. In addition, the study found that total flav-
onoids of S. glabra has a significant UA lowering effect
in mice, because it can not only up-regulate the expres-
sion of OAT1 in kidney, but also inhibit xanthine oxidase
[86]. Although SLC22A6 and SLC22A8 play a key role in
UA transport, the specific mechanism of these two genes
in HUA and gout still needs to be further studied, so as to
provide new targets for the treatment of HUA and gout.

**SLC17A**

*SLC17A* family transporters are Na⁺ dependent phos-
phate transporters, which can mediate the transmem-
brane transport of organic anions and coordinate UA
excretion [87]. Up to now, there are three major genes in
*SLC17A* family involved in UA transport (Fig. 2): *SLC17A1, SLC17A3* and *SLC17A4*, which all located on
chromosome 6p22.2. Among them, sodium dependent
phosphate transporter 1 (NPT1), encoded by *SLC17A1,*
is located in the apical membrane of renal proximal tubu-
lar epithelial cells [12]. E4BP4 down-regulates the expres-
sion of *SLC17A1* in mouse liver [64]. Sodium dependent
phosphate transporter 4 (NPT4), encoded by SLC17A3, is mainly expressed in the liver and kidney and is involved in the secretion of UA (Fig. 2) and the elimination of various anionic drugs [19]. SLC17A4 encodes sodium dependent phosphate transporter 5 (NPT5), which is mainly expressed in pancreas, liver and intestine [20], but weakly expressed in kidney [12]. Recently, it was found that SLC17A1 and SLC17A3 SNPs are related to SUA levels, which may be involved in the occurrence of gout [65]. SLC17A1 rs1165196 significantly enhances UA secretion and reduces the risk of RUE gout; while rs9393672 and rs942379 are significantly correlated with female SUA [44].

**SLC2A12**

SLC2A12 encodes glucose transporter 12 (GLUT12), which belongs to the same family as GLUT9. It is a physiological UA transporter and is widely expressed in liver and kidney [21]. GLUT12 is a sodium independent bidirectional UA transporter, which may be involved in the transport of UA from blood to liver. In the mouse model of HUA, knockout of SLC2A12 gene causes SLC2A12 dysfunction, which leads to the increase of SUA levels [21]. It can be seen that SLC2A12 deletion mutations may increase the incidence of HUA and gout.

**Other genes involved in UA regulation**

**PDZK1**

PDZ domain-containing 1 (PDZK1) is a scaffold protein located on chromosome 1q21.1 that regulates SUA levels via participating in the assembly of renal UA transporter complex [22]. Although PDZK1 is not directly involved in UA transport, it interacts with C-terminal of various UA transporters, thereby regulating the expression of related proteins [41]. In human embryonic kidney 293 cells (HEK293 cells), co-expression of PDZK1 and URAT1 enhances the transport capacity of UA [77]. PDZK1 rs12129861 is considered as a risk allele for gout [88]. PDZK1 rs1967017 up-regulates the expression of PDZK1 via altering the transcription factor binding site of HNF4A [89]. Long noncoding RNA (IncRNA) PENG up-regulates the expression of PDZK1 via secreting miR-15b [90]. In addition, ABCG2 and PDZK1 gene-gender interactions are associated with gout risk in European populations [91].

**PKD2**

Like ABCG2, PKD2 gene is also located on chromosome 4q22.1 [23, 24], encoding ion channels of transient receptor potential superfamly (TRPP2, PKD2, PC2 or polycystin-2) [92]. It is related to the development, morphology and function of renal tubules and participates in the regulation of intracellular calcium homeostasis and other signal transduction pathways [93]. Studies have confirmed that the epistatic interaction between PKD2 and ABCG2 is associated with the risk of HUA and gout [94]. The interaction between PKD2 SNP rs2725220 and nutritional factors increases the risk of HUA and gout in Koreans [95]. In addition, PKD2 expressed in B cells may be involved in B cell-mediated gout inflammation [96].

**SLC16A9**

SLC16A9 gene encodes monocarboxylic acid transporter 9 (MCT9), which is mainly expressed in kidney, parathyroid gland, trachea, spleen and adrenal gland [12]. MCT9 is mainly involved in the reabsorption of renal UA [41], and its activity is regulated by extracellular H+ and Na+ [97]. In addition, SLC16A9 SNPs are closely related to the occurrence and development of gout. Among them, rs2242206 reduces UA excretion in the intestine, which is significantly correlated with ROL gout, while rs550527563 is dramatically correlated with early-onset gout [98, 99]. Although it has been confirmed that there is a remarkable correlation between SLC16A9 gene and different types of gout, its specific regulatory mechanism is not clear. This suggests that if we can clearly clarify the specific mechanism of SLC16A9 on gout in the future research, which may provide an effective target for the precise treatment of gout.

**CARMIL (LRRC16A)**

CARMIL gene is located on chromosome 6p22.2 and encodes myosin I connectin (CARMIL). It is expressed in kidney and other epithelial tissues and participates in the maintenance of cell shape [25]. CARMIL affects the activity of actin, which interacts with UA transporter and scaffold protein on renal apical membrane, so as to affect the function of UA transporter and indirectly cause the change of SUA levels [100]. A meta-analysis showed that LRRRC16A was related to UA concentration [12]. Subsequently, Sakiyama et al. [100] found that LRRRC16A SNP rs742132 was related to gout susceptibility in Japanese population. Sakiyama and others researchers believe that LRRRC16A may participate in the occurrence and development of gout by affecting the function of UA transporter. However, there are few studies on the relationship between this gene and gout, and the specific regulatory mechanism is not clear.

**SCGN**

SCGN gene is located on chromosome 6p22.2. It encodes secretagogin, which is mainly expressed in neuroendocrine tissues and pancreatic β cells [12]. GWAS showed that SCGN was correlated with SUA levels [12]. In addition, studies on the change of SUA levels caused by this gene mutation have been reported [101]. However, the
relationship between SCGN gene and gout has not been reported.

**MAF**

MAF is a transcription factor [102] involved in the regulation of SUA, which is highly expressed in human and mouse kidneys [103]. MAF gene expression is regulated by two independent upstream genetic signals, of which IncRNA is the most prominent [41]. It not only affects the structure and function of kidney, but also participates in the regulation of renal urate, and is related to SUA and gout susceptibility [104]. Recently, Higashino et al. [104] found that a common variant rs889472 of c-MAF was related to gout susceptibility in Japanese men through univariate logistic regression analysis.

**UMOD**

Uromodulin (UMOD) is encoded by UMOD gene located on chromosome 16p12.3, also known as Tamm-Horsfall protein (THP). It is the major protein secreted in normal urine [26, 27]. Its expression is regulated by transcription factors such as SP1, TP3, POU2F1, STAT3 and RARA [105]. Researchers found that more than 90% of UMOD gene mutations occurred in exons 3 and 4 [27]. This mutation causes autosomal dominant tubulointerstitial kidney disease (ADTKD-UMOD), also known as familial juvenile HUA nephropathy (FJHN) [27, 106]. This disease is an autosomal dominant disease, which is rare in children. It is mainly characterized by HUA, gout and chronic progressive nephropathy [107]. Interestingly, recently, ADTKD-UMOD caused by a new mutation of UMOD gene (c.1648G > A, p.V550I) was found in a 3-year-old Chinese boy [108], and the child showed persistent hematuria. On the contrary, a new UMOD gene mutation (c.163 g > A) was recently identified in the Brazilian family. Although it is related to ADTKD, the affected members do not seem to show HUA and gout [109]. In addition, homozygous mutations in UMOD gene seem to be more prone to early-onset gout [27]. The study found that the methylation level of UMOD in peripheral blood was related to the risk of gout, and its methylation evaluation could predict the risk of gout [110].

**ALDH2**

Aldehyde dehydrogenase 2 family member (ALDH2) gene is located on chromosome 12q24.12 and encodes aldehyde dehydrogenase 2 (ALDH2), which participates in alcohol metabolism. ALDH2 rs671 p.Glu504Lys pathogenic mutant reduces the activity of ALDH2, which is associated with reduced risk of gout [41]. In addition, the rs671 GA + AA genotype was found to be associated with a lower risk of gout, while alcohol and BMI abnormalities were associated with a higher risk of gout in Taiwan population. Moreover, BMI and alcohol have a significant interaction on the risk of gout in patients with GG and GA + AA [111].

**UA regulatory genes related to glycolysis**

In humans, the disorder of glycometabolism can also indirectly affect purine metabolism, thus affecting SUA levels. For example, fructose can indirectly elevate SUA levels via increasing ATP degradation in the liver [112]. Moreover, many genes involved in glycometabolism (such as GCKR; PKLR; MLXIPL; PRKAG2; NFAT5; NF4G, etc.) indirectly affect SUA levels. Current studies have shown that among many genes involved in glycolysis, GCKR gene (located on chromosome 2p23.3) encoding glucokinase regulatory protein seems to be the most important gene affecting SUA levels. Its expression is regulated by lncRNAs ENST00000588707.1 and TCONS_00004187 [113]. Furthermore, GCKR gene mutations accelerate the transition from asymptomatic HUA to gout, and its SNP rs1260326 is associated with a higher risk of gout [114, 115]. Interestingly, GCKR interacts with alcohol to reduce the risk of gout [116].

**Conclusion**

This paper reviews the susceptibility genes and their variants involved in UA transport on HUA and gout. We found that SLC22A family, ABC family and SLC2A family are the most studied gene families among many susceptible genes at present. Interestingly, SLC22A family gene mutations can not only increase the risk of HUA and gout, but also reduce SUA levels and even cause severe hypouricemia. Moreover, some SNPs of SLC22A family (such as rs121907896 and rs121907892) also have significant anti-gout effects.

In summary, genomic studies on UA metabolism contribute to an in-depth understanding of the pathogenesis of HUA and gout. Generally speaking, gene level changes often precede protein level in the process of disease occurrence and development. Therefore, the study of HUA and gout at the gene level is still an important direction of our future research. If we can identify the highly specific and sensitive gene markers of elevated SUA levels, then, it will provide great help for the early diagnosis of HUA and the prevention and targeted treatment of gout patients.

**Abbreviations**

SUA: Serum uric acid; UA: Uric acid; HUA: Hyperuricemia; PRS1: Phosphoribosyl pyrophosphate synthase1; HPRT: Hypoxanthine–guanine phosphoribosyltransferase; PRPP: 5'-Phosphoribosyl-1'-pyrophosphate; IMP: Inosine monophosphate; GMP: Guanosine monophosphate; XO: Xanthine oxidase; LND: Lesch-Nyhan syndrome; APP: β-Amyloid precursor protein; ALDH16A1: Acetaldehyde dehydrogenase 16 family A1; OAT1/3/4/10: Organic anion transporter 1/3/4/10.
transporter 1/3/4/10; SNP: Single nucleotide polymorphism; GWAS: Genome-wide association studies; RUE gout: Renal underexcretion gout; URAT1: Urate transporter 1; RHUC1: Hereditary renal hypouricemia type 1; GLUT9/12: Glucosetransporter 9/12; RHUC2: Hereditary renal hypouricemia type 2; E4BP4: E4 promoter-binding protein 4; AKI: Acute renal injury; BCRP: Breast cancer resistance protein; MRP4: Multidrug resistance protein 4; NPT1/4/5: Sodium dependent phosphate transporter 1/4/5; PDZK1: PDZ domain-containing 1; HEK293 cells: Human embryonic kidney 293 cells; IncRNA: Long noncoding RNA; MCT9: Monocarboxylic acid transporter 9; ROL: Renal overload gout; CARMIL: Myosin I connexin; UMOD: Uromodulin; THP: Tamm-Horsfall protein; ADTKD-UMOD: Autosomal dominant tubulointerstitial kidney disease; FJHN: Familial juvenile hyperuricemia nephropathy.

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