ABCG2 transporter: Structural and functional associations with gout (Review)

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Abstract. ATP-binding cassette sub-family G member 2 (ABCG2) is a key regulator of urate homeostasis, and its dysfunction is a major genetic risk factor for hyperuricemia and gout in humans and animals. Initially, ABCG2 was known for its role in multidrug resistance. ABCG2 has since been identified as a high-capacity urate efflux pump, located at the apical membranes of renal proximal tubules, intestinal enterocytes and hepatic canaliculi. The present review covers the molecular structure, physiological functions and pathophysiological effects of ABCG2, with particular focus on the common Q141K (rs2231142) loss-of-function variant. The Q141K variant impairs protein stability and trafficking, reducing urate transport and increasing the risk of gout and cardiorenal comorbidities. The present review explores the central role of ABCG2 within the urate transportome, highlighting its contrasting and cooperative interactions with reabsorptive and secretory transporters, as well as its regulation by novel mechanisms, including the gut microbiome and microbial metabolites. These observations have significant clinical implications for pharmacogenomic approaches, as Q141K variant carriers exhibit a reduced response to uricosuric drugs. The present review also highlights emerging treatments that go beyond standard urate-lowering therapies, including ABCG2 activators, microbiome modulators and gene-editing techniques, offering a potential shift toward personalized gout prevention and treatment. Understanding the multifaceted role of ABCG2 is essential for developing targeted strategies to address the root cause of impaired urate excretion.

Contents

1. Introduction

Hyperuricemia (HUA) and its clinical manifestation, gout, a major metabolic disease, are recognized by the World Health Organization as major global health challenges (1). Gout is considered to be a major cause of disability and is closely associated with metabolic syndrome comorbidities (2,3). Fundamentally, gout is a disorder of urate homeostasis that occurs when serum urate concentrations exceed their physiological solubility limit (4). Physiologically, HUA is defined by elevated serum urate levels [typically >6.8 mg/dl (400 μmol/l)] (5-7). Serum urate homeostasis can be influenced by sex hormones, with men typically exhibiting higher concentrations (5.0-7.0 mg/dl) than premenopausal women (4.0-6.0 mg/dl) (5,8,9). Elevated urate levels promote the

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formation of monosodium urate crystals, which deposit in joints and soft tissues, triggering an inflammatory cascade characteristic of gouty arthritis (10). Globally, the prevalence of gout is rising, with cases projected to increase by >70% from 2020 to 2050, reaching ~95.8 million (11). This trend is mainly driven by dietary transitions toward purine-rich and fructose-laden foods, as well as by increasing obesity rates and aging populations (3,12,13).

The impact of HUA extends beyond human health to animal husbandry. In poultry, uric acid is the primary nitrogenous waste product, with serum concentrations typically ranging between 5 and 7 mg/dl; however, this can exceed 20 mg/dl under conditions of renal failure. This sharp elevation precipitates visceral gout, a fatal condition that results in high mortality rates and substantial economic losses due to reduced productivity (14,15). Research using animal models has enhanced the mechanistic understanding of the disease, as uricase-deficient mice exhibit sustained serum urate levels of 5-6 mg/dl, whereas wild-type mice require higher inducer doses to develop persistent HUA leading to gouty arthritis and renal injury, thereby closely mirroring human pathophysiology (16-18). Untreated conditions can cause chronic joint damage, tophus formation, and increased risks of kidney and cardiovascular diseases (4,19).

Urate homeostasis is maintained through a delicate balance between production and excretion. Uric acid production arises from the metabolism of purines derived from dietary sources (red meat and seafood), as well as endogenous purine nucleotide turnover, with the final conversion to uric acid catalyzed by xanthine oxidase (8,20,21). Nutritional factors serve a pivotal role in urate metabolism; high purine and fructose intake, as well as high-protein/high-calcium diets in poultry, can lead to urate overproduction and precipitate HUA (22,23). However, most patients with gout experience impaired urate excretion rather than overproduction as the main underlying disorder (2). Approximately two-thirds of systemic urate clearance occurs in the kidney, with the proximal tubule handling an intricate process of glomerular filtration, reabsorption and secretion (24). This process is controlled by reabsorbing and excreting transporters, including urate transporter 1 [URAT1; solute carrier family 22 member 12 (SLC22A12)] and glucose transporter 9 [GLUT9; solute carrier family 2 member 9 (SLC2A9)] for reabsorption, and sodium-dependent phosphate transporter 1 [NPT1; solute carrier family 17 member 1 (SLC17A1)], organic anion transporter 1 [OAT1; solute carrier family 22 member 6 (SLC22A6)], organic anion transporter 3 [OAT3; solute carrier family 22 member 8 (SLC22A8)] and ATP-binding cassette (ABC) sub-family G member 2 (ABCG2) for secretion (25,26). The intestine provides a vital complementary excretory route, in which transporters such as ABCG2 mediate direct urate secretion into the gut lumen, compensating for renal excretory dysfunction (27,28).

For decades, the ABC transporter ABCG2 [also known as breast cancer resistance protein (BCRP)] has been investigated primarily for its role in multidrug resistance, as it mediates the efflux of chemotherapeutic agents from cancer cells (29,30). The paradigm shifted when a genome-wide association study (GWAS) identified ABCG2 as a key urate transporter strongly associated with HUA and gout (26). This observation revealed a critical physiological role of ABCG2 as a high-capacity urate efflux pump localized to the apical membranes of renal proximal tubules, intestinal enterocytes and hepatic canalicular membranes, which contributes to renal, intestinal and biliary urate excretion (31,32). The pathophysiological relevance of ABCG2 is highlighted by the Q141K (rs2231142) polymorphism, which disrupts protein folding and trafficking, resulting in a 50% reduction in urate excretion (33). This variant is considered to be the primary cause of gout in East Asian populations (31,33). Beyond genetic factors, ABCG2 expression can be influenced by environmental factors, including gut microbial metabolites such as butyrate, which can upregulate transporter expression (34), as well as sex hormones such as estrogen, which may partially explain sex differences in urate levels (35). ABCG2 emerges as a key regulator of urate homeostasis and a multifunctional protein with antioxidant and immunomodulatory roles (36). It is important to explore its multifunctional contributions to HUA and gout to develop an advanced mechanistic understanding and for therapeutic development. The present review covers its molecular structure, regulatory mechanisms, pathophysiological roles, clinical importance and potential as a therapeutic target in HUA and gout.

2. ABCG2: Overview of a urate efflux transporter

Uric acid homeostasis: A delicate balance. The pathogenesis of HUA and gout results from disruption in uric acid homeostasis, reflecting an imbalance between uric acid production and excretion (37,38). Urate production via the metabolic breakdown of both dietary purines (abundant in foods such as red meat and seafood) and endogenous purine nucleotides is catalyzed by xanthine oxidase (8,39,40). Urate is the final product of purine nucleotide degradation via the salvage pathway, which involves enzymes such as adenosine deaminase and purine nucleoside phosphorylase, as well as the *de novo* pathway, regulated by phosphoribosyl pyrophosphate synthetase (PRPS) (41,42). Although enzymatic mutations in PRPS or hypoxanthine-guanine phosphoribosyltransferase cause overproduction of urate in conditions such as PRPS superactivity or Lesch-Nyhan syndrome, the majority of patients with gout exhibit HUA primarily due to impaired excretion rather than overproduction (43-45). Excretion of uric acid involves two principal pathways: Renal excretion, which accounts for approximately two-thirds of daily uric acid excretion, and extra-renal elimination through the intestines, which accounts for the remaining one-third (27). Therefore, the uric acid balance reflects a carefully regulated interaction between purine metabolism and multi-organ excretion pathways. Disruptions in urate balance, particularly due to transporter dysfunction, can lead to HUA and its progression to gout (26,46).

From drug resistance to urate transport: Rediscovery of ABCG2. The role of ABCG2 in urate homeostasis represents a compelling narrative of scientific rediscovery, illustrating how unbiased genetic approaches can reveal unexpected physiological functions of well-characterized proteins (33,47). ABCG2 is a prominent member of the ABC transporter superfamily, a large group of membrane proteins that utilize ATP hydrolysis to drive substrate translocation across cellular membranes (48).

Initially, ABCG2 was identified in chemotherapy-resistant breast cancer cells and referred to as BCRP and was characterized as a potent efflux pump mediating multidrug resistance by actively transporting a broad spectrum of chemotherapeutic agents out of cancer cells (49,50). Its substrate spectrum, including mitoxantrone, topotecan, doxorubicin and numerous tyrosine kinase inhibitors, makes it a significant obstacle in cancer treatment (51,52). Beyond oncology, ABCG2 has been recognized as a crucial component of physiological barriers, with expression at the apical membrane of enterocytes, hepatocytes and endothelial cells of the blood-brain barrier. At these sites, it limits the oral bioavailability and tissue penetration of numerous pharmaceuticals (for example, fluroquinolones, rosuvastatin, mitoxantrone and topotecan), while protecting against xenobiotic accumulation (53). The paradigm-shifting discovery emerged from GWASs, which revealed genetic variants influencing serum urate concentrations. These studies identified the ABCG2 locus as having one of the strongest associations with HUA and gout risk (54,55). This finding was remarkable because it revealed that common genetic variants in ABCG2, specifically the single-nucleotide polymorphism (SNP) rs2231142 at position 141 (Q141K), are not only modulators of drug response but also key determinants of human metabolic disease (56,57). A functional study confirmed that ABCG2 serves as a high-capacity urate transporter, and that the Q141K variant impairs plasma membrane localization and activity, thereby elevating serum urate levels (58). This rediscovery of ABCG2 broadened the understanding of its biological function, thereby establishing it as a key player in drug disposition and a critical regulator of metabolic homeostasis (59,60). This convergence of cancer biology and metabolic disease research offers novel insights for understanding transporter physiology, pharmacogenetics and the intricate regulation of urate balance, while demonstrating how genetic approaches can elucidate novel functions of previously characterized proteins and bridge different areas of biomedical research (31,61).

Tissue expression and apical localization. The physiological role of ABCG2 in urate homeostasis is critically defined by its tissue-specific expression and apical membrane localization (32), where it functions as a high-capacity urate efflux transporter, mediating urate excretion into renal tubular lumen and intestinal lumen (62). In the kidney, ABCG2 is expressed on the apical membrane of proximal tubular epithelial cells and transports urate from the cytosol into the urine duct (31,32,63). This apical localization of ABCG2 complements the activity of reabsorptive transporters such as URAT1 and GLUT9 by facilitating urate efflux into the tubular lumen, thereby counterbalancing reabsorption and contributing to the regulation of renal urate handling (64). Similarly, in the intestine, ABCG2 is highly expressed on the apical membrane of enterocytes, particularly in the ileum and jejunum, where it mediates urate excretion into the intestinal lumen (63,65). This intestinal pathway accounts for approximately one-third of systemic urate elimination in humans, underscoring its physiological significance (66). In addition, in the liver, ABCG2 is expressed at the canalicular membrane of hepatocytes, where it contributes to biliary excretion of substrates, including limited amounts of urate (67). Although biliary urate clearance is quantitatively minor compared with renal and intestinal excretion, its presence reflects the broad role of transporters in systemic detoxification (68). Together, this coordinated multi-organ apical localization establishes ABCG2 as a master regulator of urate excretion, functioning as a molecular gatekeeper that safeguards against urate accumulation and the pathological crystallization underlying HUA and gout (69).

3. Molecular architecture of the ABCG2 transporter

Structural and dysfunctional variants of ABCG2 are associated with impaired urate transportation and gout susceptibility (Fig. 1) (31,32,55,70-77). In addition to illustrating the domain organization of ABCG2 and the localization of gout-associated variants, Fig. 1 summarizes the downstream inflammatory and systemic consequences of impaired urate clearance. Reduced ABCG2 function promotes systemic urate accumulation and monosodium urate crystal deposition in articular and extra-articular tissues (58). In joints, urate crystals act as danger-associated molecular patterns and activate innate immune pathways via TLR2/4-, NF-κB-, ROS- and NLRP3 inflammasome-mediated signaling (76,77). This leads to caspase-1 activation, maturation of IL-1β and IL-18, recruitment of neutrophils, formation of neutrophil extracellular traps, dendritic-cell activation, granulomatous inflammation, tissue necrosis, and ultimately pain and disability (78,79). In severe or extra-articular disease, extensive urate deposition may contribute to visceral gout, ischemic tissue injury, systemic inflammation and, in complicated cases, sepsis-like clinical deterioration or death (80-83). These immune and systemic events are included in Fig. 1 to provide a mechanistic overview of how ABCG2 dysfunction-driven HUA may progress from urate accumulation to gouty inflammation and severe pathological outcomes, while the main focus of the present review remains ABCG2-mediated urate transport in HUA and gout.

Gene structure and genetic variants. The ABCG2 gene, located on human chromosome 4q22, spans ~66 kilobases and comprises 16 exons and 15 introns, encoding a 655-amino acid protein (62-64). This gene product functions as a half-transporter, requiring homodimerization to form a functionally active unit (84-86). The promoter region of ABCG2 is characterized by the absence of a TATA box and a high CpG content, forming a CpG island that is subject to epigenetic regulation (87,88). Within the ABCG2 promoter, critical regulatory elements have been mapped, including aryl hydrocarbon receptor (AhR) response elements involved in xenobiotic induction, NF-κB binding motifs that regulate ABCG2 expression in response to inflammatory signaling, and hypoxia inducible factor 1α sites that mediate hypoxia-driven transcriptional responses (89,90). The most clinically significant genetic variant is the SNP c.421C>A (rs2231142), which causes a glutamine to lysine substitution at codon 141 (Q141K) within the nucleotide-binding domain (NBD) (91,92). The Q141K mutation compromises NBD structural integrity by disrupting hydrogen-bond networks, leading to protein misfolding, ubiquitin-mediated proteasomal degradation (93) and an ~50% reduction in

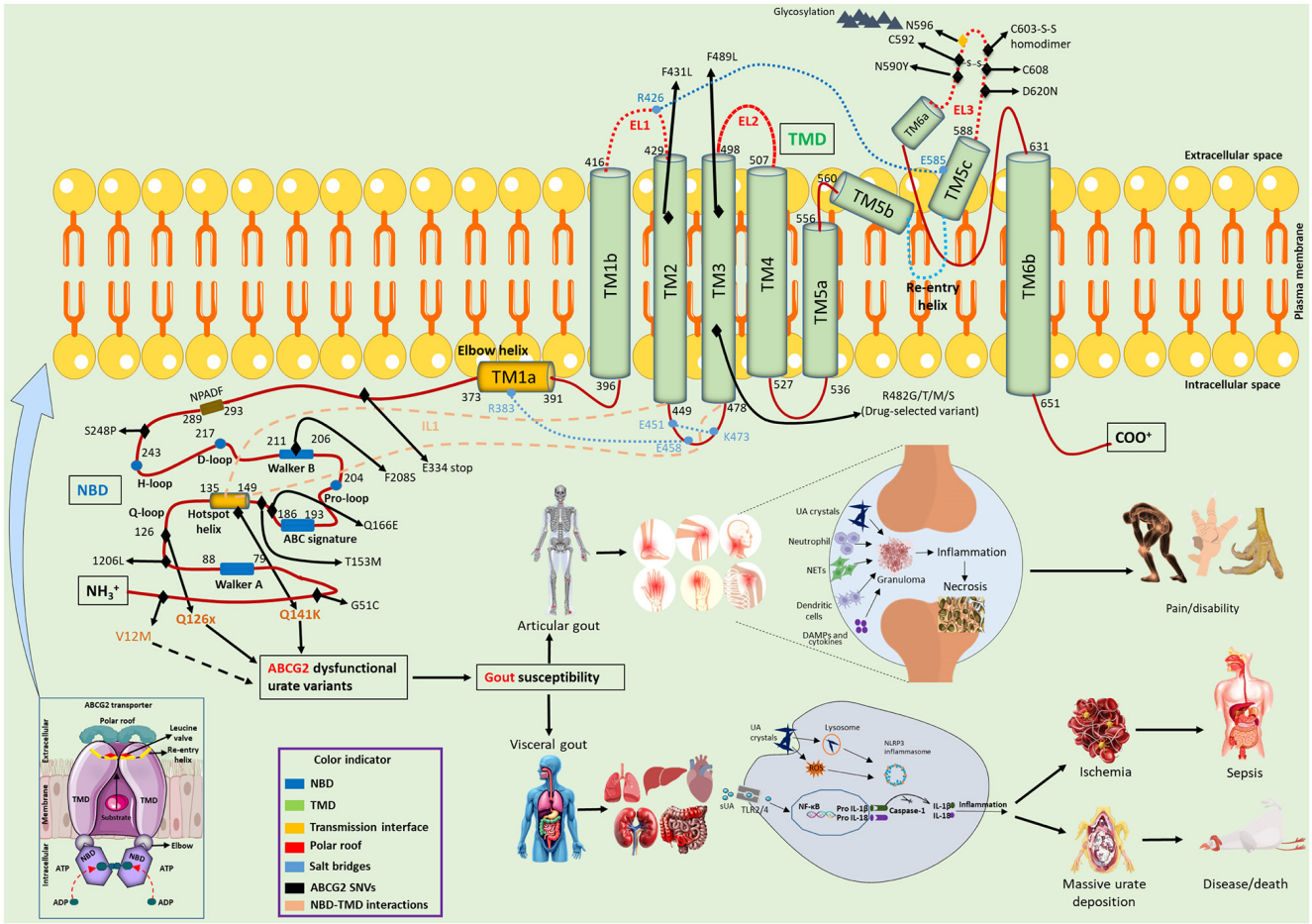

Figure 1. Structural topology and dysfunctional variants of ABCG2 associated with urate transport deficiency and gout susceptibility. Schematic representation of the structural organization of the ABCG2 transporter showing the NBD and TMD containing six transmembrane helices (TM1b, TM2, TM3, TM4, TM5a, TM5b, TM5c and TM6b), the elbow helix and the re-entry helix. Key motifs involved in ATP binding and hydrolysis (ABC signature, and Walker A and B), along with associated regulatory motifs such as Q-loop, D-loop, H-loop and Pro-loop, are indicated. Colored lines represent transmission interfaces, salt bridges, and domain interactions between the NBD and TMD. Functionally critical SNVs such as V12M, Q126x and Q141K are located within regions critical for urate transport. These dysfunctional variants impair urate efflux, resulting in hyperuricemia, monosodium urate crystal deposition and associated inflammatory responses, including articular and visceral gout, ischemia, tissue necrosis, and death. Color coding denotes structural features: NBD (blue), TMD (green), transmission interface (yellow), polar roof (red), salt bridges (blue dashed lines), ABCG2 SNVs (black) and NBD-TMD interactions (orange). ABCG2, ATP-binding cassette sub-family G member 2; NBD, nucleotide-binding domain; TMD, transmembrane domain; TM, transmembrane helix; SNV, single nucleotide variant; UA, uric acid; NETs, neutrophil extracellular traps; DAMPs, damage-associated molecular patterns; NLRP3, NOD-like receptor family pyrin domain-containing 3; TLR2/4, toll-like receptor 2/4; ROS, reactive oxygen species; ABC, ATP-binding cassette; EL, extracellular loop; sUA, serum uric acid.

urate transport due to impaired membrane localization (94). Beyond the Q141K variant, post-transcriptional mechanisms serve a key role in regulating ABCG2 expression, with the 3'untranslated region (UTR) containing binding sites for microRNAs (miRNAs/miRs) such as miR-519c and miR-520h, which suppress translation and contribute to tissue-specific expression patterns (95,96). Furthermore, the c.421C>A mutation itself creates a novel binding site for miR-124, adding an extra layer of regulation that contributes to the reduced expression observed in Q141K variant carriers (97). Epigenetic modifications, including promoter CpG island DNA methylation and histone acetylation, dynamically regulate gene expression in response to environmental stimuli and are notably altered in drug-resistant cancers, such as breast cancer, colorectal cancer and leukemia (98). Evidence from animal models underscores the functional importance of genetic variation in ABCG2. In Chinese Holstein cattle, nonsynonymous SNPs (Y367C and R578Q) alter the secondary structure of the protein, increasing random coil and turn formations while reducing β-sheet content, thereby modifying substrate transport specificity (99). Abcg2/Bcrp1 expression is 13.8-fold higher in hepatic oval cells than in differentiated hepatocytes in rodent models, suggesting a specialized protective role for the transporter in progenitor cell populations against xenobiotic insult (100). These findings across species highlight that genetic and epigenetic variation in ABCG2 is a key factor in explaining differences among individuals in transporter function, with profound implications for urate homeostasis, drug disposition and disease susceptibility.

Homodimeric structure: NBD and transmembrane domain (TMD). The functional unit of ABCG2 is an obligate homodimer, a quaternary structure that is fundamental to its mechanism as an active efflux pump (51,101). This architecture, requiring the assembly of two identical

half-transporter subunits, distinguishes ABCG2 within the ABC superfamily (102). Unlike full-length transporters (such as P-glycoprotein), which possess two NBDs and two TMDs within a single polypeptide, ABCG2 exists as a 'half-transporter', with each monomer containing only one NBD and one TMD (103,104). Therefore, homodimerization via non-covalent interactions at the NBD interface is essential for creating a functioning transporter capable of ATP hydrolysis and substrate translocation, with each monomer organized into distinct structural modules (105,106). The TMD consists of six α-helices that traverse the lipid bilayer, forming the substrate-binding cavity (107). This cavity binds a structurally diverse array of molecules, from chemotherapeutic drugs, such as mitoxantrone, to the endogenous metabolite urate. The structural specificity of the TMD, aided by specific residues lining the binding pocket, enables this broad substrate specificity (108). The NBD, connected to the TMD, is located in the cytoplasm and contains the conserved motifs responsible for ATP binding and hydrolysis, including the Walker A and Walker B motifs, and the ABC signature (commonly referred to as 'C' motif), which is positioned at the NBD dimer interface and interacts with the ATP-binding site of the opposing monomer (109,110). A defining feature of the homodimeric structure is the 'head-to-tail' arrangement, in which the NBDs of the two monomers dimerize asymmetrically such that the Walker A and Walker B motifs of one NBD interact with the ABC signature ('C') motif of the opposing NBD, forming two composite ATP-binding sites at the dimer interface, while the TMDs align to create the substrate translocation pathway (111). This assembly creates two composite ATP-binding sites at the dimer interface, which is a prerequisite for the cooperative ATP hydrolysis that powers the transport cycle (112). High-resolution structural biology, particularly cryo-electron microscopy (cryo-EM), has been instrumental in visualizing this arrangement, revealing not only the precise orientation of the transmembrane helices and the NBD dimer but also the critical role of the membrane environment, including lipid-protein interactions, in stabilizing transmembrane domain architecture, regulating substrate access and facilitating the conformational transitions required for the transport cycle (113,114). Bound phospholipids and cholesterol molecules intercalate within the TMDs, acting as structural co-factors that stabilize the dimer and potentially modulate its function (115). Furthermore, structural analysis of the common Q141K gout risk variant provides mechanistic insights into its loss of function, as the substitution of glutamine with lysine at position 141 in the NBD disrupts key hydrogen-bonding networks, and impairs communication between the ATP-binding site and the transmembrane helices, thereby reducing transport efficiency (116). The functional significance of this homodimeric structure is evolutionarily conserved. In poultry, the Abcg2 gene encodes a homologous half-transporter, and a promoter study has identified regulatory elements such as CpG islands and transcription factor binding sites for Sp1 and NF-κB, suggesting conserved mechanisms that control its expression (117). The obligate homodimeric nature of ABCG2 is therefore not merely a structural curiosity but the fundamental basis of its role as a versatile efflux pump, governing its catalytic mechanism, substrate recognition and regulatory potential.

4. Q141K variant: Dysfunction and disease

The Q141K polymorphism (rs2231142) is one of the most clinically significant genetic variants in urate homeostasis, serving as an example of how single amino acid changes can disrupt protein function and lead to systemic metabolic disease (118,119).

Molecular pathogenesis: Impaired folding and trafficking. The Q141K variant (c.421C>A) of ABCG2 is among the most clinically relevant genetic alterations influencing urate homeostasis and drug disposition (120). This nonsynonymous SNP results in a glutamine-to-lysine substitution at position 141 within the NBD of the transporter (96,121). The mutation profoundly impairs ABCG2 function through combined structural, cellular and regulatory mechanisms, making it a key molecular determinant of HUA and gout risk (122,123). In the wild-type protein, Q141 forms a stabilizing hydrogen bond with N158 in a neighboring α-helix, thereby facilitating the conformational changes required for ATP binding and hydrolysis (124). The Q141K variant mutation disrupts this bond, destabilizes the structure and uncouples ATP hydrolysis from transport, thereby impairing urate efflux (31). At the cellular level, the Q141K variant exhibits defective protein folding and trafficking, thereby reducing ABCG2 delivery to the plasma membrane (125). *In vitro* studies using mammalian expression systems have shown that the ABCG2 Q141K variant undergoes enhanced ubiquitination and proteasomal degradation, resulting in a shortening of its half-life and markedly limiting surface expression (126,127). Membrane localization assays consistently demonstrate that only a fraction of Q141K variant protein reaches the apical membrane of polarized epithelial cells compared with the wild-type protein (128,129). This impaired trafficking contributes substantially to reduced functional capacity, and a study using transfected cell models and membrane vesicles has suggested that the Q141K variant retains only 50% of wild-type urate transport activity (125). The deficit arises from both reduced transporter density at the cell surface and diminished turnover efficiency (130). Beyond quantitative impairment, the ABCG2 Q141K variant exhibits altered substrate recognition, characterized by modified specificity and increased sensitivity to pharmacological inhibitors, including tyrosine kinase inhibitors and certain statins (70,131). The molecular pathology of the ABCG2 Q141K protein variant is further exacerbated by post-transcriptional regulation, whereby the c.421C>A polymorphism that gives rise to the Q141K substitution has also been reported to create a novel miRNA binding site within the 3' UTR of ABCG2 mRNA (132). This mechanistic insight explains the heightened susceptibility to drug-drug interactions in individuals with the variant, underscoring its clinical relevance beyond urate metabolism (8). This c.421C>A polymorphism facilitates selective miRNA binding, leading to translational repression and tissue-specific suppression of expression. This regulatory mechanism may explain the tissue-dependent manifestation of the Q141K variant protein phenotype, particularly its stronger impact in the kidney and intestine, which are the main sites of urate clearance (33). Human genetic and population-based GWASs consistently identify the ABCG2 Q141K variant as a major determinant of HUA and gout, demonstrating strong

associations with elevated serum urate levels across diverse ethnic groups (73,133,134). Consistent with these findings, animal models reinforce the pathogenic role of the ABCG2 Q141K variant, as knock-in mice with the orthologous mutation exhibit defective intestinal and renal urate clearance, recapitulating the human phenotype (135). These molecular pathologies collectively explain its strong clinical association with HUA, gout and drug sensitivity, establishing the ABCG2 Q141K variant as a central target for pharmacogenetic research and therapeutic intervention. Studies have also demonstrated associations between other variants and HUA and gout risk (Table I) (136-151).

Clinical sequelae: HUA, gout and beyond. The ABCG2 Q141K variant has wide-ranging clinical implications because it impairs ABCG2 transporter function, thereby contributing to HUA and gout, and influencing drug disposition, disease progression and the therapeutic response. Clinical data indicate that carriers are more likely to progress to tophaceous gout and experience increased flare frequency, reflecting its role in sustaining urate burden (82). A hallmark of Q141K variant-associated disease is the variability in treatment response, as carriers often exhibit reduced efficacy of uricosuric agents, such as benzbromarone and lesinurad, due to impaired intestinal and renal urate excretion that cannot be fully restored pharmacologically (8,129). Furthermore, altered ABCG2 function affects the pharmacokinetics of xanthine oxidase inhibitors (XOIs), as the Q141K variant reduces intracellular transport of allopurinol and its active metabolite oxypurinol, leading to suboptimal urate-lowering in some carriers (152). Similar effects are observed with febuxostat, where impaired efflux alters drug disposition (153,154). These findings underscore the need for precision dosing in managing HUA among Q141K variant carriers, as the variant contributes not only to articular disease but also to the renal and extra-renal complications (155). Epidemiological studies have demonstrated an association between the Q141K variant of ABCG2 and uric acid nephrolithiasis, likely due to impaired intestinal urate clearance, which shifts urate elimination toward the kidney and increases urinary uric acid load (156,157). *In vivo* mouse models of HUA and gout support this mechanism, as they exhibit HUA, elevated urinary urate levels and heightened susceptibility to crystal-induced renal injury compared with wild-type controls (18,158). Beyond articular manifestations, the Q141K variant may exacerbate systemic conditions, including hypertension, insulin resistance and coronary artery disease, via urate-mediated endothelial dysfunction, oxidative stress and chronic inflammatory pathways that are central to cardiometabolic disease (159,160). The Q141K variant influences not only urate metabolism but also drug pharmacology and toxicity, as ABCG2, a pleiotropic transporter with broad substrate specificity, mediates the transport of diverse compounds, including chemotherapeutics such as mitoxantrone, topotecan and methotrexate (30,161). *In vitro* studies have demonstrated that Q141K variant-expressing mammalian cell lines exhibit reduced drug efflux, increased intracellular accumulation of chemotherapeutic drugs and enhanced drug-induced cytotoxicity (128,162). Clinically, this variant has been linked to a higher risk of drug toxicity in patients with cancer, suggesting that pharmacogenetic testing may be warranted in chemotherapy protocols (163). The convergence of human epidemiology, animal knock-in models and mechanistic studies emphasizes the unique role of ABCG2 in health and disease, supporting the value of integrating ABCG2 genotyping into precision medicine frameworks for both metabolic disorders and pharmacotherapy. The role of ABCG2 and associated transporters in the disposition of representative drugs and drug classes, including transporter-mediated mechanisms, pharmacokinetic/pharmacodynamic relevance, associated adverse effects and therapeutic categories, are summarized in Table II (164-192).

Population genetics and ethnic disparities. The ABCG2 Q141K variant (c.421C>A; rs2231142) shows pronounced ethnic and regional variation, contributing to population-level differences in urate metabolism and gout prevalence (119,193). GWASs and large-scale population studies have demonstrated that the minor A allele (lysine at position 141) is most prevalent in East Asian individuals (27-35%), occurs at intermediate frequencies in European individuals (8-11%) and is relatively rare in African individuals (1-3%) (194,195). These population patterns suggest evolutionary selection, potentially influenced by dietary transitions, pathogen burden or the adaptive advantage of specific transporter variants (163). The higher allele frequency in East Asian populations results in a disproportionately greater population-level risk of HUA and gout (196). In Japanese cohorts, the Q141K variant is estimated to account for ~10% of total gout cases and almost 30% of early-onset cases (129). These findings highlight the strong impact of this variant in populations with high prevalence, helping explain ethnic disparities in gout epidemiology. In African ancestry populations, the low prevalence of the Q141K variant partly explains its limited contribution to disease burden despite gout being influenced by other genetic and environmental factors (197). Notably, its functional impact on urate handling is genotype-dependent. Cohort studies have revealed a gene-dosage effect of the ABCG2 Q141K variant on serum urate levels, with heterozygotes showing intermediate increases and homozygotes exhibiting the highest levels and the greatest risk of HUA (198,199). Such a gene-dosage pattern underscores the mechanistic role of this variant as a loss-of-function allele, where decreased expression and impaired trafficking compromise urate excretion in the kidney and intestine (200). The Q141K variant exerts a comparable impact on serum urate levels across populations despite wide differences in allele frequency. Meta-analyses of GWAS data have demonstrated that each copy of the A allele increases serum urate levels by 0.2-0.3 mg/dl, regardless of population origin (201,202). This suggests that the molecular consequences of the Q141K variant substitution are functionally consistent across genetic backgrounds, and that population-level differences mostly result from variations in allele frequency rather than differences in penetrance (118). Nonetheless, the clinical impact of the Q141K variant is shaped by gene-environment interactions, as evidenced in East Asian and Polynesian cohorts, where carriers adopting Westernized diets rich in purines, alcohol and fructose show a substantially higher gout risk compared with those maintaining traditional dietary patterns (203). A similar trend has been observed in a migrant study, in which carriers of the Q141K variant showed

Table I. ATP-binding cassette sub-family G member 2 variants associated with HUA and gout.

Authors, year	Nucleotide variants	Localization	Pathological risk	(Refs.)
Matsuo *et al*, 2009; Zámbó *et al*, 2020	V12M (rs2231137)	N-terminal	Controversial association with gout	(137,138)
Higashino *et al*, 2017; Gotanda *et al*, 2015	Q126X (rs72552713)	NBD	HUA, early risk of gout	(139,140)
Roberts *et al*, 2017; Limviphuvadh *et al*, 2018	Q141K (rs2231142)	NBD	HUA, gout risk	(141,142)
Zámbó *et al*, 2018; Stiburkova *et al*, 2017	R147W (rs372192400)	NBD	HUA, gout risk	(143,144)
Stiburkova *et al*, 2017; Toyoda *et al*, 2019	T153M (rs753759474)	NBD	Impaired urate transport, HUA	(144,145)
Ishikawa *et al*, 2010; Skoglund *et al*, 2014	F208S (rs1061018)	NBD	Impaired urate transport, HUA	(136,146)
Zelinski *et al*, 2012; Tanaka *et al*, 2014	R246X (rs200190472)	NBD	Gout risk	(147,148)
Skoglund *et al*, 2014	P269S (rs34678167)	Linker	Gout risk	(136)
Mózner *et al*, 2019; Higashino *et al*, 2017	K360del (rs750972998)	Linker	HUA, gout risk	(139,149)
Zámbó *et al*, 2020; Toyoda *et al*, 2019	F373C (rs752626614)	Linker	HUA, gout risk	(138,145)
Stiburkova *et al*, 2017; Zámbó et al., 2020	T421A (rs199854112)	ECL1	HUA, gout risk	(138,144)
Stiburkova *et al*, 2017; Zámbó *et al*, 2020	T434M (rs769734146)	TMD2	HUA, gout risk	(138,144)
Higashino *et al*, 2017; Sjöstedt *et al*, 2017	S441N (rs758900849)	TM2	Absence of urate transport, gout	(139,150)
Stiburkova *et al*, 2017; Toyoda *et al*, 2019	S476P (rs752408502)	TM3	HUA, gout risk	(144,145)
Ishikawa *et al*, 2010; Deppe *et al*, 2014	F489L (rs192169063)	TM3	Impaired urate, gout risk	(146,151)
Stiburkova *et al*, 2017; Toyoda *et al*, 2019	S572R (rs200894058)	TM5	HUA, gout risk	(144,145)
Mózner *et al*, 2019; Toyoda *et al*, 2019	D620N (rs34783571)	ECL3	HUA, gout risk	(145,149)

HUA, hyperuricemia; NBD, nucleotide-binding domain; TM, transmembrane helix; ECL1, extracellular loop 1; ECL3, extracellular loop 3; TMD, transmembrane domain.

Table II. Role of ABCG2 and related transporters in drug transport and therapeutic pathways.

Authors, year	Drug/class	Localization	Transporters involved	Transporter-mediated disposition and interaction mechanisms	PK/PD	Adverse effects	Therapeutics	(Refs.)
McDonagh *et al*, 2014; Wright *et al*, 2010	Uricosurics	Kidney	ABCG2, NPT1, NPT4, OAT1, OAT3	Uric acid excretion into the glomerular filtrate/ lumen	PD	Gout and impaired uric acid secretion	Musculoskeletal agents	(168,169)
Barnes *et al*, 2007; Mazaleuskaya *et al*, 2015	Acetaminophen	Liver	ABCC2, ABCB1, ABCG2, ABCC4, ABCC5	Excretion of acetaminophen into the bile	PK	Fever and pain	Pain, anti-inflammatory and immunomodulating agents	(170,171)
Crumpacker, 1996; Maillard *et al*, 2022	Acyclovir/ ganciclovir	Liver	ABCG2, ABCC4, OAT1, OAT2, OAT3	Excretion of acyclovir and ganciclovir into the urine	PK/PD	Hematologic toxicity, neurotoxicity and nephrotoxicity	Anti-infective agents	(172,173)
Swainston Harrison and Perry, 2004;	Aripiprazole	Liver	ABCG2, ABCB1	Inhibits the action of ABCG2	PK	Influences drug clearance	Neurological agents	(174,175)
Nagasaka *et al*, 2012 Birmingham *et al*, 2015; Fukunaga *et al*, 2016	Atorvastatin	Liver	ABCG2, ABCB1, ABCC2, OATP1B1	Excretion of atorvastatin into the bile, limits the intestinal absorption	PK	Cardiovascular disease and hypercholesterolemia	Cardiovascular agents	(167,176)
Wang *et al*, 2008; Thorn e*t al*, 2018	Clozapine	Liver, brain	ABCB1, ABCG2, ABCC1	ABCG2 may influence clozapine systemic exposure, clozapine can inhibit ABCG2	PK	Tobacco use disorder and orthostatic hypotension	Neurological agents	(177,178)
Kamath *et al*, 2008; Whirl-Carrillo *et al*, 2021	Dasatinib	Liver	ABCB1, ABCG2	ABCB1 and ABCG2 pump dasatinib out of cells, thereby reducing its intracellular accumulation and tissue exposure	PK	Leukemia, hepatotoxicity and nephrotoxicity	Anticancer agents	(179,180)
Whirl-Carrillo *et al*, 2021; Daly *et al*, 2007	Diclofenac	Kidney, liver	ABCC2, ABCC3, ABCG2	Kidney eliminates diclofenac in urine, liver eliminates diclofenac in bile	PK	Hepatotoxicity and gastrointestinal toxicity	Pain, anti-inflammatory and immunomodulating agents	(180,181)

Table II. Continued.

Authors, year	Drug/class	Localization	Transporters involved	Transporter-mediated disposition and interaction mechanisms	PK/PD	Adverse effects	Therapeutics	(Refs.)
Nagata *et al*, 2002; Young *et al*, 2001; Thorn *et al*, 2011	Doxorubicin	Cancer cells (lung, ovarian, gastric, thyroid and breast)	ABCB1, ABCC1, ABCC2, ABCG2	ABCG2 pumps out intracellular doxorubicin from cancer cells	PD	Cytotoxicity and cardiotoxicity	Anticancer agents	(166,182, 183)
Whirl-Carrillo *et al*, 2021; Shi *et al*, 2007	Erlotinib	Liver	ABCB1, ABCG2	ABCG2 regulates erlotinib absorption and clearance, erlotinib blocks the activity of ABCB1 and ABCG2	PK	Diarrhea, exanthema and neoplasms	Anticancer agents	(180,184)
Beach, 1998; Ghodke *et al*, 2012	Zidovudine	Cell membrane	ABCB1, ABCC4, ABCC5, ABCG2	Mostly renal elimination into urine by membrane transporter	PK/PD	Hematological toxicity, hepatosteatosis and mitochondrial toxicity	Anti-infective agents	(185,165)
Allen *et al*, 2000; Oshiro *et al*, 2009	Taxane	Liver	ABCB1, ABCC1, ABCC2, ABCG2, OATP1B3	Elimination through biliary excretion via feces	PK	Neutropenia and toxicity	Anticancer agents	(186,187)
van Erp *et al*, 2009; Miura *et al*, 2014	Sunitinib	Liver	ABCB1, ABCG2	Both transporters mediate sunitinib efflux, influencing toxicity and efficacy, and regulating its biliary elimination	PK/PD	Diarrhea, hand-foot syndrome, mucositis, neutropenia and thrombocytopenia	Anticancer agents	(188,189)
Fiegenbaum *et al*, 2005; Mangravite *et al*, 2006	Statin	Liver, kidney	ABCB1, ABCB11, ABCC2, ABCG2	Major elimination via liver into bile, less excretion through kidney into urine	PK	Cardiovascular disease and atherosclerosis	Cardiovascular agents	(190,191)
Choi *et al*, 2008; Ramakumari *et al*, 2018	Rosuvastatin	Liver	ABCB11, ABCC2, ABCG2, OATP1B1, OATP1B3	ABC transporter-mediated biliary excretion	PK	Myopathy and myalgia	Cardiovascular agents	(192,164)

ABCG2, ATP-binding cassette sub-family G member 2; ABCB1, ATP-binding cassette sub-family B member 1; ABCB11, ATP-binding cassette sub-family B member 11; ABCC1, ATP-binding cassette sub-family C member 1; ABCC2, ATP-binding cassette sub-family C member 2; ABCC3, ATP-binding cassette sub-family C member 3; ABCC4, ATP-binding cassette sub-family C member 4; ABCC5, ATP-binding cassette sub-family C member 5; OAT1, organic anion transporter 1; OAT2, organic anion transporter 2; OAT3, organic anion transporter 3; NPT1, sodium-dependent phosphate transporter 1; NPT4, sodium-dependent phosphate transporter 4; OATP1B1, organic anion-transporting polypeptide 1B1; OATP1B3, organic anion-transporting polypeptide 1B3; PK, pharmacokinetics; PD, pharmacodynamics.

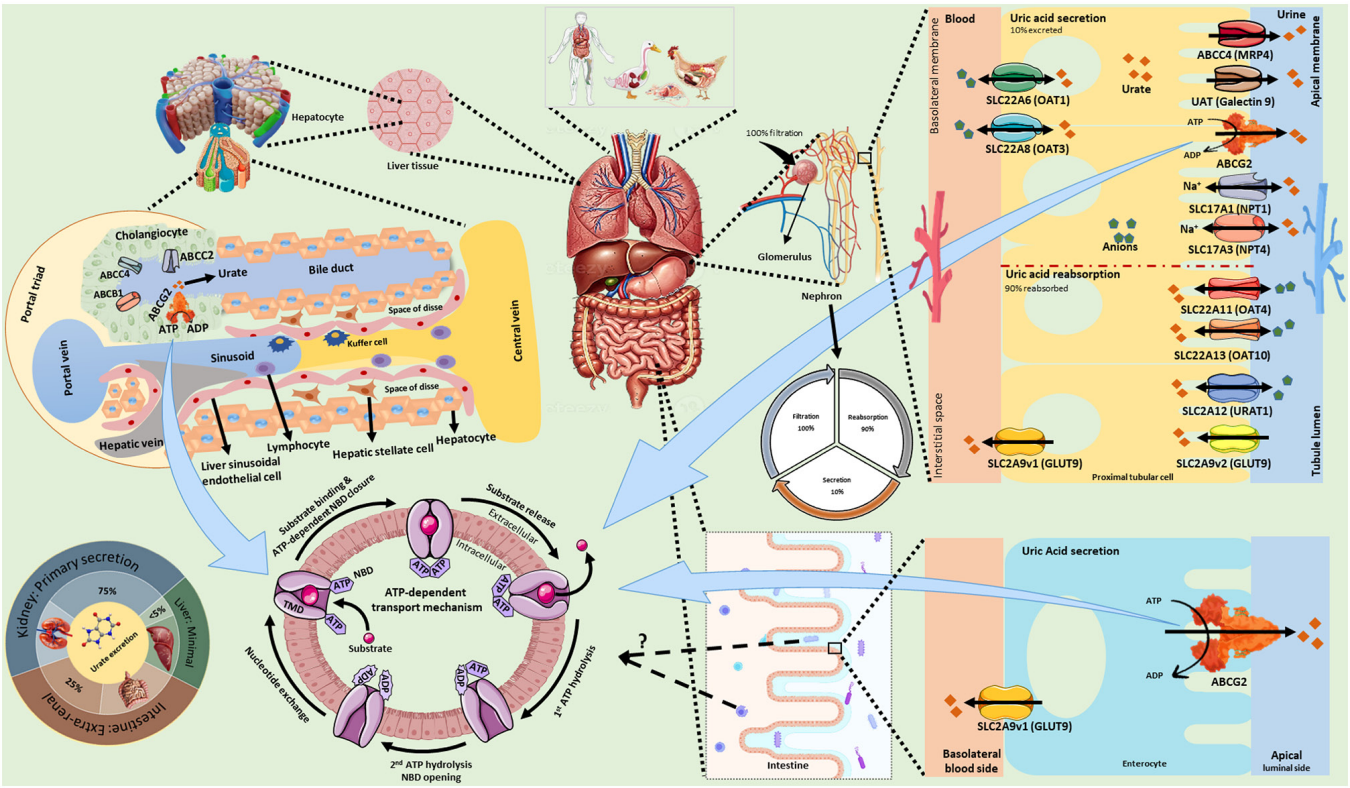

Figure 2. Multi-organ urate transport network and ATP-dependent excretory function of ABCG2. Illustration of systemic uric acid handling across the kidney, liver and intestine, emphasizing the cooperative roles of ABCG2 and other urate transporters (OAT1/3, NPT1/4, UAT, ABCB1, ABCC2 and ABCC4). In the kidney, reabsorption of urate is mediated by GLUT9, URAT1 and OAT4/10. ABCG2 mediates ATP-dependent efflux of urate from the intracellular space to luminal compartments, as illustrated in the liver (bile duct), kidney (tubular lumen) and intestine (apical lumen) panels. The pie chart summarizes relative organ contributions to urate clearance: Kidney (75%), intestine (25%) and liver (minimal). The diagram emphasizes the coordinated renal-hepatic-intestinal axis maintaining systemic urate homeostasis. ABCG2, ATP-binding cassette sub-family G member 2; ABCC4, ATP-binding cassette sub-family C member 4; MRP4, multidrug resistance-associated protein 4; ABCC2, ATP-binding cassette sub-family C member 2; ABCB1, ATP-binding cassette sub-family B member 1; OAT, organic anion transporter; SLC22A, solute carrier family 22; UAT, urate transporter; URAT1, urate transporter 1; NPT, sodium phosphate transporter; SLC17A, solute carrier family 17; GLUT9, glucose transporter 9; SLC2A9v1, solute carrier family 2 member 9 isoform 1; SLC2A12, solute carrier family 2 member 12; TMD, transmembrane domain; NBD, nucleotide-binding domain.

stronger HUA responses under Westernized lifestyles than in their native environments (204). These findings emphasize that the penetrance of the Q141K variant is not static but is influenced by environmental exposures, particularly those associated with modern dietary transitions. These observations are reinforced by a study using knock-in mice with the orthologous Q140K mutation, which showed impaired intestinal urate clearance and increased serum urate levels, consistent with human manifestations (205). These effects are exacerbated under dietary conditions that elevate purine load, reinforcing the role of the environment in modulating the impact of the variant (33). These insights are crucial for guiding population-specific precision medicine interventions targeting HUA and gout.

5. Physiological roles in urate excretion

The multi-organ urate transport network and ATP-dependent excretory mechanism of ABCG2 are shown in Fig. 2 (8,25,32, 47,65,68,202,206-213).

Renal secretion: The primary pathway. The kidney is the principal organ responsible for systemic urate homeostasis, with the proximal tubule being the critical site for regulating urate balance (8,214). Renal urate handling involves a complex sequence of filtration, reabsorption, secretion and post-secretory reabsorption, with only ~10% of filtered urate ultimately excreted in urine (68). This complex mechanism highlights the precise regulatory capacity of renal tubular transporters in maintaining plasma urate homeostasis (26,215). ABCG2 has emerged as an essential component of this regulatory system, predominantly localized to the apical membrane of renal proximal tubular epithelial cells in both humans and mice, where it functions as a high-capacity efflux transporter (8,27). Functionally, ABCG2 operates as an ATP-dependent pump that mediates active urate transport against concentration gradients, contributing substantially to the secretory flux that balances extensive tubular reabsorption (25). This transporter functions in coordination with other apical efflux proteins, notably multidrug resistance-associated protein 4 [MRP4; ATP-binding cassette sub-family C member 4 (ABCC4)], while counteracting major reabsorptive transporters, including URAT1 (SLC22A12) on the apical membrane and GLUT9 (SLC2A9) on the basolateral membrane (216,217). *In vitro* models using membrane vesicles from ABCG2-expressing cells have provided mechanistic insights into renal function, confirming that urate transport is ATP-dependent, saturable and pharmacologically inhibitable, consistent with its

function as a primary active transporter (36,73). Paradoxically, Abcg2-knockout mice develop HUA despite increased renal urate excretion (206), suggesting compensatory upregulation of alternative secretory or intestinal pathways (209). In humans, Q141K variant carriers exhibit elevated serum urate levels but with no marked change in fractional urate excretion, contrasting with observations in mice and highlighting species-specific differences in urate regulation (33). Clinically, ABCG2 serves a critical role in modulating drug responses, as inhibition by frequently prescribed drugs such as diuretics, angiotensin II receptor blockers and calcineurin inhibitors may trigger drug-induced HUA (218,219). Understanding these interactions is particularly important for patients with pre-existing ABCG2 deficiency due to genetic variants, who may be more susceptible to such adverse effects (143). The positioning of ABCG2 at the apical membrane facilitates its direct role in regulating the final urinary urate concentration, making it a key determinant of net renal urate excretion and a promising target for therapeutic interventions aimed at enhancing urate elimination (8).

Intestinal excretion: A critical extra-renal route. The intestine is recognized as a major extra-renal pathway for urate elimination, accounting for approximately one-third of total excretion in humans (207). ABCG2 is highly expressed on the apical membrane of enterocytes, particularly in the ileum and jejunum, where it functions as a high-capacity urate efflux transporter, promoting urate secretion into the intestinal lumen for subsequent fecal elimination (63). ABCG2 is more abundantly expressed in the intestine than in the kidney, indicating the importance of the intestine as a major route for urate elimination (66). Animal studies employing *in situ* closed-loop perfusion with radiolabeled uric acid have demonstrated intestinal urate excretion, revealing the intestine rather than the liver and bile as the predominant site of extra-renal urate elimination (206,220). Since rodents possess uricase, an enzyme absent in humans, pharmacological inhibition with oxonate is required to model human-like HUA (221). In these models, ABCG2 deficiency reduces intestinal urate excretion by 40-50% (36). These observations are further supported by studies in Abcg2-knockout and Q140K knock-in mice, which have demonstrated decreased intestinal secretion despite largely preserved renal elimination (32,200). These findings identify intestinal ABCG2 as a major determinant of extra-renal urate clearance, while also suggesting the presence of additional unidentified gut transporters (199). Translational evidence from humans, obtained through endoscopic sampling of intestinal fluid, has demonstrated progressively rising urate concentrations, confirming that intestinal elimination is mediated by active transport rather than passive diffusion (62,222). Carriers of dysfunctional ABCG2 variants, such as the Q141K or Q126X variants, exhibit markedly reduced intestinal urate excretion, which is associated with elevated serum urate levels and increased gout risk (223). Notably, a number of these individuals develop HUA despite normal renal urate handling, demonstrating that impaired intestinal elimination alone can drive systemic urate accumulation (224). This contrasts with renal transporters such as URAT1 or GLUT9, dysfunction of which generally presents as altered fractional urate excretion (225). These discrepancies indicate that renal and intestinal urate transport pathways operate in parallel while remaining mechanistically independent (68). In patients with chronic kidney disease (CKD) and compromised renal clearance, intestinal ABCG2-mediated urate excretion becomes a compensatory mechanism to limit further urate accumulation (208). In CKD, intestinal ABCG2 expression is often upregulated as an adaptive response, whereas dysfunctional ABCG2 alleles in patients impair this compensatory mechanism, exacerbating HUA (199). This synergistic relationship between renal impairment and transporter polymorphisms highlights the intestine as a crucial determinant of urate burden in disease contexts. Furthermore, the gut microbiome can modulate intestinal urate elimination through ABCG2, as hippuric acid produced by *Alistipes indistinctus* activated peroxisome proliferator-activated receptor γ (PPAR-γ) signaling, increased ABCG2 expression and reduced HUA in a mouse model (226,227). This highlights a dynamic interplay among host genetics, microbiome activity and transporter function in regulating urate homeostasis.

Biliary excretion: A minor contributor. Biliary excretion serves a minor role in overall urate elimination compared with renal and intestinal pathways (210). Although its role in urate clearance is limited, the liver remains essential to systemic metabolism (169). The presence of ABCG2 at the canalicular membrane of hepatocytes has highlighted its potential role in urate transport. This strategic localization enables ABCG2 to actively efflux substrates from the hepatocyte cytoplasm into bile, using energy derived from ATP hydrolysis (228,229). While ABCG2 can transport urate into bile, similar to its role in renal and intestinal urate excretion, rodent studies have revealed that biliary excretion makes only a small contribution to overall urate clearance (74,230). Furthermore, studies using Abcg2-knockout mice described that, despite controlled renal and intestinal urate handling, biliary urate excretion did not differ from that of wild-type controls (67,231). This finding indicates that hepatic ABCG2 contributes only a small proportion to total urate elimination, with biliary excretion accounting for ~5% of overall urate clearance (198,232). Even under hyperuricemic conditions induced by uricase inhibition, biliary urate excretion remains comparatively low, supporting the concept that biliary secretion is not a primary determinant of serum urate homeostasis (233). Genetic studies demonstrating ABCG2 dysfunction (such as the Q141K variant) in HUA and gout suggest that it is important to carefully evaluate whether reduced biliary efflux may contribute to disease pathophysiology (233,234). While impaired ABCG2 function in the liver may not markedly reduce urate clearance, it could alter the hepatobiliary handling of other substrates involved in urate metabolism (232). Beyond urate excretion, ABCG2 in hepatocytes serves an essential role in the biliary secretion of endogenous metabolites, dietary toxins and xenobiotics. For example, ABCG2 actively transports chemotherapeutic substrates such as mitoxantrone and topotecan, promoting multidrug resistance in hepatocellular carcinoma (235,236). ABCG2 also effluxes heme and porphyrins, thereby protecting hepatocytes from porphyrin-mediated oxidative stress (237). Furthermore, ABCG2 has been implicated in the efflux of itaconate, a metabolite with immunoregulatory functions, suggesting that hepatic ABCG2 may link metabolic

reprogramming to inflammatory responses (238). Although urate secretion via bile is relatively negligible, ABCG2 activity in the liver remains critical for maintaining hepatocellular homeostasis and systemic detoxification (211,212). Dysregulation of ABCG2 could therefore influence urate metabolism indirectly through substrate competition or modulation of hepatic redox and inflammatory states (209,239).

ATP-dependent transport mechanism. ABCG2 mediates ATP-dependent urate efflux, consistent with the alternating access model of ABC transporters (31,75). The cycle is initiated with ABCG2 in an inward-facing conformation, allowing urate and other substrates to bind within the TMD cavity (71). Binding of two ATP molecules at the NBD interface promotes a conformational switch to an outward-facing state, exposing the binding pocket to the extracellular space or apical lumen and releasing the substrate (240). Subsequent ATP hydrolysis restores the transporter to its inward-facing state, completing the catalytic cycle (213). Cryo-EM studies at physiological resolution have revealed that ABCG2 adopts distinct transport cycle ('turnover') conformations depending on substrate type: Small molecules such as E1S stabilize the Turnover-2 state with semi-closed NBDs, whereas larger substrates such as topotecan are associated with the Turnover-1 state characterized by a more open binding pocket (72,241). These findings highlight the structural adaptability of ABCG2 in handling chemically diverse substrates. Human genetic variation in ABCG2 further illustrates how slight changes in the ATP-driven cycle affect transport efficiency (242). Functional analysis has demonstrated that the G462R variant severely reduces both protein expression and transport activity, likely due to disruption of conformational coupling between NBDs and the TMD (243). By contrast, the I456V variant enhances transport activity, suggesting optimization of ATP-dependent cycling (244). These observations provide a molecular explanation for altered urate efflux and variable gout risk among carriers of ABCG2 polymorphisms. The ATP-dependent function of ABCG2 is also associated with cellular stress protection (245). In broiler chickens exposed to heat stress, upregulation of ABCG2 has been linked to activation of the ERK1/2 signaling pathway, suggesting a role in cellular protection against oxidative and metabolic stress beyond substrate transport (246,247). These findings support the broader concept that ATP-driven ABCG2 activity integrates urate handling with cellular defense mechanisms.

Urate transportome: ABCG2 and its interacting partners. Urate homeostasis is not controlled by a single transporter but results from the complex interaction among multiple transporters that constitute the urate transportome. Within this network, ABCG2 functions not in isolation but as part of an integrated system of transporters that collectively determine the net urate balance (214).

Antagonists: Reabsorptive transporters (URAT1 and GLUT9). ABCG2 operates within a precisely regulated urate transport network in the renal proximal tubule, where urate secretory activity is balanced by strong reabsorptive mechanisms (31). Among the reabsorptive transporters, URAT1 (encoded by SLC22A12) and GLUT9 (encoded by SLC2A9) are the principal reabsorptive transporters, collectively mediating the majority of urate reabsorption and thereby strongly influencing systemic urate homeostasis (248,249). URAT1 is localized to the apical membrane of proximal tubular epithelial cells, where it facilitates urate reabsorption from the tubular lumen into the intracellular space through an anion exchange mechanism (250). A functional study in *Xenopus* oocytes and mammalian expression systems has demonstrated that URAT1 mediates urate transport in exchange for organic anions such as lactate and nicotinate (251). Human genetic studies have highlighted URAT1 as a central regulator of urate homeostasis, as loss-of-function variants in SLC22A12 reduce renal urate reabsorption, leading to hypouricemia, whereas gain-of-function variants enhance urate retention, increasing susceptibility to HUA and gout (252,253). Clinical pharmacology further reinforces this role. Selective URAT1 inhibitors such as lesinurad and verinurad increase urinary urate excretion and reduce serum urate concentrations in patients with gout (254). These observations establish URAT1 as the dominant reabsorptive transporter opposing ABCG2-mediated urate secretion (255). Complementing this system, GLUT9 is primarily expressed on the basolateral membrane of proximal tubule cells, where it facilitates urate transport from the cytoplasm into the bloodstream, thereby completing the reabsorptive cycle (256,257). GLUT9 exists in two splice variants with tissue-specific expression: GLUT9L localized to the basolateral membrane of renal epithelial cells (258) and GLUT9S localized to the apical membranes of other tissues such as the liver (259). *In vitro* studies in oocyte and 293 systems have demonstrated that GLUT9 functions as a high-capacity urate transporter with bidirectional activity depending on electrochemical gradients (260-262). GWASs consistently identify SLC2A9 as one of the key genetic determinants of serum urate levels across diverse populations (263-265). Variants associated with reduced GLUT9 function confer a protective effect against HUA and gout, thereby underscoring its critical role in urate reabsorption (266). Conversely, pathogenic variants or increased GLUT9 activity enhance urate reabsorption and elevate serum urate concentrations (267). The interplay between ABCG2 and these reabsorptive transporters is fundamentally antagonistic (268). While ABCG2 actively secretes urate into the tubular lumen against a concentration gradient, URAT1 reabsorbs urate across the apical membrane, and GLUT9 transports it back into the circulation via the basolateral membrane of renal proximal tubular cells (25,130). This creates a dynamic equilibrium in which secretory and reabsorptive transporters are finely balanced, maintaining systemic urate levels within tightly regulated physiological limits (269). Disruption of this balance has pathophysiological consequences. Enhanced reabsorptive activity or transporter overexpression effectively neutralizes ABCG2-mediated secretion, leading to net urate retention and HUA (8,31). Experimental evidence supports this antagonism, as SLC22A12 knockout mice exhibit increased urinary urate excretion, confirming the reabsorptive dominance of URAT1 (270). Human studies with URAT1 inhibitors have further illustrated that pharmacological inhibition of URAT1 enhances the relative role of ABCG2 and other efflux transporters in urate clearance (271,272). The relationship among ABCG2, URAT1 and GLUT9 defines

the central mechanism of renal urate regulation, in which ABCG2 mediates high-capacity urate secretion, whereas URAT1 and GLUT9 mediate complementary reabsorption. Consequently, genetic variation, physiological states or pharmacological modulation of either side of this balance decisively impacts serum urate levels (273). Thus, therapeutic strategies that inhibit reabsorptive transporters not only reduce net urate retention (274) but also enhance the effectiveness of ABCG2-mediated secretion (275), offering a rational and synergistic approach to managing HUA and gout.

Collaborators: Secretory transporters (NPTs, MRP4 and OATs). Although ABCG2 is a central mediator of renal urate secretion, it functions within a broader and highly coordinated network of efflux transporters that together form the renal secretory mechanism of the urate transportome (31,276). This system includes the sodium-dependent phosphate transporters NPT1 (SLC17A1) and NPT4 [solute carrier family 17 member 3 (SLC17A3)] (277), the ABC transporter MRP4 (ABCC4) (216), and members of the organic anion transporter (OAT) family (278). Collectively, these transporters maintain efficient urate clearance and systemic homeostasis (279,280). Both NPT1 and NPT4 are expressed on the apical membrane of proximal tubule epithelial cells, where they function in coordination with ABCG2 to excrete urate into the tubular lumen (47,281). Functional studies in *Xenopus* oocyte and cell-based systems have demonstrated that NPT1 and NPT4 are voltage-sensitive urate transporters whose activity is stimulated by extracellular chloride (282,283). GWASs highlight SLC17A1 and SLC17A3 as genetic determinants of urate homeostasis and predisposition to gout (284-286). Reduced-function alleles in SLC17A1 are associated with diminished urate clearance and HUA in humans, thereby establishing these transporters as key apical collaborators of ABCG2 (287). Additionally, MRP4 (ABCC4) also contributes substantially to apical urate efflux (216). Studies using membrane vesicles and MRP4-overexpressing cell lines have demonstrated ATP-dependent urate transport by MRP, which was inhibited by classical ABC transporter inhibitors (216,288). *In vivo*, Abcc4-deficient mice exhibit impaired renal urate clearance (251,289), whereas Abcg2-knockout mice exhibit compensatory upregulation of renal Abcc4, underscoring the role of MRP4 in maintaining urate levels and compensating for ABCG2 dysfunction (290,291). The UA-excreting transporters OAT1 and OAT3, expressed at the basolateral membrane, mediate the uptake of urate and related metabolites from the circulation into proximal tubule cells (292). This process supplies intracellular urate for extrusion by apical transporters, including ABCG2, NPT1/4 and MRP4 (250). *In vitro* transport assays have demonstrated that OAT1 and OAT3 exchange urate for intracellular dicarboxylates, providing a directional driving force for secretion (293). Consistent with these findings, knockout mouse models have demonstrated that Oat1/Oat3-deficient mice exhibit impaired clearance of urate and organic anions (294,295). Studies have further implicated OATs in urate homeostasis, as genetic variants in SLC22A6 and SLC22A8 are associated with altered serum urate levels and modified gout susceptibility (278,296). The coordinated activity of OATs (basolateral uptake) with ABCG2, NPT1/4 and MRP4 (apical secretion) establishes a directional mechanism for urate clearance across proximal tubule cells (74,297). This multi-transporter collaboration ensures continuous urate elimination and protects against systemic accumulation. Disruption at any point in this cascade, whether through genetic variants, pharmacological inhibition or disease-related dysfunction, impairs urate excretion (26,130). For instance, simultaneous impairment of ABCG2 and NPTs results in a sharp decline in intestinal and renal clearance, whereas reduced OAT activity limits substrate availability for apical transporters (298,299). Conversely, compensatory upregulation of MRP4 or OATs may partially mitigate ABCG2 dysfunction (300). Understanding this interplay provides a foundation for developing therapeutic strategies that target multiple transporters to optimize urate elimination.

6. Compensatory mechanisms in health and disease

The urate transportome exhibits remarkable adaptability, enabling systemic homeostasis even when specific transporters are impaired. This redundancy is particularly evident in ABCG2 dysfunction, where alternative excretory routes are upregulated to maintain urate clearance (199). This compensatory capacity underscores the evolutionary importance of urate regulation, and contributes to inter-individual variability in serum urate levels and gout susceptibility (8). While the kidney is the predominant site of urate excretion, the intestine provides critical compensation, accounting for nearly one-third of clearance (301). However, dysfunctional ABCG2 variants, particularly the Q141K variant, impair intestinal secretion despite intact renal function, leading to systemic HUA (302). These findings highlight that renal adaptation to ABCG2 loss involves transporter cross-regulation, with MRP4 (ABCC4) acting as a key compensatory efflux transporter (216,288). *In vitro* vesicle assays have confirmed the role of MRP4 in ATP-dependent urate efflux (303-305), while Abcg2-deficient mice exhibit proximal tubular Abcc4 upregulation that partially sustains renal clearance, but remains insufficient to normalize serum urate levels (306,307). Metabolic feedback complements transporter redundancy (308), whereas impaired urate excretion drives altered purine flux and increased xanthine oxidase activity (18,309). Although these shifts may buffer acute imbalance, chronic upregulation promotes oxidative stress and inflammation, with sex-specific factors further modulating compensatory capacity (310,311). Estrogen has been shown to transcriptionally activate ABCG2 via estrogen response elements in its promoter (312). Consistent with this mechanism, premenopausal women exhibit lower serum urate levels and reduced gout prevalence compared with men (313). In rodent models, estrogen supplementation enhances Abcg2 expression and increases urate clearance, highlighting this protective effect (35). Despite these adaptive mechanisms, the compensatory capacity is finite; with aging, declining renal function (314) or the coexistence of multiple transporter variants (for example, variants in ABCG2 together with SLC22A12 or SLC17A1), the cumulative burden exceeds this capacity, ultimately resulting in HUA and clinical gout (315). This threshold effect explains why ABCG2 dysfunction alone may not invariably cause disease but becomes pathogenic when combined with genetic or environmental stressors.

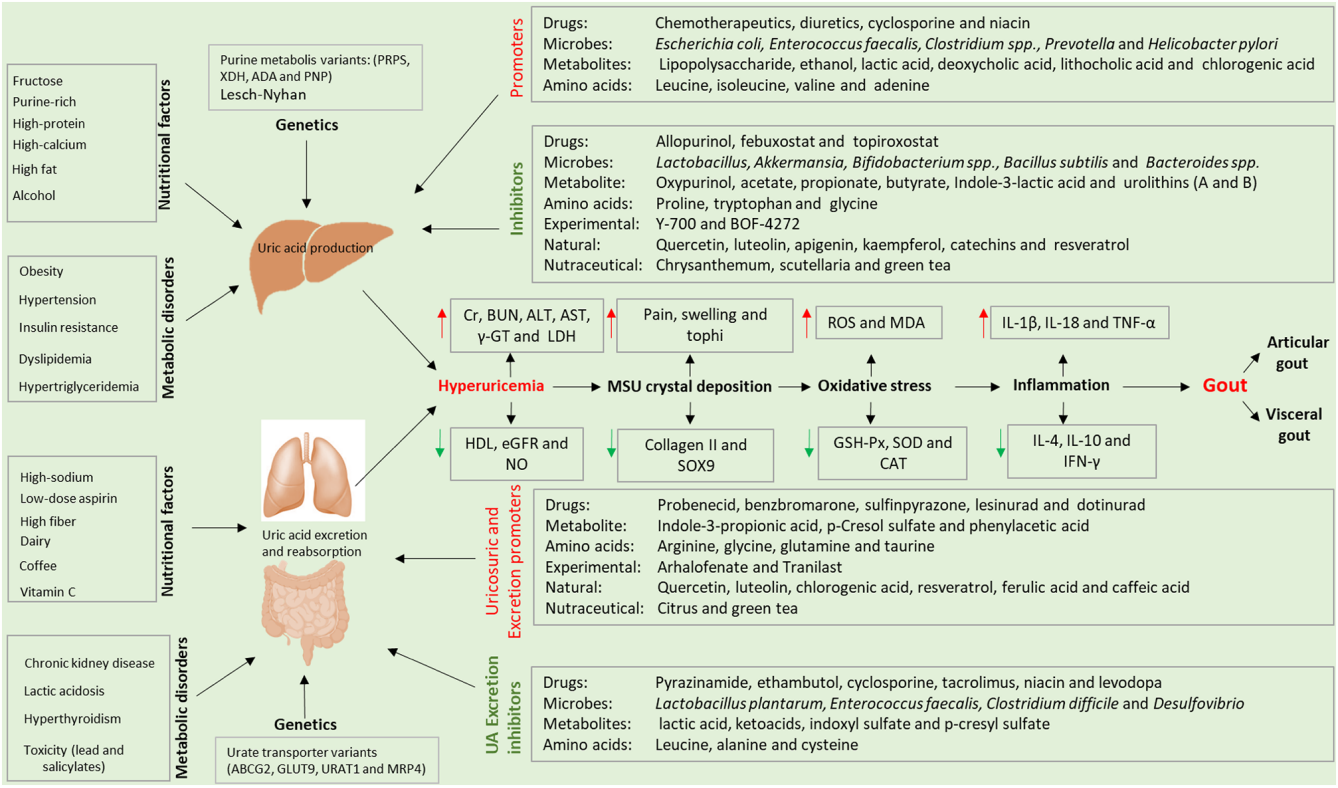

Figure 3. Multifactorial regulation of UA metabolism and progression from hyperuricemia to gout. Integrative overview of genetic, metabolic, nutritional and microbial determinants influencing UA production, excretion and pathological outcomes. Excess UA promotes MSU crystal deposition, oxidative stress and pro-inflammatory cytokine release, driving gout pathogenesis. Promoters and inhibitors of urate metabolism are classified as drugs, metabolites, amino acids, and experimental, natural and nutraceutical factors. MSU, monosodium urate; PRPS, phosphoribosyl pyrophosphate synthetase; XDH, xanthine dehydrogenase; ADA, adenosine deaminase; PNP, purine nucleoside phosphorylase; ABCG2, ATP-binding cassette sub-family G member 2; GLUT9, glucose transporter 9; URAT1, urate transporter 1; MRP4, ATP-binding cassette sub-family C member 4; Cr, creatinine; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transferase; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; NO, nitric oxide; SOX9, SRY-box 9; ROS, reactive oxygen species; MDA, malondialdehyde; GSH-Px, glutathione peroxidase; SOD, superoxide dismutase; CAT, catalase; UA, uric acid; LDH, lactate dehydrogenase.

Understanding the compensatory network of the urate transportome provides a basis for therapeutic strategies that enhance natural defenses, such as pharmacological activation of intestinal ABCG2, upregulation of renal MRP4 or modulation of OAT-mediated substrate exchange, which may improve urate clearance while minimizing the side effects associated with conventional urate-lowering therapies (13,316).

Regulation of ABCG2 expression and activity. The functional capacity of ABCG2 in urate homeostasis is not static but dynamically regulated through multiple interconnected mechanisms that respond to physiological, environmental and pharmacological factors. Understanding these regulatory networks is essential for elucidating how ABCG2 activity is modulated in health and disease, and for developing targeted therapeutic strategies (Fig. 3) (58,61,312,317-332).

Transcriptional and epigenetic control. The regulation of ABCG2 expression is controlled by a highly dynamic network of transcription factors and epigenetic modifications, ensuring precise control across tissues and in response to physiological stress (318). Among these regulators, nuclear factor erythroid 2-related factor 2 (Nrf2) functions as a key sensor of oxidative and xenobiotic stress (319). Studies of human intestinal and renal epithelial cells have demonstrated that Nrf2 activation, triggered by electrophiles such as sulforaphane or tert-butylhydroquinone, enhances ABCG2 promoter activity via antioxidant response elements (AREs), leading to increased mRNA and protein expression (320,321). This induction supports the protective function of ABCG2 in mediating the efflux of urate and other reactive metabolites under oxidative stress conditions. Conversely, loss of Nrf2 reduces Abcg2 expression in the kidney and intestine, compromising urate clearance and enhancing oxidative injury, which emphasizes the functional importance of Nrf2-ABCG2 interactions (333,334). By contrast, as a central regulator of inflammation, the NF-κB pathway exerts context-dependent control over ABCG2, whereby pro-inflammatory cytokines suppress its expression in some human cell models, particularly hepatocytes, while in others, NF-κB activation enhances transcriptional expression, reflecting tissue-specific regulation (312,323). These findings suggest that ABCG2 coordinates urate and metabolite clearance with immune responses, with ABCG2 expression and transporter activity modulated by inflammatory signaling in a tissue-specific manner (31). Findings from animal models of systemic inflammation have indicated that NF-κB-driven cytokine release modulates Abcg2 expression in hepatic and intestinal tissues (324,335). Epigenetic regulation of ABCG2 further involves promoter DNA methylation, which suppresses transcription in cancer and metabolic disorders, as well as

histone modifications that regulate chromatin accessibility and transcriptional activity (87,336,337). These reversible modifications highlight the potential of epigenetic therapies to modulate ABCG2 in gout, CKD and drug resistance conditions (58,61). miRNAs provide post-transcriptional control of ABCG2, as miR-519c, miR-520h and miR-328 directly bind to its 3'-UTR, suppressing protein expression in cancer and kidney cells (338-340). The Q141K polymorphism establishes a functional miR-124 binding site, which has been experimentally validated *in vitro*, that drives mRNA destabilization and reduces transporter expression in variant carriers (341,342). This interaction provides a mechanistic explanation for the reduced ABCG2 activity observed in hyperuricemic individuals carrying the allele (33,118). Understanding these mechanisms not only explains the inter-individual differences in urate handling but also offers potential strategies to modulate ABCG2 expression in HUA and related comorbidities.

Gut-kidney axis: Microbial metabolite regulation. The gut microbiome profoundly influences urate homeostasis by producing metabolites that regulate ABCG2 expression and activity in intestinal, hepatic and renal tissues (325,326). Short-chain fatty acids (SCFAs), produced by microbial fermentation of dietary fibers, enhance ABCG2 expression by activating its promoter and increasing protein levels (72,241,242). Studies using Caco-2 intestinal cells have demonstrated that butyrate activates PPAR-γ (343) and inhibits histone deacetylases, thereby increasing ABCG2 transcription (327). Human biopsies show that fecal SCFA levels are positively associated with intestinal ABCG2 expression, highlighting the role of diet-microbiota interactions in regulating transporter-mediated urate handling (344,345). Secondary bile acids produced in microbial cholesterol metabolism activate ABCG2 via farnesoid X/pregnane X signaling in liver and intestinal cells, whereas dysbiosis-associated alterations in bile acid composition impair transporter function and urate clearance, reflecting regulation along the gut-liver-kidney axis in both humans and rodents (329,346,347). Beyond SCFAs and bile acids, microbial metabolites derived from amino acids and polyphenols also regulate ABCG2. For example, indole derivatives from microbial tryptophan metabolism, such as indole-3-propionic acid (IPA), activate AhR signaling and upregulate ABCG2 in *in vitro* intestinal epithelial cell models (328,330,348). Microbial biotransformation of dietary polyphenols produces phenolic acids, including ferulic and protocatechuic acids, which upregulate ABCG2 via Nrf2-dependent antioxidant pathways, as shown *in vitro* and in rodent models (349-351). Flavonoids and their microbial metabolites, such as quercetin, resveratrol, and catechins, further enhance transporter expression and activity, predominantly through Nrf2/ARE activation and antioxidant effects (352,353). Gut microbiota convert flavonoids into smaller phenolic catabolites with often stronger bioactivity. For example, microbial quercetin metabolites upregulate ABCG2 transcription in colon cells, while resveratrol-derived catabolites increase renal Abcg2 expression and promote urate clearance in mice (354,355). Animal studies have highlighted the importance of microbial metabolites, as microbiota depletion via antibiotics reduced Abcg2 expression in the gut and kidney, leading to defective urate excretion (356,357). Colonization of bacterial communities that metabolize SCFAs and flavonoids regulates ABCG2 expression and lowers serum urate levels, highlighting the functional link between microbiota and transporter regulation. These findings underscore the therapeutic potential of microbiome-targeted dietary strategies, including diets enriched in fiber and flavonoid or probiotic supplements, to enhance ABCG2 function and improve urate elimination in cases of HUA and gout (358). In addition to microbial metabolites that directly regulate ABCG2, several diet-derived factors may influence urate homeostasis through gut-kidney interactions, renal urate handling and systemic metabolic pathways. For example, acute milk intake reduced serum urate levels in a randomized crossover trial discussing orotic acid as a uricosuric component that may compete with uric acid for renal tubular exchange (359). A review has reported an inverse relationship between low-fat dairy intake and gout risk and revealed moderate urate-lowering effects in intervention studies (360). Meta-analysis evidence indicates that vitamin C supplementation can lower serum uric acid levels (361). Recent population-based data reveal that dietary vitamin C intake is inversely associated with gout/hyperuricemia, while supplementation effects are less consistent (362). Systematic review evidence suggests that moderate coffee intake may help prevent hyperuricemia and gout (363). A Mendelian randomization study revealed that habitual coffee consumption was inversely associated with gout risk, and this protective association persisted after excluding potentially pleiotropic genetic instruments, suggesting that coffee may reduce gout risk independently of serum urate levels (364). A review chapter summarized possible mechanisms, including xanthine oxidase inhibition and increased renal uric acid clearance, potentially mediated by caffeine and other coffee-derived bioactive compounds (365).

Pharmacological and hormonal modulation. Clinically, ABCG2 function is regulated by hormonal and pharmacological factors that affect urate handling and drug metabolism (32,63). ABCG2 serves as a multi-specific efflux transporter for a broad spectrum of xenobiotics, whose roles as substrates, inhibitors or inducers alter transporter-mediated urate clearance and drug handling in clinically relevant ways (366,367). *In vitro* and vesicle-based assays have demonstrated that multiple tyrosine kinase inhibitors (368), including imatinib, gefitinib and erlotinib, inhibit ABCG2, suppressing ATP-dependent efflux and increasing intracellular substrate retention (369-371). By contrast, uricosuric agents, including benzbromarone and probenecid, enhance ABCG2-mediated urate transport in cell-based systems (217,283,308), while cardiovascular agents, including losartan and fenofibrate, modestly upregulate the efflux capacity in proximal tubule systems (372,373). Animal studies have further confirmed that ABCG2 inducers, such as empagliflozin (374), bergenin (375) and *Cichorium intybus* extract (376), lower serum urate levels by increasing renal and extra-renal excretion, highlighting the therapeutic potential of pharmacological induction (18,377). ABCG2 serves a pivotal role in drug-drug interactions, with inhibitors increasing substrate toxicity (378,379) and potent agents, such as cyclosporine or eltrombopag, markedly elevating systemic exposure, highlighting transporter-mediated risks in pharmacotherapy (380,381). Such inhibition can also impair urate

elimination, contributing to secondary HUA in predisposed individuals (209). ABCG2 is also regulated by hormones, as 17β-estradiol promotes its activity and protein expression in renal and intestinal cells via estrogen receptor-mediated transcriptional regulation (331,382,383). Rodent studies have further demonstrated estrogen-mediated upregulation of Abcg2, which promotes intestinal and renal urate elimination and likely contributes to sex-specific urate handling and the lower incidence of gout in premenopausal women (35,384). Observational studies have suggested that menopausal transition and hormone therapy influence urate metabolism; however, confirmatory prospective human data are limited (385,386). Glucocorticoid signaling also influences ABCG2 regulation, with dexamethasone promoting transcription via response elements in *in vitro* and *in vivo* studies, confirming changes in liver- and kidney-specific expression (332,387,388). These effects have two key clinical implications: ABCG2 represents a key target for therapeutic induction to enhance urate clearance and careful attention is required to avoid drug-transporter interactions that could worsen HUA or compromise the safety and efficacy of substrates. Future translational studies should systematically map inducer/inhibitor profiles and evaluate targeted pharmacologic or hormonal strategies to optimize ABCG2 regulation in HUA management.

Clinical implications: From HUA to gout. In clinical practice, ABCG2 serves a multifaceted role, with genetic variants, pharmacologic interventions and comorbid conditions collectively influencing disease presentation and treatment response (32,236). Understanding these interactions is vital for developing personalized strategies for HUA and gout management, especially considering the effects of ABCG2 on multiple organ systems.

ABCG2 as a genetic risk factor. ABCG2 is an important genetic determinant of HUA and gout. Q141K variant carriers (rs2231142) exhibit reduced intestinal and renal urate excretion, leading to elevated serum urate levels in blood and an increased risk of gout (33,58,389). The Q141K variant influences gout risk in a gene expression manner, as homozygotes exhibit more severe phenotypes. Variations in allele frequency among populations contribute to the differences in HUA and gout prevalence (119,390). East Asian individuals have the highest frequency of Q141K mutation, increasing the risk of HUA and gout at the population-level, while the functional impacts of the variant on urate handling, transporter function and pharmacological responses are uniform across populations (196,391). The Q141K variant not only increases the risk of HUA and gout but also reduces the response to standard therapies, including uricosurics and XOIs (59). The variant contributes to uric acid nephrolithiasis, increases the renal urate load, and is associated with an increased risk of hypertension, insulin resistance and cardiovascular disease (392,393). Pharmacogenetically, carriers of the Q141K variant exhibit altered drug disposition and an increased toxicity risk, emphasizing the need for personalized therapy (128). Clinical identification of the ABCG2 Q141K variant may support precision medicine by helping to stratify gout risk, predict the treatment response, and guide individualized prevention and management strategies for HUA and gout.

Pharmacogenetics: Guiding urate-lowering therapy. ABCG2 variants serve a pivotal role in pharmacogenetics, influencing the treatment of HUA and gout. Among them, the Q141K polymorphism exerts the greatest influence, highlighting the importance of precision medicine approaches (58,199). Clinical and experimental evidence has demonstrated that impaired ABCG2 function affects the disposition, efficacy and safety of urate-lowering therapies, supporting the use of genotyping in treatment algorithms (141,394). A pharmacogenetic study in humans has demonstrated that the Q141K variant reduces the efficiency of uricosuric agents, notably benzbromarone and lesinurad (395). Although these agents primarily target renal transporters URAT1 (SLC22A12) (396) and OAT4 [solute carrier family 22 member 11 (SLC22A11)] (397), their maximal urate-lowering efficacy also depends on intact extra-renal urate clearance via ABCG2 (32). Dysfunctional ABCG2 compromises intestinal urate clearance, reducing the overall excretory capacity and attenuating uricosuric efficacy (67,207). Benzbromarone is an ABCG2 substrate, and impaired transporter function in Q141K variant carriers decreases both its elimination and pharmacodynamic potency, as shown in ABCG2-overexpressing transfected cell models (398). This dual mechanism indicates the complexity of drug-transporter interactions in HUA management. XOIs, notably allopurinol and febuxostat, exhibit consistent therapeutic effects in suppressing urate synthesis (399,400) independently of ABCG2-mediated excretion (366). However, clinical cohort studies have suggested that Q141K variant carriers frequently require combination therapy, indicating that impaired urate handling may indirectly influence XOI response (33,401). ABCG2 is a key pharmacogenetic determinant across multiple drug classes, influencing the handling of statins, calcium channel blockers, antivirals and anticancer therapies (402,403). For example, patients with cancer with dysfunctional ABCG2 exhibit reduced elimination of tyrosine kinase inhibitors, including gefitinib and imatinib, requiring careful dose modification (404-406). Therefore, ABCG2 polymorphisms exert clinical impacts beyond gout, influencing the efficacy and safety of various drug classes (407,408). Murine knockout models have been used to mimic human carriers, with Abcg2 deficiency disrupting drug pharmacokinetics and reducing the urate-lowering effect of benzbromarone (205,206). These mechanistic insights provide translational confirmation that ABCG2 function shapes both urate homeostasis and drug disposition. Genotype-guided therapeutic approaches based on ABCG2 polymorphisms are particularly relevant for refractory gout or HUA, where transporter dysfunction may cause therapeutic resistance. Although clinical adoption is still progressing, combined data from multiple models strongly support ABCG2 testing as a tool for treatment optimization and risk reduction (58,408).

Association with CKD and cardiovascular disease. ABCG2 dysfunction has emerged as a systemic risk factor, with epidemiological evidence linking it not only to gout but also to CKD and cardiovascular disorders (32,409). Impaired extra-renal urate excretion elevates serum urate levels, causing systemic injury via both crystal-related and crystal-independent pathways (8). GWASs and large cohort studies across Japan, China and Europe have consistently implicated the ABCG2 Q141K variant

in both CKD and cardiovascular diseases (391,410). Japanese cohorts have shown that carriers of the ABCG2 Q141K variant exhibit accelerated estimated glomerular filtration rate decline compared with wild-type individuals, independent of serum urate levels, while European and Chinese biobank analyses have linked the Q141K variant to incident CKD, progression to end-stage renal disease, hypertension, coronary artery disease and heart failure, underscoring its systemic impact on renal and cardiovascular pathology (411-413). These associations remain evident beyond urate levels, implicating ABCG2 in broader pathogenic pathways. Inflammation, oxidative stress and vascular dysfunction cause transporter impairment in both renal injury and cardiovascular diseases (414,415). Animal studies have demonstrated that elevated urate levels drive vascular stiffness and nitric oxide loss (393,416,417), and ABCG2 dysfunction further exacerbates endothelial injury by restricting efflux of oxidative metabolites and signaling molecules (418,419). ABCG2-knockout mice exhibit HUA, reduced intestinal urate elimination and renal urate accumulation compared with wild-type controls. Furthermore, high-purine feeding accelerates renal microvascular injury, tubular damage and interstitial fibrosis, recapitulating human CKD pathology (69,209,420). ABCG2-deficient mice develop cardiac hypertrophy and vascular dysfunction, suggesting a cardioprotective role for ABCG2 beyond urate handling (245,421). Furthermore, cell-based models have confirmed ABCG2 expression in endothelial cells and cardiomyocytes, demonstrating that ABCG2 promotes the transporter-dependent efflux of xenobiotics and oxidative intermediates, thereby reducing their intracellular accumulation and protecting cells from oxidative injury (60,379,422). Loss or inhibition of ABCG2 function exacerbates oxidative stress and compromises angiogenesis, highlighting its direct contribution to vascular cytoprotection (419,423). In proximal tubule cell models, ABCG2 knockdown enhances urate-driven inflammatory signaling, increasing renal vulnerability of variant carriers (25,73). These pathological mechanisms, including oxidative stress, impaired angiogenesis and urate-driven inflammatory responses, are evident in both gout and asymptomatic HUA, emphasizing the broader clinical and public health relevance of ABCG2 dysfunction. Targeting ABCG2 function, either by enhancing its activity or through compensatory approaches, represents a promising approach for integrated management of HUA and cardiorenal comorbidities (32,63).

7. Therapeutic targeting of ABCG2

Current strategies: XOI vs. uricosuric efficacy. Emerging evidence indicates that the risks associated with urate dysregulation extend beyond gout to asymptomatic HUA, highlighting a broader public health burden (424). Accordingly, strategies that restore or augment ABCG2 activity may offer a dual advantage by promoting urate clearance and protecting cardiorenal health (425-427). In the context of ABCG2 dysfunction, pharmacotherapy for HUA and gout primarily relies on XOIs to reduce urate generation and uricosuric agents to augment renal clearance (155,233,428). The effectiveness of urate-lowering therapy is influenced by ABCG2 polymorphisms, particularly the Q141K polymorphism (57,133). Despite this, XOIs such as allopurinol and febuxostat remain first-line treatments because their inhibition of xanthine oxidase reduces urate levels across different genotypes, as confirmed by large clinical trials and post-marketing studies (429-431). The reliability of XOIs derives from their ability to reduce urate synthesis rather than from their influence on excretion pathways (68,432). ABCG2 dysfunction does not impair their pharmacodynamics, although pharmacokinetic fluctuations may occur when co-administered with ABCG2 substrates (51,433). By contrast, the efficacy of uricosuric therapies is largely genotype-dependent. Unlike XOIs, uricosuric agents such as benzbromarone, lesinurad and probenecid inhibit reabsorptive transporters, including URAT1 (SLC22A12) and OAT4 (SLC22A11), thereby enhancing renal urate clearance (233,434,435). The therapeutic efficacy of uricosurics depends on the functional secretory capacity mediated by ABCG2 and complementary efflux transporters (32). Pharmacogenetic evidence shows that Q141K variant carriers respond poorly to uricosurics (116), as inhibition of reabsorption (URAT1) cannot compensate for impaired secretion by secretory transporters (42). Mechanistic and translational studies have demonstrated that uricosuric efficacy is constrained by ABCG2 function, while Q140K knock-in mice exhibit HUA and fail to respond to benzbromarone or lesinurad, but retain normal sensitivity to allopurinol and febuxostat (436-438). ABCG2 pharmacogenetics has important clinical implications in East Asian populations, where the Q141K allele frequency exceeds 30%, and may contribute to reduced efficacy of uricosuric agents, suggesting that these drugs may be less suitable as first-line therapy in this population (391,439). ABCG2 genotyping enables selection of XOIs over uricosurics in Q141K variant carriers, particularly in high-prevalence populations (54,440). This strategy not only improves treatment efficacy but also minimizes unnecessary drug exposure, adverse effects and healthcare costs, ensuring that treatment selection is tailored to individual transporter function and genetic background (236,407).

Novel approaches: Activators, microbiome modulators and gene editing. Recent advances in molecular pharmacology and precision medicine have expanded the therapeutic options for ABCG2-related HUA beyond conventional urate-lowering drugs (441). Novel strategies are emerging, which aim to restore or enhance ABCG2 function through pharmacological activation, microbiome modulation, secondary metabolite interactions and gene editing (442,443). These interventions promote urate clearance and alleviate renal, vascular and inflammatory complications associated with ABCG2 dysfunction (444). Pharmacological activators have gained attention for the restoration of transporter function. High-throughput screening platforms using 293 and Caco-2 cells have identified small molecules that enhance ABCG2 expression and activity (445-447). Natural compounds such as curcumin, resveratrol, sulforaphane and quercetin stabilize ABCG2 membrane localization, while sulforaphane additionally promotes methylation to enhance transcription (448-450). Synthetic scaffolds, including phthalazinone derivatives, improve Q141K variant folding defects (451), and some clinically approved drugs have been shown to enhance ABCG2 expression or activity as off-target effects. For example, febuxostat improves ABCG2 expression in intestinal epithelial cells (366,452,453). In

rodent HUA models, chronic administration of curcumin or phthalazinone analogs reduces serum urate levels and renal oxidative injury, supporting their translational relevance by demonstrating therapeutic efficacy *in vivo* and suggesting potential applicability in the treatment of hyperuricemia and related renal complications (454,455). Microbiome modulation represents a complementary approach via the gut-kidney axis. Since ABCG2 is highly expressed in the intestine, enhancing microbial metabolism of urate or secondary metabolites can augment urate excretion (456). Clinical studies have shown that supplementation with engineered *Lactobacillus* strains 06CC2 and XL-1 reduces serum urate levels by 15-20%, enhances intestinal ABCG2 expression (345) and reduces systemic inflammation (457,458). Prebiotics, such as inulin and resistant starch, promote the production of SCFAs, which can modulate intestinal ABCG2 expression (459-461). In animal studies, butyrate supplementation activated intestinal Nrf2 signaling (462), enhanced ABCG2-mediated urate secretion (463,464) and improved renal histology (465). *In vitro* colonocyte experiments have confirmed that SCFAs function not only as energy substrates but also as epigenetic regulators, decreasing promoter methylation and increasing ABCG2 transcription (466-468). Secondary metabolites derived from diet microbiome interactions provide an additional regulatory layer (469). Polyphenol-derived metabolites such as urolithin A (from ellagitannins) and enterolactone (from lignans) activate antioxidant pathways (470,471) and increase ABCG2 expression in intestinal models (472). Similarly, microbial tryptophan metabolites, including IPA and indole-3-acetic acid, enhance intestinal barrier integrity and stimulate Nrf2/ARE signaling (473), indirectly promoting ABCG2-mediated urate transport (474,475). In rodent models, urolithin A supplementation improved intestinal ABCG2 localization and reduced serum urate levels (476,477), while IPA attenuated renal oxidative stress under hyperuricemic conditions (478). Gene editing is a precise approach for ameliorating ABCG2 dysfunction (337). CRISPR-CRISPR-associated protein 9-mediated correction of the Abcg2 Q140K variant in knock-in mice reinstated wild-type transporter expression in the intestine and kidney, leading to normalized urate excretion with no detectable off-target effects (479,480). Treated mice also displayed reduced renal inflammation and systemic oxidative stress (481), highlighting the systemic benefits of transporter restoration (482). Advances in base and prime editing, along with virus-free delivery systems, increase the translational feasibility (483-485). Additional innovations include epigenetic therapies that reverse promoter hypermethylation (486,487) and nanocarrier-based delivery systems that enhance tissue-specific targeting of ABCG2 substrates (488,489). By integrating pharmacological activators, microbiome interventions, secondary metabolite modulators and gene editing, future therapies could move beyond symptomatic urate-lowering to directly restoring transporter function, with benefits extending to renal, vascular and metabolic health.

Towards personalized medicine for gout. The identification of the ABCG2 Q141K variant as a major determinant of uricosuric efficacy advances personalized medicine in gout treatment (490). The integration of ABCG2 genetics into clinical practice exemplifies the shift from population-based therapy to individualized therapy in rheumatology (491). Among urate transporter gene variants, ABCG2 variants [Q141K (rs2231142)] are strongly associated with HUA, gout and drug responsiveness (492). Carriers of the ABCG2 Q141K variant exhibit differential responses to uricosurics and XOIs, underscoring the value of preemptive ABCG2 genotyping to guide therapy (144) and ensure that treatment choices align with individual transporter function and genetic background (168,493). Beyond pharmacogenetics, *in vitro* screenings have identified dietary polyphenols and microbial metabolites (resveratrol, quercetin and kaempferol) as ABCG2 modulators, suggesting the potential of nutrigenetic interventions (494-496). Genotype-based stratification of patients, particularly according to ABCG2 Q141K status, enables clinicians to prioritize XOIs over uricosurics in Q141K variant carriers, thereby enhancing therapeutic efficacy (497,498). Clinically, the Japanese Society of Gout and Nucleic Acid Metabolism already recommends ABCG2 testing in patients with early-onset or drug-refractory gout (499). Effective implementation will require multidisciplinary collaboration among rheumatologists, pharmacologists, genetic counselors and nutritionists (500,501), supported by digital health tools such as algorithm-based decision systems and mobile applications that integrate genotype data with serum urate levels, comorbidities and adherence metrics (502-504).

8. Conclusion and future directions

ABCG2 has emerged as an important determinant of systemic urate homeostasis and a molecular link connecting transporter mechanisms, metabolic regulation and pharmacogenetics. The present review emphasizes compelling evidence that ABCG2 is one of the main urate transporters, serving as a high-capacity ATP-dependent efflux pump, serves a central role in coordinating renal and extra-renal urate excretion, and acts as a key regulator of the systemic urate balance. Its strategic apical distribution in proximal renal tubules, intestinal mucosa and hepatobiliary canaliculi mediates urate and xenobiotics excretion into luminal spaces, thereby enhancing systemic urate elimination and protecting against HUA and gout. Within this excretory framework, ABCG2 operates synergistically and antagonistically with other urate-regulating transporters, forming a dynamic and compensatory urate transportome that helps to maintain homeostasis even when individual transporters are functionally impaired. The ABCG2 Q141K polymorphism demonstrates the principles of precision medicine in gout by illustrating how a single genetic variant can disrupt protein folding, trafficking and function, leading to a ~50% reduction in urate excretion capacity. This ABCG2 dysfunction is a major contributor of early-onset and severe gout across populations, with the Q141K variant being particularly prevalent among East Asian individuals. Beyond genetics, ABCG2 extends its role as a dynamic sensor of the internal environment, regulated by the gut microbiome via microbial metabolites such as SCFAs, hormonal signals such as estrogen and dietary components. ABCG2 dysfunction necessitates a shift in therapeutic strategy, favoring XOIs over uricosurics in Q141K variant carriers, highlighting the need for pharmacogenetic screening and expanding treatment approaches beyond simple urate-lowering to include individualized therapy, modulation of transporter function,

and management of associated metabolic and inflammatory pathways.

Future research on ABCG2 must address several unresolved questions to fully explore its therapeutic potential. First, resolving high-resolution structures of ABCG2 in multiple turnover states remains a priority for rational drug design. Despite advances, atomic-level characterization of the dynamic conformational states of ABCG2 is still lacking, limiting the ability to develop selective modulators that could enhance urate transport while preserving its critical role in xenobiotic efflux. Second, a critical challenge lies in quantifying the tissue-specific contributions of ABCG2 to systemic urate elimination. While the kidney, intestine and liver each contribute, their relative importance varies with genetic and ethnic/cultural background, age, comorbidities, and disease state. Advanced tracer studies, combined with tissue-targeted knockouts and humanized models, are needed to precisely map tissue-specific ABCG2-mediated urate transport and excretion pathways. Third, microbiomes offer underexplored therapeutic approaches, as microbial metabolites such as hippuric acid have been shown to modulate ABCG2 activity via host signaling pathways. Harnessing such microbiome-transporter interactions could enable non-pharmacological strategies for enhancing intestinal urate clearance. Finally, expanding the scope beyond gout is essential, as ABCG2 also influences outcomes in CKD, cardiovascular disease and cancer through its roles in oxidative stress regulation, drug resistance and metabolism. Clarifying these broader disease associations may reveal opportunities for cross-disease therapeutic targeting. Collectively, these research priorities include defining ABCG2 conformational structures, quantifying tissue-specific urate transport, elucidating microbiome-transporter regulation and clarifying ABCG2 involvement in CKD and cardiovascular disease. Addressing these priorities will require integrative approaches that combine structural biology, systems physiology, microbiome science and clinical investigations. Such efforts will help resolve unanswered questions and aid the translation of ABCG2 biology into effective therapies.

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Authors' contributions

MAA contributed to the conception and design of the review, performed the literature search and wrote the original draft. ZZ contributed to literature extraction, and organization and interpretation of data related to ABCG2 variants, pharmacogenetics and clinical associations, and prepared and critically revised the tables and figures. BEM critically reviewed and edited the manuscript for important intellectual content and contributed to interpretation of the clinical and mechanistic evidence. UN contributed to the interpretation of evidence related to animal models, urate excretion mechanisms and ABCG2 dysfunction, and critically revised the figures and relevant manuscript sections. JS contributed to the literature review and interpretation of ABCG2 structure, transporter function and urate transport mechanisms, and assisted with figure revision. ZW and YC contributed to literature extraction and interpretation of transporter-related, pharmacological and therapeutic data, and critically revised the tables and related text. SH contributed to the interpretation of evidence related to ABCG2 regulation, therapeutic targeting and disease associations, and critically revised the manuscript for important intellectual content. LB and YS contributed to the conception and design of the review, supervised the study, acquired funding, helped design the overall framework of the article and critically revised the manuscript for important intellectual content. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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