Chapter

Personalized Medicine of Urate-Lowering Therapy for Gout

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Abstract

Gout is a common and complex form of arthritis that is characterized with hyperuricaemia. It is required urate-lowering therapy (ULT) for lifelong management. ULT includes decreasing uric acid product in serum, increasing renal urate excretion and promoting uric acid to allantoin for excretion. Whole genome association studies in gout identified more than 40 genetic loci that influenced the serum uric acid levels. Most associated genes were found to affect renal urate excretion. Pharmacogenetics and pharmacogenomics approaches on ULT had revealed several genes that underlined the effectiveness and the adverse events of medications for gout. Together with the researches on epigenetic factors such as DNA methylations, miRNAs; and the discovery of environmental factors such as microbiota and metabolites, the current progress provides the opportunities for personalized management of ULT for treating hyperuricaemia and gout.

Keywords: gout, hyperuricaemia, pharmacogenetics, pharmacogenomics, urate-lowering therapy

1. Introduction

The term "gout" was firstly used around 1200 AD. It means "a drop" of liquid from the Latin word gutta [1]. The first description of gout as a disease was from Egypt in 2600 BC as arthritis of the big toe. Gout is now referred as a form of inflammatory arthritis characterized by recurrent attacks of a red, tender, hot, and swollen joint [2]. It is one of the most common forms of arthritis and the prevalence is increasing worldwide. The prevalence is various in different regions across the world and is about 1–4%. In westernized countries, the prevalence is about 3–6% in men and about 1–2% in women. Prevalence can increase up to 10% in some countries. For people aged more than 80 years old, it could rise up to 10% in men and 6% in women [3, 4]. In the USA, the prevalence of gout in adults was estimated to be approximately 3.9% [5]. From 1990 to 2015, the number of prevalent gout cases rose by 30% in Nordic region [6]. In China, the pooled prevalence of gout was 1.1% between 2000 and 2016 [7].

Hyperuricaemia is the key biochemical abnormality in gout. Uric acid is a $C_5H_4N_4O_3$ (7,9-dihydro-1H-purine-2,6,8(3H)-trione) heterocyclic organic compound with a molecular weight of 168 Da. Uric acid is the product from the conversion of the two purine nucleic acids, adenine and guanine [8]. Hyperuricaemia is defined as serum urate level more than 0.42 mmol/l. It results in the formation of monosodium urate (MSU) crystals. MSU crystals precipitate within joints and soft tissues to cause an inflammatory response. The prominent clinical features

of gout are attacks of tendonitis, formatting collections of MSU crystals as tophi, joint destruction and chronic gouty arthritis. MSU crystals can also deposit in the interstitium of the kidneys to form renal stones. Hyperuricaemia was associated with hypertension and ischemic heart diseases [9, 10]. The causes of hyperuricaemia are either under excretion of uric acid in the kidneys or increase of production of uric acid in serum [11]. Two key enzymes regulate the production of uric acid. One is xanthine oxidase that makes xanthine to uric acid; the other is urate oxidase that transfers uric acid to allantoin. Allantoin is the end product of purine catabolism in all mammals except humans, great apes, and one breed of dog, the Dalmatian. An animal model of hyperuricaemia from Dalmatian dog revealed the importance of *SLC2A9* gene for uric acid transport in mammals [12]. Together with renal excretion of uric acid, these are three clinical management paths of uric acid to maintain the lower level of uric acid in serum. These include to decrease uric acid production (xanthine oxidase inhibitors—allopurinol, febuxostat), increase renal urate excretion (uricosurics—benzbromarone, probenecid, lesinurad), or promote uric acid to allantoin which is more water soluble and readily excreted (recombinant uricases—pegloticase) [11]. Environmental factors and genetic factors are the major causes to influence the drugs' efficiencies and side effects for gout.

2. Clinical managements of gout

Effective treatment of acute gout attacks and long-term urate lowering therapy are clinical managements of gout. An acute attack should be treated as soon as possible with non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine as first line treatment options. For patients who do not respond NSAIDs or colchicine, systemic corticosteroids generally are applied [13]. Long-term management of gout with ULT is required for patients who are confirmed as diagnosis of gout and tophi. The diagnosis includes more than two times gout attacks per year, renal stones or stage 2 or worse chronic kidney disease. A sustained reduction of serum urate to less than 0.36 mmol/l (6 mg/dl) is generally recommended and a lower target of less than 0.30 mmol/l (5 mg/dl) is recommended in patients with tophi [14, 15]. A xanthine oxidase inhibitor is the recommended as first-line choice for ULT. A uricosuric can be serviced as second-line medication for ULT. It is for patients who do not response xanthine oxidase inhibitors well. Uricases are the third-line treatments for patients who have refractory disease and are intolerant to oral ULTs. Optimizing therapy for improving the outcomes with affordable drugs such as allopurinol, as well as rationalizing the use of new, more expensive agents is an important clinical goal. The roles of pharmacogenetics and pharmacogenomics are becoming more and more important to predict drug response and adverse events of medications. Rationalization and combination of common medications with genetic screening and other environmental factors will revolutionize gout managements in near future.

3. Pharmacogenetics and pharmacogenomics in ULT

"Pharmacogenetics" was a term originally to describe clinical observations of inherited differences in drug effects in 1950s [16]. It is now defined as the study of individual DNA variants that are related to drug responses [17, 18]. Genetic variants also underlie the differential susceptibility to diseases and the sensitivity to drug adverse events. Most drug effects are determined by the interplay of several proteins that influence the pharmacokinetics and pharmacodynamics of medications, including inherited differences in drug targets such as receptors, drug disposition

such as metabolizing enzymes and transporters, drug metabolism, and drug adverse reaction. In human, about 20–95% of variability in drug disposition and effects are determined by genetic polymorphisms in the genome [18]. For all practical purpose, the terms pharmacogenetics and pharmacogenomics may be synonymous, but pharmacogenomics normally refers genome-wide approaches to investigate all genes in the genome that influence drug responses while pharmacogenetics implies the study of a single gene's interactions with drugs. The pharmacogenomics approach tends to be applied to identify genes in the search for novel drug targets. This is in contrast to traditional drug design that depends on a prior knowledge of the target and is based on high-throughput screening to identify small-molecule antagonists or agonists.

3.1 Genetic and genomic approaches of hyperuricaemia and gout

Genetic approaches for complicated diseases and associated traits such as gout and hyperuricaemia are to identify genetic variants in genome that underlie the diseases and syndromes. There are many kinds of genetic variants in human genome. Single nuclear polymorphisms (SNPs) are the most frequent variants found in the genome, accounting for 90% of human genetic variation. Total 84.7 million SNPs were found in 26 human populations [19]. SNPs can be found within coding sequences and noncoding regions of genes, as well as within intergenic regions. Insertion and deletion of short segments of DNA (INDEL) is another type of common polymorphism. More than 3.6 million short insertions/deletions are distributed throughout the human genome, with approximately 36% of them being located within promoters, introns, and exons of known genes [19, 20]. They can have a significant impact on gene function not only when present in exonic coding sequence but also when within a gene intron [21]. Variable number of tandem repeats (VNTRs) polymorphisms is widespread in the genome and contain variable numbers of repeated nucleotide sequences that result in alleles of varying lengths. VNTR loci typically have high levels of heterozygosity that make them very informative for genetics research. There are about 60,000 structural variants around human genome [19]. Inversions may involve larger regions of the genome in which a segment of a chromosome is reversed end to end and occur when a chromosome breaks in two places. A copy number variant (CNV) is a segment of DNA for which there are more than two copies in the genome. The genetic segment involved may range from one kilobase to several megabases in size [22]. Many techniques can allow the detection and discovery of CNVs including cytogenetic techniques such as fluorescent in situ hybridization, comparative genomic hybridization, array comparative genomic hybridization, and by large-scale SNP genotyping.

The genetic approaches to hyperuricaemia and gout include candidate gene studies, positional cloning studies and genome-wide association studies (GWASs). Candidate gene study needs to have relatively big case and control groups to increase the power for statistical analysis. Positional cloning is another genetic approach that identifies disease genes by progressive dissection of linkage regions that are consistently co-inherited with the disease. Nowadays, GWASs have been rapidly changing the landscape of the search of the genes that underlie complicated diseases such as hyperuricaemia and gout. It is a powerful approach to overcome the limitations of candidate gene and positional cloning studies. It examines the relationships between allele frequencies and disease status or associated traits with a large number of genetic polymorphism markers covering of whole genome [23]. GWASs provide the opportunity to identify novel mechanisms of disease pathogenesis that are caused by previously unsuspected genes or regulatory regions. About 10,000 strong associations have been reported between genetic variants and one or more complex traits [24].

3.2 GWASs for hyperuricaemia and gout

More than 30 GWASs papers on hyperuricaemia and gout have been published so far. The first GWAS study identified the associations of three genetic loci with uric acid concentration and risk of gout [25]. The three loci were *SLC2A9*, *ABCG2* and *SLC17A3*. Since then, many GWSs papers have been published across the world and discovered more than 40 genes that showed the associations with hyperuricaemia or gout. Many genes identified by GWASs encode urate transporters and interacting proteins. The identified genetic variation can only explain less than 10% level of variance for serum uric acid levels [26]. The rest could be explained by environmental factors and the interactions of genetic factors and environmental factors. We listed 10 genes that were frequently identified in GWASs studies worldwide in **Table 1** and also discussed the genes' potential function roles in regulating uric acid metabolism in serum.

3.2.1 SLC2A9

SLC2A9 was a gene that was identified in almost every GWAS across the world. The gene is located on human chromosome 4p16 and encodes a member of the

Genes	Encoded protein	Chr.	Ref.	Populations	Possible function roles
SLC2A9	Solute carrier family 2 member 9: GLUT9	4p16	[25, 27–37]	African, Asian, European	Regulating renal and gut excretion of uric acid
ABCG2	ATP binding cassette subfamily G member 2	4q22	[25, 29, 30, 33, 35, 36, 45]	Asian, European	Regulating extra-renal uric acid under-excretion
SLC17A cluster	Sodium phosphate transporters	6p22	[25, 33, 35, 45]	Asian, European	Regulating renal and excretion of uric acid
GCKR	SIS (Sugar ISomerase) family protein	2p23	[33, 35, 45]	Asian, European	Regulating glucokinase in cells
SLC22A cluster	Integral membrane proteins	11q12	[28–30, 33, 35, 45]	African, Asian, European	Preventing potentially harmful organic anions
PDZK1	PDZ domain-containing scaffolding protein	1q21	[33, 35, 36]	Asian, European	Regulating the high-density lipoproteins
INHBC and INHBE	TGF-beta superfamily of proteins	12q13	[33, 45]	Asian, European	Regulating numerous cellular processes
A1CF	APOBEC1 complementation factor	10q11	[33, 35]	Asian, European	Regulating RNA-binding subunit
MAF	Leucine zipper-containing transcription factor	16q23	[30, 33]	Asian, European	Regulating several cellular processes
SLC16A9	Solute carrier family 16 member 9	10q21	[33, 35]	Asian, European	Regulating monocarboxylic acid transporter

Chr: chromosome; Ref: reference.

Table 1.
The 10 most replicated genes in GWAS studies for hyperruricemia and gout.

SLC2A facilitative glucose transporter family GLUT-9. The associations with hyperuricaemia and gout were found in populations from Africa American, Asia, Europe and the United States [25, 27–37], but not found in Hispanic American [38]. Variation in *SLC2A9* was the most statistically significant genetic determinant of serum urate; accounting for 3.4–8.8% of the variance in women and 0.5–2.0% of the variance in men [25, 31, 34, 37, 39, 40]. The encoded protein is involved in p21-activated protein kinase (PAK) pathway for transport of glucose, bile salts, organic acids, metal ions and amine compounds. Recent studies showed that GLUT-9 was participated in renal and gut excretion of uric acid and was implicated in antioxidant defense [41–43]. There are two distinct N-terminal isoforms of human GLUT-9: GLUT-9a (540 residues) and GLUT-9b (511 residues) [44]. These isoforms are generated by alternative splicing of 5′ ends and differ in membrane trafficking. GLUT-9b has a more substantial role in urate homeostasis than GLUT-9a. GLUT-9a is likely to function as the exit site for urate from proximal tubule cells, whereas GLUT-9b might transport urate into the proximal tubule cells across the apical membrane [26].

3.2.2 ABCG2

ABCG2 gene is located in human chromosome 4q22. It encodes ATP binding cassette subfamily G member 2. ABC proteins transport various molecules across extra- and intra-cellular membranes. The gene was also found to have associations with hyperuricaemia and gout in Asian, European and the United States [25, 29, 30, 33, 35, 36, 45]. The gene product is involved primarily in extra-renal uric acid under-excretion. Multiple transcript variants encoding different isoforms had been found for this gene [46]. ABCG2 is expressed in the brush border membrane of the proximal tubules of the kidney and has a role in the apical [47]. The ABCG2 Q141 K variant is highly likely to be causal and results in internalization of *ABCG2*, which can be rescued by drugs [48]. The SNP rs2231142 in *ABCG2* gene had significant associations between gout and controls, between gout and hyperuricaemia, and between hyperuricaemia and controls, respectively. In a cell model investigation it showed significantly higher IL-8 release from endothelial cell (EC) combined with *ABCG2* knockdown [49]. The Glu141Lys polymorphism was accounted for 0.57% of the variation in serum urate from a meta-analysis of GWAS data [35]. The polymorphism had a significantly larger effect on serum urate levels in men than in women. The Glu141Lys substitution was shown that it caused a 53% reduction in the rate of ABCG2-assocaited urate transport [35]. The polymorphism of the gene could also affect the response to allopurinol [50].

3.2.3 SCL17A gene cluster

SCL17A gene cluster is located on human chromosome 6p21 containing three members of the *SLC17* gene family (*SLC17A3, SLC17A1* and *SLC17A4*). The polymorphisms of the genes were identified as a significant predictor of uric acid levels and gout in many GWASs [25, 33, 35, 45]. The strongest association was with SNP rs1165205 within intron 1 of *SLC17A3*. The *SLC17A3* gene encodes a sodium phosphate transporter (NPT4) which is expressed at the apical membrane of renal proximal tubule cells. The *SLC17A1* gene lies immediately downstream of *SLC17A3* and encodes sodium phosphate transporter NPT1, which is expressed in the human kidney and can transport uric acid in vitro [51]. SNP rs1183201 within *SLC17A1* was identified as the strongest predictor of serum urate in a meta-analysis of GWAS [35]. Further investigations will be required to identify the causal SNPs in the gene cluster that regulate uric acid levels and susceptibility to gout [52].

3.2.4 GCKR

GCKR gene is located on human chromosome 2p23. The gene encodes a protein belonging to the glucokinase regulator (GCKR) subfamily. It inhibits glucokinase in liver and pancreatic islet cells by binding non-covalently to form an inactive complex. This gene is also considered a susceptibility candidate gene for a form of maturity-onset diabetes of the young (MODY) and it has been found to have association with gout or hyperuricaemia in many populations [25, 33, 35, 45].

3.2.5 SLC22A cluster

SLC22A cluster is located on human chromosome 11q13. The cluster contains *SLC22A11* and *SLC22A12*. The encoded proteins are involved in the sodium-independent transport and excretion of organic anions. They are integral membrane proteins and are found mainly in the kidney and in the placenta, where they may act to prevent potentially harmful organic anions from reaching the foetus. The cluster was found to have associations to hyperuricaemia and gout in many populations [28–30, 33, 35, 45]. Selected rare variants in SLC22A12 were validated in transport studies, confirming three as loss-of-function (R325W, R405C, and T467M) and providing the therapeutic potential of the new URAT1-blocker lesinurad [53].

3.2.6 PDZK1

PDZK1 gene is located on human chromosome 1q21. This gene encodes a protein containing a PDZ domain. It mediates the subcellular localization of target proteins. *PDZK1* mediates the localization of cell surface proteins and plays an important role in cholesterol metabolism by regulating the high-density lipoproteins (HDL) receptor. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene. The gene was showed to have associations with gout and hyperuricaemia in many populations [33, 35, 36]. The maximally associated genetic variant SNP rs1967017 at the *PDZK1* locus was found to elevated *PDZK1* expression. Transcriptional factor hepatocyte nuclear factor 4 alpha (HNF4A) physically binds the rs1967017 region. The urate-raising T allele of rs1967017 enhances HNF4A binding to the *PDZK1* promoter to increase *PDZK1* expression [54].

3.2.7 INHBC and INHBE

The INHBC and INHBE genes are located on human chromosome 12q13. The genes encode members of the TGF-beta (transforming growth factor-beta) superfamily of proteins. These proteins were implicated in regulating numerous cellular processes including cell proliferation, apoptosis, immune response and hormone secretion. They may be upregulated under conditions of endoplasmic reticulum stress, and may inhibit cellular proliferation and growth in pancreas and liver. The GWAS investigation found the genes had associations with gout and hyperuricaemia in some populations [33, 45].

3.2.8 A1CF

The *A1CF* gene is located on human chromosome 10q11. The encoded protein has three non-identical RNA recognition motifs and belongs to the heterogeneous ribonucleoproteins (hnRNP) family of RNA-binding proteins. It has been proposed that this complementation factor functions as an RNA-binding subunit and docks APOBEC-1 to deaminate the upstream cytidine. Studies suggest that the protein may

also be involved in other RNA editing or RNA processing events. Several transcript variants encoding a few different isoforms have been found for. This gene was showed to have associations with gout and hyperuricaemia in some populations [33, 35].

3.2.9 MAF

The *MAF* gene is located on human chromosome 16q23. The encoded protein is a DNA-binding, leucine zipper-containing transcription factor and acts as a homodimer or as a heterodimer. It plays a role in the regulation of cellular processes, development, apoptosis and chondrocyte differentiation. Two transcript variants encoding different isoforms have been found for this gene. The polymorphisms of the gene were showed to have associations with gout and hyperuricaemia in some populations [30, 33].

3.2.10 SLC16A9

The *SLC16A9* gene is located on human chromosome 10q21. The encoded protein has importer activity and monocarboxylic acid transmembrane transporter activity. GWAS studies found gene to have associations with gout and hyperuricaemia in some populations [33, 35].

GWASs also discovered other genes in some populations. These genes were *TRIM46, ACVR2A, LRP2, CNTN4, MUSTN1, SFMBT1, FAM134B, TMEM171, RREB1, VEGFA, SGK1, MLXIPL, PRKAG2, STC1, HNF4G, A1CF, DIP2C, SLC16A9, OVOL1, HNF1A, ACVR1B, ACVRL1, USP2, ATXN2, TSHR, IGF1R, NFAT5, HLF, BCAS3, PRPSAP1, ALDH16A1, ZNF160* [55]. It is likely these genes contribute small portion of risks in the development of hyperuricaemia and gout. Other genes that are responsible for some Mendelian syndromes are also associated with hyperuricaemia and gout. These genes are *HPRT1, PRPS1, G6PC, SLC37A4, AGL, PYGM, PFKM, AMPD1, CPT2, AMPD1, ACADS, ALDOB, UMOD*. These are responsible for the diseases caused congenital errors of purine metabolism, excessive cell death and urate generation and reduced renal excretion of uric acid [26].

3.3 Pharmacogenetics and pharmacogenomics of LUT for gout

The current pharmacogenetics and pharmacogenomics majorly focus on the medications on the three paths that balance the uric acid levels in the serum. Together with treating acute gout, there are about 10 genetic loci that modify the common medications' effectiveness or adverse events in gout management.

3.3.1 The genes that influence xanthine oxidase inhibitors (XOIs)

XOIs are the first line medications in the long-term treatment of hyperuricaemia and gout. Allopurinol and febuxostat are two important XOIs. Allopurinol is transformed into its active metabolite oxypurinol that reversibly blocks xanthine oxidase while febuxostat is a non-purine-selective inhibitor of xanthine oxidase [56]. Allopurinol is a common efficacious ULT but it associates with rare serious adverse drug reactions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [57]. The human leukocyte antigen B allele *HLA-B*5801* was reported to be a genetic marker for allopurinol-induced side effects [58, 59]. Strong associations between *HLA-B*5801* and allopurinol-induced TEN/SJS were found in Hong Kong [60], Korea [61] and Thailand [62]. Genome-wide association study of Stevens-Johnson syndrome and toxic epidermal necrolysis also confirmed that the *HLA-B*5801* allele was associated with allopurinol-induced symptoms in Europe [63]. Patients who are *HLA-B*5801* carriers can be alternatively given febuxostat.

The clinical consideration is the cost of febuxosat as it is much higher than the administration of allopurinol. There is a paucity of evidence about economic value of such testing as allopurinol is an affordable medication. Testing *HLA-B*5801* prior to allopurinol management is cost-effective for Asians and African American, but not for Caucasians or Hispanic in the United States [64]. In Thailand it was also shown highly potential cost-effective intervention [65]. Chinese Han population is a high risk group of the side-effects of allopurinol [14]. In our previous retrospective investigation of *HLA-B*5801* in hyperuricaemia patients in a Han population of China, we found 30 carriers of *HLA-B*5801* allele in 253 cases of hyperuricaemia or gout patients in Chinese Han population (11.9%). Most importantly allopurinol was prescribed in both *HLA-B*5801* positive and negative groups. We also assessed four models with or without genetic screening and management of allopurinol or febuxostat, the results indicated the *HLA-B*5801* screening had significant cost benefit for clinical management for gout patients. The other alleles of HLA locus (for example *HLA-B*1502*) are also responsible for SJS/TEN induced by other drugs [66]. The prevalence of *HLA-B*5801* in hyperuricaemia patients in a Han population of China indicated the importance of genotyping the allele to prevent the severe side-effects induced by allopurinol. *HLA-B*5801* should be screened in all allopurinol-induced TEN patients no matter what their races are. To all SJS/TEN patients, if allopurinol was not administrated, other HLA allele screening should be considered [67, 68]. HLA-DR9 and HLA-DR14 were also found to have associations with the allopurinol induced hypersensitivity in hematologic malignancy [69]. Genetic variation in aldehyde oxidase (AOX1), encoding the enzyme responsible for the conversion of allopurinol to oxypurinol, also was reported to be associated with allopurinol dose and change in serum urate [70]. *ABCG2*, encoding an efflux pump, was associated with SUA reduction and a missense allele (rs2231142) was associated with a reduced response to allopurinol [50].

3.3.2 The genes that influence uricosurics

Uricosurics are the second line of choice to treat hyperuricaemia and gout clinically. Currently three medications are working as uricosurics for renal excretion of uric acid. They are probenecid, benzbromarone (BBR) and lesinurad. BBR and its metabolite 6-hydroxybenzbromarone block the renal reabsorption of uric acid by inhibiting URAT1 in proximal renal tubular cells [11]. BBR undergoes hepatic hydroxylation to 1′-hydroxy BBR and 6-hydroxy BBR. The BBR elimination in serum was affected by genetic polymorphism in drug metabolism [71]. It was demonstrated that CYP2C9 was the main enzyme responsible for the 6-hydroxylation of BBR [72, 73]. *CYP2C9* is highly polymorphic gene and it has around 57 variant alleles [11]. SNP rs1799853 (Cys144Arg) and SNP rs1057910 (Ile359Leu) were the most common poor metabolizer polymorphisms, existing in about 15–22% of Caucasians and 1–9% of Africans. SNP rs1799853 was rare in Asians, while rs1057910 frequencies range from 2 to 11% [74]. rs1799853 could typically results in a 20–30% reduction in maximum velocity (Vmax) for drug substrates whereas rs1057910 can reduce Vmax by as much as 70% [75]. The 144Arg substitution could affect the interaction of CYP2C9 with CYP450 reductase [76], whereas the 359Leu substitution can alters substrate recognition [77]. *CYP2C9*3* homozygotes have significantly reduced clearance of BBR and therefore may be at increased risk of hepatotoxicity [78].

3.3.3 The genes that influence uricase

Rasburicase is an urate oxidase. It is a peroxisomal liver enzyme to catalyze the oxidation of uric acid into the more water-soluble substrates. Urate oxidase is an

endogenous enzyme can be found in most mammals but not in humans. The inactivation of the hominoid urate oxidase gene was caused by independent nonsense or frame-shift mutations during evolution [79] . Two nonsense mutations were found in the human urate oxidase gene that makes it non-functional in human [80, 81]. Pegloticase is a recombinant uricase for the treatment of severe, treatment-refractory, chronic gout. It is a third-line treatment for patients who do not tolerate to other treatments [56, 82]. Pegloticase also catalyze uric acid to allantoin which is 5–10 times more soluble than uric acid. Pegloticase is in pegylated form so it can increase its elimination half-life from about 8 hours to 10 or 12 days, and this can decrease the immunogenicity of the foreign uricase protein. Among patients with chronic gout, the use of pegloticase 8 mg either every 2 weeks or every 4 weeks for 6 months resulted in lower uric acid levels compared with placebo [56]. A case of pegloticase-related methemoglobinemia and haemolytic anaemia was reported as it was cause by two mutations in glucose-6-phosphate dehydrogenase (*G6PD*) gene known to confer G6PD deficiency [83]. It was recommended that avoiding the use of rasburicase in patient's homo/hemizygous for G6PD variants that confer deficiency [84].

Loci	Chr	Affecting drug	Uric acid path or gout	Key reference	Pharmaceutical effects
HLA-B5801	6p21	Allopurinol	Uric acid formation, XO inhibitors	[58]	Adverse effect: drug allergic response
HLA-DR9	6p21	Allopurinol	Uric acid formation, XO inhibitors	[69]	Adverse effect: inducing hematologic malignancy
HLA-DR14	6p21	Allopurinol	Uric acid formation, XO inhibitors	[69]	Adverse effect: inducing hematologic malignancy
AOX1	*2q33*	Allopurinol	Uric acid formation, XO inhibitors	[70]	Dose and change in serum urate
ABCG2	*4q22*	Allopurinol	Uric acid formation, XO inhibitors	[50]	Reducing dose response
CYP2C9	10q23	Benzbromarone	Uric acid renal excretion	[71]	Reducing drug clearance and hepatic failure
G6PD	Xq28	Pelgoticase	Uric acid transforming	[83]	Adverse effects: inducing haemolytic anaemia
PTGS2	1q31	NSAID	Acute gout	[86]	Drug response: Aspirin insensitivity
ITGA2	5q11	NSAID	Acute gout	[88]	Drug response: Aspirin insensitivity
ABCB1	7q21	Colchicine	Acute gout	[90]	Drug response

Table 2.
The pharmacogenetic loci that regulating ULT.

3.4 The genes that influence medications for acute gout

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to quickly relieve the pain and swelling of an acute gout episode and can shorten the attack, but NSAIDs may not be suitable for patients with other comorbidities. A proton pump inhibitor should be offered to people at high risk of NSAID-related gastrointestinal complications [85]. Cyclooxygenase-2 (COX-2) is encoded by prostaglandin-endoperoxide synthase 2 (*PTGS2*). COX-2 catalyzes arachidonic acid to prostaglandin (PG) G2 and H2. A promoter SNP variant of PTGS2-765G>C (rs20417) was shown evidence of association with NSAID response [86, 87]. A recent meta-analysis reported a significant association of the variant with aspirin insensitivity in Chinese population [88]. The variant rs1126643 of integrin subunit alpha 2 gene (*ITGA2*) genetic defects might also increase the risk of having aspirin insensitivity [88]. Colchicine works by decreasing swelling and lessening the build-up of uric acid crystals that cause pain in the affected joint (s). ATP binding cassette subfamily B member 1 (*ABCB1*) gene is highly polymorphic and codes for the drug efflux pump MDR1, and as such is considered an important gene that influences drug metabolisms [89]. The occurrence of colchicine unresponsiveness was significantly higher in patients who were homozygous or heterozygous for the major allele (*ABCB1* 3435C) than in minor allele homozygotes [90]. To date, there is no information on whether these polymorphisms are associated with nonresponse in patients with gout.

The potential pharmacological loci for hyperuricaemia and gout were listed in **Table 2**.

4. Epigenetic factors and environmental factors for hyperuricaemia and gout

4.1 DNA methylation

GAWs have identified dozens of loci associated with gout, but for most cases, the risk genes and the underlying molecular mechanisms contributing to these associations are unknown. Epigenetics studies investigate heritable change in gene expression caused by molecules that bind to DNA without change the actual DNA sequence. There are three main classes of epigenetic marks as DNA methylation, modification of histone tails and noncoding RNAs. DNA methylation has been found to associate with many complicated diseases. Hypomethylation at the promoter region of the gout-risk gene *NRBP1* can lead to enhanced gene expression both in vitro and in vivo, contributing to the development of gout [91]. Chinese Han population with gout had a significant association between *CCL2* promoter hypomethylation and the risk of the disease [92]. Hypermethylation of uromodolin (UMOD) observed in gout patients might reduce the gene expression, leading to an augmented risk of gout [93]. A research on genetic variations in the DNA methyltransferases (DNMTs) gene identified *DNMT1* SNP rs2228611 polymorphism may be involved in the pathogenesis of gout [94].

4.2 miRNA

MicroRNAs (miRNAs) are non-coding RNA species that are highly evolutionarily conserved in human. Up to 5000 miRNAs were identified in human cells. miRNAs are key regulators of the expression of numerous targets at the post-transcriptional level [95]. They are implicated in various cell processes including

cell differentiation, metabolism, and inflammation. Experimental evidence suggests that metabolic deregulation is a commonality between these different pathological entities, and that miRNAs are key players in the modulation of metabolic routes [96]. Recent studies have shown that interleukin (IL)-1β is a key inflammatory mediator in acute gouty arthritis (GA), and its level is regulated by miRNAs. Five miRNAs (hsa-miR-30c-1-3p, hsa-miR-488-3p, hsa-miR-550a-3p, hsa-miR-663a, and hsa-miR-920) were found to possibly target IL-1β. MSU crystals in GA patient could inhibit expression of miR-488 and miR-920 and the two miRNAs could directly target the 3′-UTR of IL-1β [97]. MSU crystal-induced IL-1 secretion can be targeted for the new therapeutic strategies in the treatment of acute gout [98].

4.3 Exosomes

Exosomes are best defined as extracellular vesicles that are released from cells upon fusion of an intermediate endocytic compartment, the multivesicular body (MVB), with the plasma membrane. Exosomes can be produced by most cell types. Exosomes derived from immunosuppressive dendritic cells (DCs) have been found to confer potent and lasting immunosuppressive effects, similar to their parental DC [99, 100]. Their protein content largely reflects that of the parental cells and is enriched in certain molecules including adhesion molecules, membrane trafficking molecules, cytoskeleton molecules, heat-shock proteins, cytoplasmic enzymes, signal transduction proteins, and cell-specific antigens [101–103]. Exosomes also contain functional mRNA and microRNAs molecules [104]. Certain types of exosomes have been shown to confer immunosuppressive effects in different disease models including RA and gout. It is likely that exosomes represent a novel effective and safe therapeutic approach for treating arthritis [105]. In a neutrophil-derived microvesicles (PMN-Ecto) studied for a murine model of MSU-induced. PMN-Ecto from joint aspirates of patients with gouty arthritis had similar anti-inflammatory properties [106]. In a study for investigating the effects of MSU on synovial fibroblasts to elucidate the process of MSU-mediated synovial inflammation, human synovial fibroblasts were stimulated with MSU in the presence or absence of serum amyloid A [107]. MSU stimulation resulted in the activation of caspase-1 and production of active IL-1β and IL-1α. These findings provide insight into the molecular processes underlying the synovial inflammatory condition of gout [108].

4.4 Microbiota

The human microbiota consists of the 10–100 trillion symbiotic microbial cells in each person including primarily bacteria in the gut. The human microbiome refers the genes these cells harbor [109]. Microbiota was found to play the important roles for the development of personalized medicine. Whole microbial genome sequencing revealed the extraordinary diversity of microorganisms and their vast genetic and metabolic repertoire [110]. In a cohort study with 33 healthy and 35 gout patients, the intestinal microbiota of patients were highly distinct from healthy individuals in both organismal and functional structures. In gout, there were more Bacteroides caccae and Bacteroides xylanisolvens, there were less or absence Faecalibacterium prausnitzii and Bifidobacterium pseudocatenulatum. Intestinal microbiota of gout is more similar to those of type-2 diabetes than to liver cirrhosis, whereas depletion of Faecalibacterium prausnitzii and reduced butyrate biosynthesis were shared in each of the metabolic syndromes [111].

4.5 Metabolites

Metabolites are the intermediate products of metabolic reactions catalyzed by various enzymes that naturally occur within cells and play vital roles in cell growth, differentials and proliferations. In a study analyzing 355 metabolites in 1764 individuals and constructed a metabolite network around serum urate. The effect of sex and urate lowering medication on all 38 metabolites assigned to the three network. The three network included the well-known pathway of purine metabolism, as well as several dipeptides, a group of essential amino acids, and a group of steroids. Of the 38 assigned metabolites, 25 showed strong differences between sexes. The findings highlight pathways that are important in the regulation of serum urate and suggest that dipeptides, amino acids, and steroid hormones are playing a role in its regulation [112].

4.6 The relationships between genetic factors and environmental factors for hyperuricaemia and gout

The genetic influence and environmental factors should be considered equally importance for hyperuricaemia and gout. Determining the extent to which environmental versus genetic factors are responsible for particular phenotypes such as gout or hyperuricaemia is a central question in gout or hyperuricaemia research. Elucidating associations between genotype and phenotype has been a central goal in human health research for some time [113]. The complications in cellular process of hyperuricaemia mean many genes may have interactions with each other for the regulation of the products of uric acid in cells; they may not be identifiable even in approaches with GWASs. The environmental factors can also interact with genetic factors that make the process even more complicated. For clinicians, it is important to understand the etiological causes for complicate diseases and always consider both genetic and environmental factors play important roles in hyperuricaemia and gout.

5. Personalized medicine for ULT and gout

The personalized medicine aims to provide the right treatments in the right time for individual patients with hyperuricaemia and gout. The genetics variants that underlie diseases and influence the medications will play great roles for the management of gout in near future. Therapeutics best suited for an individual's genotype genetic origins of disease and drug response for LUT including adverse events. Precision medicine has made great progress due to the rapid development of pharmacogenomics research. Clinically, patients' age, race, and gender are all associated with epigenetic status [114]. Together with the developments of miRNA profiling, epigenetics investigation, metabolites screening and microbiota research it will make personalized medicine possible for gout management.

5.1 Intrinsic factor assessment

For intrinsic factor assessment, patients age, gender, geographic residence, social economic status and other conditions for heart, kidney and liver, allergic status are all important factors to be considered for clinical managements of hyperuricaemia and gout. These factors should be considered to decide the medication choice, the dosage of medications. The decision should be managed to benefit for individual patients with hyperuricaemia and gout.

5.2 The life style assessment

In clinical practice, lifestyle changes are frequently urged for prevention and management of gout [115]. It is advocated to promote healthy eating and drinking for gout patients, such as reducing intake of beer, sugar-sweetened drinks, and purine-rich foods such as meat, offal and seafood. Increased intake of cherries, omega-3 fatty acids, low fat milk and coffee are also advocated [116]. There was evidence for a non-additive interaction of sugar-sweetened drinks consumption with a urate-associated variant of *SLC2A9* for the risk of gout [117] . Alcohol intake with T allele of lipoprotein receptor-related protein 2 gene (*LRP2*) rs2544390 was reported in determining the risk of hyperuricaemia and gout [118, 119].

5.3 The genetic inheritance and epigenetic affect

The studies of genetic inheritance of gout and hyperuricaemia provide a lot useful information. More than 40 genetic loci only can explain less than 10% of high uric acid levels in serum. We also need to consider the genetic background in different ethnical populations. The further efforts will be to understand the functional roles of the novel genes in the pathways of uric acid metabolism. The investigation can identify the new pharmacological target for gout and bring new therapeutic tools from preventing to treating gout patients [55]. miRNAs and epigenetic screening are also helpful to identify the regulator elements for potential gout gene's expression.

5.4 Microbiome and metabolite factors

Microbiome and metabolite factors are also need to be considered when managing gout patients clinically. At the present times, not enough reports have been published in the field. It can be useful to exam the intestinal levels of Bacteroides caccae, Bacteroides xylanisolvens, Faecalibacterium prausnitzii, Bifidobacterium pseudocatenulatum in gout patients. Screening key metabolites in serum may also helpful in clinical management of gout and hyperuricaemia patients.

5.5 The pharmacogenetic consideration

Total about 10 genetic loci were identified to influence the medications of gout. These loci can be used to predict the drug's response and adverse effects. For

Assessments	Considering factors
Intrinsic factor assessment	Age; gender; geographic residence; other conditions for heart, kidney and liver, allergic history etc
Life style assessment	Diet and activities; the in-taking of food with rich purines—such as meat, poultry, and seafood; alcohol consumption etc
Genetic inheritance	Suspected gene screening such as *SLC2A9, ABCG2, GCKR*, *PDZK1* and other SLC loci etc.
Epigenetic factors	miRNA; methylation screening for suspected loci; histone methylation etc
Environmental factors	Microbiota; metabolites screening
Pharmacogenetics consideration	For NSAIDs, screening *PTGS2, ABCG2;* for colchicine, screening *ABCB1;* for XO inhibitor allopurinol, screening *HLA-B5801, HLA-DR9, HLA-DR14, AOX1* and *ABCG2;* for Benzbromarone, screening *CYP2C9; for* Pelgoticase, screening *G6PD*

Table 3.
Personalized medicine approaches for management of LUT for gout.

treating acute gout with NSAIDs, *PTGS2, ABCG2* should be screened as the variants affect aspirin sensitivity. For colchicine treatment, *ABCB1* should be screened as the variant affect drug's response; For XO inhibitor allopurinol, *HLA-B5801*, *HLA-DR9*, *HLA-DR14*, *AOX1*and *ABCG2* should be screened as the variants may induce adverse events or response changes. For benzbromarone, *CYP2C9* should be screened as the variant may affect drug clearance and cause side effects. For pegloticase, *G6PD* should be screened as the variant may have adverse effects to induce haemolytic anaemia.

The personalized factors have been summarized in **Table 3**.

6. Summary

Personalized medicine has made great progress due to the development of the technology in genetic and genomic approaches. The ultimate goal for personal medicine of gout management is to provide the best medical advice and best medical treatment according to conditions of individual patients. The patient conditions including age, gender, ethnic group, life styles, genetic variations for common gout associated genes are important factors for clinical managements. Most importantly the pharmacogenetic loci for the common medications for gout provide useful guidance for individual patients. The developments of miRNA profiling, epigenetics investigation, metabolites screening and microbiota research will make personalized medicine even more in great details for management. It will revolutionize medical cares for gout patients in near future.

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Abbreviations

ABC	ATP-binding cassette
ABCB1	ATP binding cassette subfamily B member 1
ABCG2	ATP binding cassette, subfamily G, member 2
ADRB3	adrenergic receptor beta-3
AHS	allopurinol hypersensitivity syndrome
BBR	benzbromarone
CCA4	congenital cerulean cataract 4
COX2	cyclooxygenase-2
CNV	copy number variant
DCs	dendritic cells
DNMTs	DNA methyltransferases
EC	endothelial cell
GA	gouty arthritis
GCKR	glucokinase regulator
GWAS	genome-wide association study
G6PD	glucose-6-phosphate dehydrogenase
HDL	high-density lipoproteins
hnRNPs	heteregeneous ribonucleoproteins
HNF4G	hepatocyte nuclear factor 4 gamma

HNF4A	hepatocyte nuclear factor 4 alpha
HLA	human leukocyte antigen
INDEL	insertion and deletion of short segments of DNA
ITGA2	integrin subunit alpha 2
LRP2	lipoprotein receptor-related protein 2
miRNA	micro RNA
MODY	maturity-onset diabetes of the young
MSU	monosodium urate
MVB	multivesicular body
NSAIDs	nonsteroid anti-inflammatory drugs
PAK	p21-activated protein kinase
PTGS2	prostaglandin-endoperoxide synthase 2
SAA	serum amyloid A
SCAR	serious cutaneous adverse reactions
SNPs	single nuclear polymorphisms
siRNA	small interfering RNA
SJS	Stevens-Johnson syndrome
SU	serum urate
SUA	serum uric acid
TEN	toxic epidermal necrolysis
TGF	transforming growth factor
ULT	urate-lowering therapy
UMOD	uromodolin
Vmax	maximum velocity
VNTRs	variable number of tandem repeats
XOI	xanthine oxidase inhibitor

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