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PharmGKB summary: uric acid-lowering drugs pathway, pharmacodynamics

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Introduction

Disorders involving uric acid including gout, hyperuricemia and resultant kidney failure are prevalent. There are three main groups of pharmaceuticals used for modulating uric acid: 1. Drugs that reduce the generation of uric acid (allopurinol and febuxostat), 2. Those that increase the removal of uric acid (rasburicase, pegloticase), (both depicted in Figure 1) or 3. Those that inhibit the reabsorption of uric acid (depicted in Figure 3). This summary briefly describes the mechanisms of action and the candidate genes and genetic variants associated with response to these drugs. Clinically relevant genetic variants have been identified for allopurinol and rasburicase, and CPIC guidelines have been published that recommend selection of alternative treatments for some individuals. A more extensive description and interactive version can be found for each pathway at www.pharmgkb.org.

1) Drugs that reduce the generation of uric acid: allopurinol and febuxostat

Pharmacodynamics

Allopurinol is a drug indicated for the treatment of gout, prophylaxis of hyperuricemia in patients undergoing chemotherapy, and prevention of kidney stones recurrence [1].

Allopurinol and its metabolite oxypurinol are analogues of hypoxanthine and xanthine,

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Conflicts of Interest

None to declare.

respectively, and work by binding to and inhibiting xanthine dehydrogenase (XDH), preventing the formation of uric acid (Figure 1) [1–5]. Hypoxanthine and xanthine are cleared in the urine or reutilized in the synthesis of nucleotides and nucleic acids [1, 6]. Febuxostat (Uloric[®]) is a non-purine inhibitor of XDH that can bind to and inhibit both oxidized or reduced forms of XDH (Figure 1) [2, 7, 8]. It is indicated for the treatment of hyperuricemia in patients with gout (but not for asymptomatic hyperuricemia) [9], and is an alternative therapy for patients where allopurinol has been contraindicated due to allergic responses [7, 8, 10]. A downside to allopurinol/febuxostat treatment is that existing high levels of plasma uric acid are not cleared and, as xanthine is less soluble than uric acid, xanthine kidney stones or xanthine nephropathy may result [3, 6].

Pharmacogenomics

A small proportion (0.1 to 0.4%) of patients receiving allopurinol develop life-threatening severe cutaneous adverse reactions (SCARs) that include drug hypersensitivity syndrome (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [11]. The allopurinol hypersensitivity reaction is completely distinct from the drug's intended pharmacodynamic pathway: SJS and TEN are thought to occur via cytotoxic T cell-induced keratinocyte death by a drug-specific, HLA class I-restricted and granulysin-mediated pathway [12, 13]. NK cells may also be involved [13].

The *HLA-B*5801* allele is currently the most well-established genetic association with allopurinol-induced SCAR and has been demonstrated in numerous populations (Table 1). The human *HLA-B* gene is the most polymorphic in the genome, with over 1500 alleles that are made up of many variants [14–16]. Historically, these alleles were identified by antigen binding assays but more recently sequencing and genotype techniques are utilized (see Table 1). Single Nucleotide Polymorphisms (SNPs) that tag the *HLA-B*5801* allele differ in different populations [17]. The mechanism behind *HLA-B*5801*-specific allopurinol-induced hypersensitivity is not fully understood, however several hypotheses proposed for HLA-dependent T cell stimulation by drugs could be applicable (depicted in Figure 2) [11, 12, 18, 19]. Allopurinol or oxypurinol may bind self-protein/peptide to create a haptenated product which undergoes antigen processing and is presented specifically by *HLA-B*5801* to activate antigen-specific T cells (the hapten concept) [18]. They may interact with the *HLA-B*5801*-MHC-peptide complex and TCR directly at the cell surface, rather than undergoing antigen processing (the pi concept) [18, 20]. During folding of *HLA-B*5801* in the endoplasmic reticulum, allopurinol/oxypurinol may become incorporated into the peptide-binding groove, potentially changing the repertoire of self-peptides *HLA-B*5801* is able to present, resulting in alloreactivity due to the presentation of novel peptides (the anchor site modification/occupation model) [18]. A recent *in vitro* study suggests evidence for the pi concept, and that oxypurinol has higher affinity for the *HLA-B*5801* molecule compared to allopurinol in docking experiments [20].

A meta-analysis calculated the odds ratios for allopurinol induced SJS/TEN in *HLA-B*5801* carriers as 96.6 compared to allopurinol-tolerant matched controls, or 79 compared to population controls [21]. The American College of Rheumatology (ACR) guidelines recommend screening only patients who are in high risk populations (Koreans with stage 3

chronic kidney disease, Han Chinese and Thai patients), and those found to be positive for *HLA-B*5801* should be prescribed an alternative drug [PMID: 23024028] [22]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines also recommend not using allopurinol in patients who are known carriers of *HLA-B*5801* [11]. The FDA-approved drug label for allopurinol currently carries no information regarding *HLA* genotype, despite FDA scientists publishing a study assessing the clinical usefulness of allopurinol pharmacogenetics and reporting a strong and highly significant association between *HLA-B*5801* and likelihood of allopurinol-associated SCAR [1, 23].

In some populations (Han Chinese, Thai, Korean) *HLA-B*5801* explains 80–100% of the SCAR cases, whereas in other populations (Japanese, European) *HLA-B*5801* explains around 55% of the cases [24–30] suggesting that there are additional risk alleles and genetic variants that are also important for SCAR. *In vitro* experiments also suggest that allopurinol/oxy-purinol-induced reactions are not strictly restricted to the *HLA-B*5801* molecule [20]. Additional alleles associated with allopurinol-induced SCAR include: rs9263726 A (which is in complete linkage with *HLA-B*5801* in Japanese patients), rs2734583, rs3094011, GA005234, rs2844665 C, rs3815087 A, rs3130931 C, rs3130501 G, rs3094188 A, rs9469003 C, HLA-A*33:03, HLA-C*03:02, HLA-C*08:01, HLA-Cw3, HLA-A33, HLA-DR13, HLA-D3, HLA-Cw*0302, HLA-A*3303, HLA-DRB1*0301, rs3117583, rs1150793, rs2855804, rs2268791, rs1594, rs2304224 (details of each study are available at (<http://www.pharmgkb.org/drug/PA448320>) [24, 28–31].

Febuxostat was associated with hypersensitivity in two reported cases of patients who previously had adverse reactions to allopurinol [32, 33] – to our knowledge the genetic mechanisms behind this have not been described, as yet. No pharmacogenetic studies related to febuxostat are currently found.

2) Drugs that increase the removal of uric acid: urate oxidase (uricase), rasburicase, pegloticase

Pharmacodynamics

One strategy for enhancing uric acid excretion is to add exogenous urate oxidase enzyme not expressed in humans. Urate oxidase breaks down uric acid to 5-hydroxyisourate, which is then spontaneously degraded to allantoin without the aid of enzymes (Figure 1) [2–4]. Allantoin has 5–10 fold increased solubility compared to uric acid, and thus is more readily excreted via the kidneys [3, 4, 6]. Uricozyme[®] is urate oxidase extracted from *Aspergillus flavus*, however due to product-related impurities it is associated with acute hypersensitivity reactions [2, 6]. A recombinant form of urate oxidase, rasburicase, was developed to reduce the occurrence of these reactions [2, 6]. Rasburicase rapidly reduces uric acid plasma concentrations and exposure [2, 34–37]. Rasburicase however is unsuitable for the treatment of gout due to its short half-life, thus pegloticase (or PEG uricase, Krystexxa[®]) is recombinant urate oxidase conjugated to polyethylene glycol that is thought to result in an increased half-life compared to rasburicase [2, 38].

Pharmacogenomics

Rasburicase and pegloticase (forms of urate oxidase) are contraindicated in G6PD deficient individuals due to an increased risk of hemolytic anemia and methemoglobinemia, conditions involving red blood cells (RBCs) [39–41]. This increased risk stems from G6PD's role in producing NADPH in RBCs (see the PharmGKB Pentose Phosphate Pathway) [42]. When rasburicase breaks down uric acid into allantoin, hydrogen peroxide (H_2O_2) is released as a by-product, a reactive oxygen species that can cause damage in RBCs and may ultimately result in cell turnover (hemolysis). Under normal conditions, the H_2O_2 is reduced to water and oxygen molecules by regulatory mechanisms, many of which require NADPH (See the PharmGKB Oxidative Stress Regulatory Pathway). Methemoglobin (MetHb) is formed through the oxidation of heme iron atoms in hemoglobin and cannot transport oxygen or carbon dioxide; it is maintained at levels of around 1% in order to prevent methemoglobinemia (>1% MetHb), which can lead to cyanosis and tissue hypoxia (see the PharmGKB Methylene Blue Pathway, PD) [42]. G6PD deficient RBCs are unable to enhance NADPH production and are thus more susceptible to oxidative damage that can ultimately result in methemoglobinemia and/or hemolysis [39, 43–49]. More than 180 genetic variants within the *G6PD* gene have been described to date, and many confer deficiency of the G6PD enzyme in RBCs (see the PharmGKB G6PD VIP summary for more detailed information www.pharmgkb.com/vip/PA28469) [44, 50–53]. Several cases of methemoglobinemia and hemolytic anemia subsequent to treatment by rasburicase or urate oxidase have been reported in G6PD deficient individuals, though the underlying G6PD variant is often not reported and few studies report genotyping (Table 2). CPIC guidelines recommend avoiding the use of rasburicase in patients homo/hemizygous for *G6PD* variants that confer deficiency – in all other patients an enzyme test for G6PD deficiency is recommended prior to rasburicase use [54].

Deficiencies in anti-oxidant mechanism pathways, not just in the G6PD enzyme, may further contribute to risk of rasburicase-induced methemoglobinemia/hemolysis [42, 55]. Individuals with acatalasemia are homozygous for a catalase gene (*CAT*) variant that affects catalase mRNA expression (Japanese Type I; OMIM 115500.0001, II; OMIM 115500.0002, Hungarian Type A; OMIM 115500.0003, B-D) or have the unstable Swiss protein variant, resulting in minimal catalase activity in erythrocytes [56, 57]. Heterozygotes of Japanese and Hungarian *CAT* variants have hypocatalasemia, with around half of the normal catalase blood levels [56, 57]. Takahara's disease can develop in patients with acatalasemia from the production of H_2O_2 by oral microorganisms [56]. Higher levels of methemoglobin are seen in Japanese acatalasemia erythrocytes compared to normal erythrocytes when exposed to nitrogen monoxide or dioxide [57], and treatment of murine acatalasemia erythrocytes with H_2O_2 induces hemolysis *in vitro* [58]. Methemoglobinemia developed in a patient with the *CAT* Japanese Type genetic variant when H_2O_2 disinfectant was used pre-surgery [59]. In conclusion, catalase deficient patients may be more susceptible to methemoglobinemia and hemolysis with rasburicase treatment due to the release of H_2O_2 , though direct cases have yet to be reported to our knowledge [55]. Cases of individuals with combined G6PD and catalase deficiency have been reported [56] and thus these individuals may be at a higher risk of rasburicase-induced methemoglobinemia and/or hemolysis. Patients with cytochrome b5 reductase (*CYB5R3*, NADH-dependent methemoglobin reductase) deficiency

are less able to reduce methemoglobin, and may be more susceptible to drug-induced methemoglobinemia and hemolysis [60–64], along with individuals with hemoglobin variants e.g. Hasharon [62, 65], or deficiency in glutathione reductase (GSR) [65].

3) Drugs that inhibit the reabsorption of uric acid: uricosurics

Pharmacodynamics

Uricosuric drugs (e.g. probenecid, benzbromarone, sulfinpyrazone) inhibit reabsorption of uric acid in the renal proximal tubule by targeting transporters (Figure 3) [2, 5]. Probenecid is recommended by the ACR as an alternative first line therapy in patients with gout in whom allopurinol/febuxostat are contraindicated [22]. Numerous transporters have a putative role in the secretion and reabsorption of uric acid across the luminal apical membrane of the renal proximal tubule and across the basolateral interstitial membrane; however, a clear picture of the mechanisms of uric transport has still to be defined [66, 67]. Recent genetic analyses such as genome wide association studies (GWAS) have identified variants in novel genes associated with uric acid levels or gout and have helped in the elucidation of which proteins may be important in uric acid transport and plasma levels in humans [66–73]. The current model involves a complex of proteins: the urate or uric acid ‘transportasome’ [66, 67, 69]. The transporters of the transportasome are involved in the transport of other compounds; however, here we focus on uric acid.

URAT1 (*SLC22A12*) is a transporter protein found on the apical surface of renal proximal tubule epithelial cells with a major role in the uptake of uric acid from the lumen [66, 68, 69, 74, 75]. Variants in the *SLC22A12* gene identified in renal hypouricemia patients lack uric acid transport activity or display significantly decreased activity compared to wild-type URAT1 *in vitro* [74, 76]. Also expressed on the apical membrane of renal proximal tubule cells with a role in uric acid secretion into the glomerular filtrate/lumen are transporters encoded by *SLC17A1* (NPT1), *SLC17A3* (NPT4) and *ABCG2* (BCRP) [66, 68, 69]. GLUT9 (*SLC2A9*) is expressed on the basolateral membrane, with a chief role in the transport of uric acid into the interstitium and blood [66, 68, 69]. Evidence suggests that two isoforms of GLUT9 exist – GLUT-9a (isoform 1) on the basolateral side, and GLUT-9b (isoform 2 or GLUT9 N) on the apical side, though the role of the latter remains unclear [66, 68, 69]. *In vitro*, both isoforms are capable of transporting uric acid in stably expressing cells [77]. Validating their role in uric acid transport, two recent meta-analyses of different GWAS studies (both in more than 28,000 individuals of European descent/White ethnicity), found SNPs associated with serum uric acid levels in loci containing the *SLC22A12*, *SLC2A9*, *SLC17A1*, *SLC17A3* and *ABCG2* genes, amongst other novel loci [78, 79]. A GWAS meta-analysis examining four phenotypes related to kidney function verified *SLC2A9*, *ABCG2* and *SLC22A12* loci were associated with uric acid concentration in 33,074 East Asian individuals [73]. GWAS meta-analysis of >140,000 individuals of European descent from the Global Urate Genetics Consortium (GUGC) identified 10 previously known and 16 novel loci associated with serum urate concentrations at genome-wide significance [72]. These loci explain 7% of the variance in urate concentrations, with *SLC2A9* and *ABCG2* loci contributing to 3.4% of this [72]. 17 of the loci associated with urate concentrations were also associated with gout [72], as has been shown previously for *SLC2A9* and *ABCG2* loci

[79]. Many of the SNPs associated with uric acid concentrations in the European analysis were also associated in cohorts of African-Americans (n=5,820), Japanese (n=15,286) and individuals of Indian ancestry (n=8,340), though differences are observed and may be due to variation in allele frequencies between the four different populations [72]. Interestingly, novel loci associated with uric acid concentrations reported in recent GWAS meta-analyses include genes encoding transcription factors and genes implicated in glucose homeostasis and kidney function, revealing possible new avenues for drug discovery for reducing urate levels and preventing kidney disease [72, 73, 78, 79].

Several other genes shown in the shaded section of Figure 3 have a potential role in uric acid transport in the human renal proximal tubule. These all have *in vitro* evidence, and some have also been identified in GWAS related to serum uric acid concentrations and/or gout [66–69, 72, 78–83].

Probenecid prevents the reabsorption of organic anions such as uric acid from the renal proximal tubule predominantly by inhibiting URAT1 (*SLC22A12*) transporter protein activity [5, 66, 74, 75, 84]. It may also act upon OAT1 (*SLC22A6*), OAT4 (*SLC22A11*) and OAT10 [83–85]. *In vitro* probenecid does not seem to have an effect on GLUT9 (*SLC2A9*) at an effective pharmacological concentration of 1mM [77]. Benzbromarone inhibits uric acid transport by URAT1 (*SLC22A12*) and GLUT-9 (*SLC2A9*) *in vitro*, though at therapeutic doses its action upon GLUT-9 may be minimal [69, 74, 75, 77, 84, 86, 87]. It also displays action against uric acid uptake by OAT1 (*SLC22A6*) *in vitro* [85]. Sulfapyrazone inhibits uric acid uptake by URAT1 (*SLC22A12*) *in vitro*, and reduces serum uric acid *in vivo* [74, 88, 89].

Used for hypertension treatment, losartan is a unique angiotensin II receptor antagonist in that it also increases uric acid secretion and significantly decreases plasma levels by targeting URAT1 (*SLC22A12*) [74, 86, 90]. Tranilast is an anti-inflammatory, however also exhibits uricosuric properties by inhibiting URAT1 and GLUT9, thus these combined effects make it a potential gout therapeutic [84]. Vitamin c is thought to act as a uricosuric by inhibiting reabsorption of uric acid by URAT1 (*SLC22A12*) [91]. Studies have revealed that doses of 500mg/daily may reduce serum uric acid and doses of >1000mg/daily may reduce risk of gout [38]. Salicylate/salicylic acid and indomethacin also inhibit uric acid uptake by URAT1 (*SLC22A12*) *in vitro* [74, 75].

Pharmacogenomics

As well as influencing plasma uric acid levels and risk of gout, polymorphisms in transporter genes may also affect the efficacy of uricosurics to inhibit reabsorption. However, currently there are few published pharmacogenetic studies investigating these drugs; below are the genetic associations with uricosurics found in an extensive literature search. Figure 3 illustrates genes that express proteins involved in the regulation of uric acid transport, highlighting potential novel drug targets and potential genes of interest for future pharmacogenetic studies. Polymorphisms in genes involved in the metabolism of these drugs may also influence their toxicity and efficacy.

Numerous variants within *SLC22A12* have been identified in patients with hypouricemia, some of which display reduced uric acid uptake *in vitro* [74, 76, 92, 93]. There is some evidence to suggest that these variants may affect response to uricosuric and anti-uricosuric drugs that act upon URAT1. Amongst hypertensive patients (without hypouricemia) with wildtype *SLC22A12*, benzbromarone or losartan treatments significantly increase in uric acid clearance (Cur)/creatinine clearance (Ccr) ratio (indicating a decrease in serum uric acid). In patients with hypertension and hypouricemia who were homozygous or compound heterozygous for variants in the *SLC22A12* gene, benzbromarone or losartan treatment had no effect on the Cur/Ccr ratio (indicating a lack of effect on serum uric acid levels). Losartan was still able to maintain its hypotensive effect on blood pressure in these patients [86]. These variants included rs121907896 G269A (Arg90His) and rs121907892 G774A Trp258Ter (c.NM_144585.2); both identified in patients with idiopathic renal hypouricemia, associated with reduced uric acid uptake *in vitro* and lower residuals of serum uric acid levels compared to wild-type in subjects [74, 76, 93]. This lack of response to benzbromarone in hypouricemia patients with *SLC22A12* variants that reduce uric acid transport is supported by another study, which also observed an effect on the anti-uricosuric activity of pyrazinamide [76].

Due to reports of fatal hepatotoxicity, benzbromarone was withdrawn from the market by one of its main manufacturers, though it is still available from other drug companies in several countries across the globe [87, 94]. Genetics could be a factor that influences toxicity risk. Benzbromarone is metabolized by CYP2C9 to form the active metabolite 6-hydroxybenzbromarone (which has inhibitory activity upon URAT1 uric acid uptake) and by CYP3A4 to form 1'-hydroxybenzbromarone [75, 87, 94, 95]. 6-hydroxybenzbromarone is further metabolized to 5,6-dihydroxybenzbromarone by CYP2C9 and CYP1A2 [94]. A small study in 20 healthy individuals saw reduced metabolism and clearance of benzbromarone in an individual with the *CYP2C9**3/*3 genotype compared to those with *1/*1 or *1/*3 genotypes, and a significantly higher elimination half life of 6-hydroxybenzbromarone in patients with the *1/*3 genotype compared to *1/*1 [96]. Whether *CYP2C9* genotype may have a clinically relevant effect on benzbromarone pharmacodynamics is unknown; the study saw no differences in uric acid excretion or plasma concentrations [96]. Polymorphisms in *CYP2C9* that result in higher plasma levels of benzbromarone and reduced metabolism to 6-hydroxybenzbromarone could contribute to toxicity: benzbromarone, 1'-hydroxybenzbromarone and 5,6-dihydroxybenzbromarone have been associated with toxicity *in vitro* [95, 97]. The CYP2C9 dependent sequential oxidations forming the 5,6-catechol has the potential for forming a reactive quinone, which is supported by forming glutathione adducts *in vitro* [87, 95]. This reaction profile is typical of several other hepatotoxic drugs. It has been recommended that CYP2C9 genotyping be carried out in cases of benzbromarone-induced hepatotoxicity [87], in order to begin to capture more evidence for whether an association between CYP2C9 genotype and benzbromarone toxicity exists.

Intrinsic clearance of sulfapyrazone by UGT1A9 glucuronidation was shown to be significantly lower in cells expressing the *UGT1A9* variant Met33Thr (rs72551330 allele C) compared to Met33 (allele T) [98].

Conclusions

Unlike other animals, humans and some apes do not have the ability to break down uric acid into a more soluble form; high levels of plasma uric acid are a feature of pathologies such as gout and Tumor Lysis Syndrome and can result in kidney failure. Pharmaceuticals have been developed to either inhibit the formation of uric acid, increase its excretion or inhibit its reabsorption. Here we have outlined the mechanisms of action of uric acid-lowering drugs, the genes that express proteins targeted in these pathways and genetic variants associated with response to these drugs. Allopurinol and rasburicase are not recommended in individuals with particular genetic polymorphisms due to adverse reactions. Few pharmacogenetic studies are published for uricosurics and a full picture of the uric acid transportosome is still emerging; further research into the effects of polymorphisms in transporter genes on the uricosuric action of these drugs may provide insights into treatment efficacy or novel targets for drug development.

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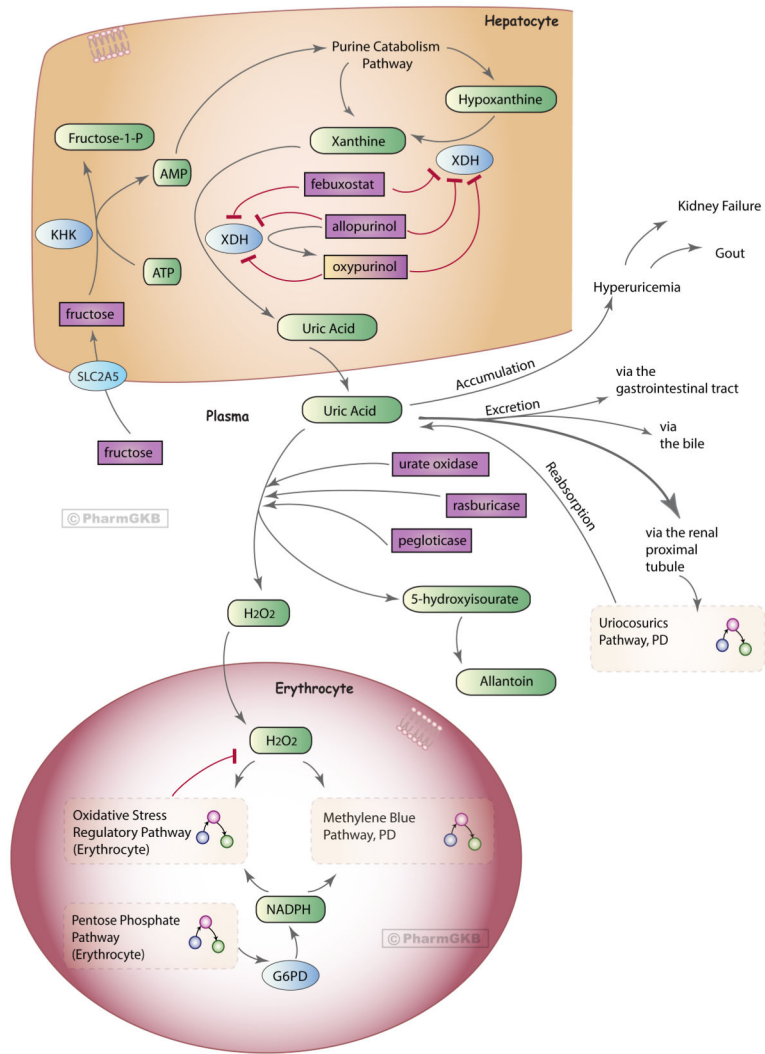
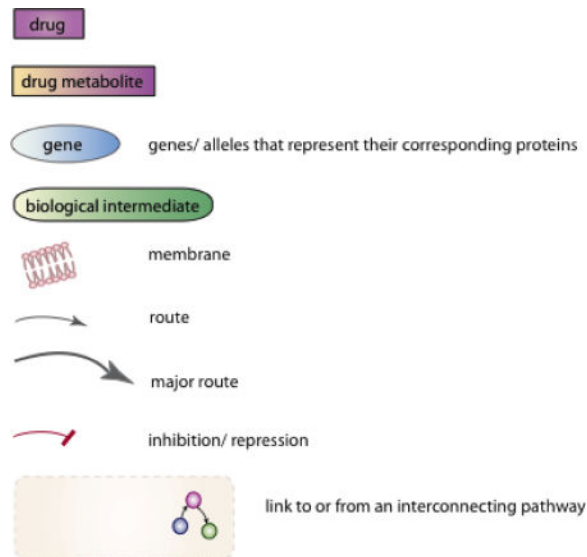


Figure 1. Uric acid-lowering drugs pathway, Pharmacodynamics



Uric acid is the end product of the purine catabolism pathway in humans. Here is a representation of the drugs involved in lowering plasma uric acid levels, depicting their mechanism of action by either 1) preventing the formation of uric acid in hepatocytes by inhibition of xanthine dehydrogenase enzyme (XDH): allopurinol and febuxostat, or 2) breaking down uric acid in the plasma to a more soluble form: urate oxidase, rasburicase and pegloticase. Proteins/enzymes are represented by their genes (using HGNC approved symbols). Drugs involved in preventing the reabsorption of uric acid in the renal proximal tubule are depicted in the interconnecting Uricosurics Pathway (Figure 3). The majority of uric acid found at physiological pH is in the form of urate anion [68]; here we used the term 'uric acid' to encompass urate. The mechanisms depicted in the erythrocyte show the neutralization of hydrogen peroxide (H_2O_2), produced in the break down of uric acid. In G6PD deficient erythrocytes this is defective, and may ultimately result in methemoglobinemia and or hemolysis. See the main text description and the three interconnecting pathways for further details. An interactive version of this pathway can be found at <http://www.pharmgkb.org/pathway/PA165980774>.

Abbreviations:

AMP = adenosine monophosphate; ATP = adenosine triphosphate; ER = endoplasmic reticulum; G6PD = glucose-6-phosphate dehydrogenase; H_2O_2 = hydrogen peroxide; HGNC = HUGO Gene Nomenclature Committee; HLA-B = major histocompatibility complex, class I, B; KHK = ketohexokinase (fructokinase); NADPH = nicotinamide adenine dinucleotide phosphate; PD = pharmacodynamic; PharmGKB = Pharmacogenomics Knowledgebase; SLC2A5 = solute carrier family 2 (facilitated glucose/fructose transporter) member 5; XDH = xanthine dehydrogenase.

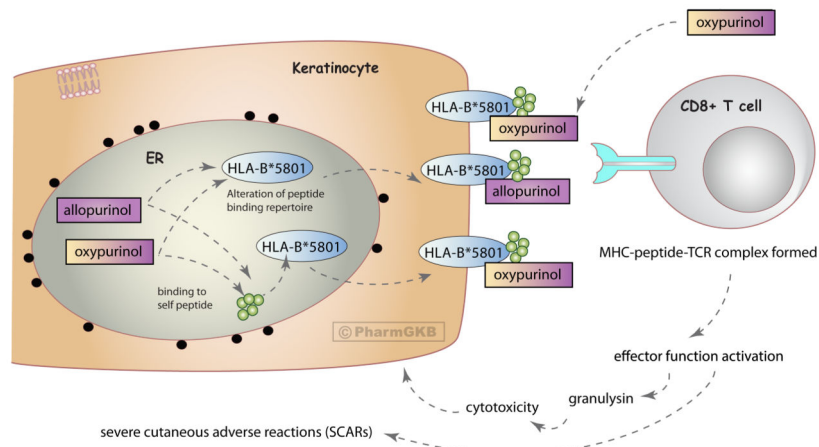
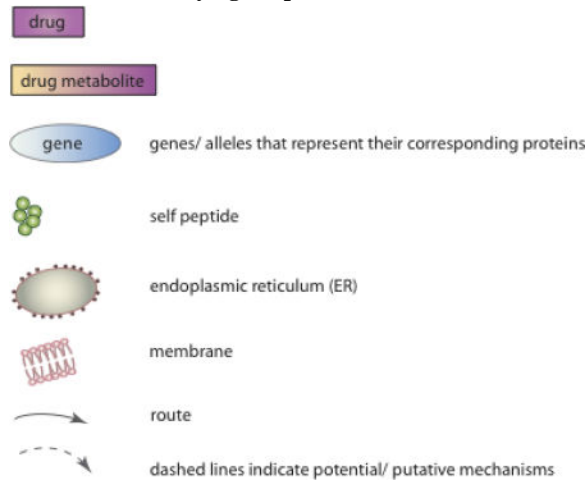


Figure 2. Potential mechanisms underlying allopurinol-induced SCARs



Dashed arrows represent hypothesized mechanisms of action that may underly allopurinol-induced severe cutaneous adverse reactions (SCARs) linked to the *HLA-B*5801* allele (see main text for further description).

HLA = human leukocyte antigen

MHC = major histocompatibility complex

TCR = T cell receptor

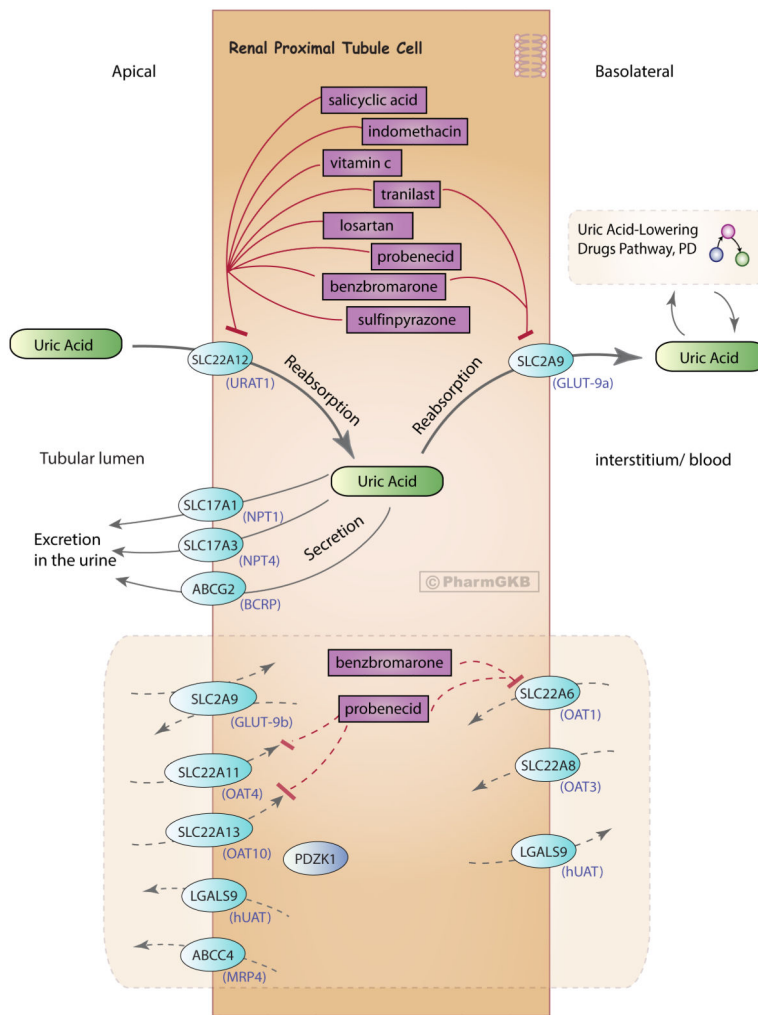
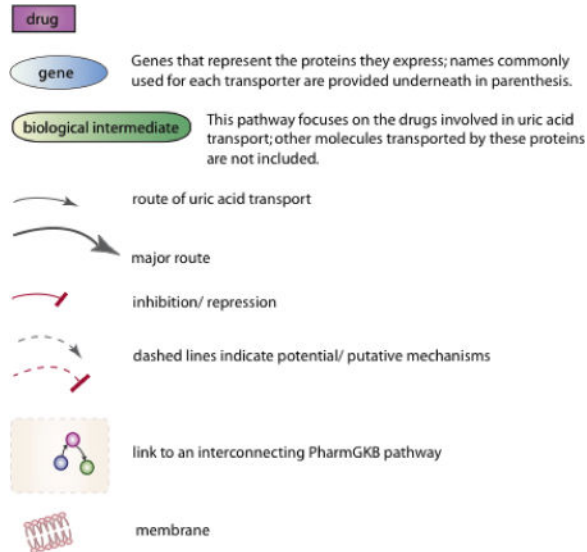


Figure 3. Uricosurics pathway, Pharmacodynamics



A representative diagram of a renal proximal tubule epithelial cell and the drugs that are involved in preventing the reabsorption of uric acid into the body. Uric acid is reabsorbed into the interstitium/blood by transport from the tubular lumen across the apical membrane into the cell and then across the basolateral membrane. It is transported across the apical membrane for excretion in the urine. Depicted are genes that represent the transporters involved in uric acid transport across the apical and basolateral membrane of the cell. Commonly used names for the transporter proteins are indicated in parenthesis under the gene name. Uric acid in the blood links to the interconnecting Uric Acid-Lowering Drugs Pathway (Figure 1). Genes/proteins that are putatively involved in uric acid transport are also shown in the shaded bottom half of the diagram, representing potential novel drug targets or the potential for repurposing of drugs known to target these proteins. An interactive version of this pathway can be found at <http://www.pharmgkb.org/pathway/PA166114721>. The majority of uric acid found at physiological pH is in the form of urate anion [68]; here we used the term ‘uric acid’ to encompass urate.

Table 1

Reported associations between HLA-B*58:01 and risk of allopurinol-induced SCARs

Study Type	Cases	Controls	OR (95% C.I.)	P value	Patient Population	Race/ethnicity	Typing and genotyping method	Reference
Case/control study	n=7 (SJS, SJS ocular type, erythema exudativum multiforme (EEM) minor).	n=25 (no ADRs).	65.6 (2.9–1497)	9.733×10^{-4}	Hyperuricemia.	Japanese.	PCR+rSSO and PCR-SBT.	PMID: 23669020 [99]
Case/control study	n=25 (SJS, SJS/TEN, DRESS).	n=23 allopurinol-tolerant.	39.11 (4.49–340.51)	5.9×10^{-4}	Asymptomatic hyperuricemia, gouty arthritis or nephropathy.	Portuguese.	PCR+rSSO and SSO-HR typing kit.	PMID: 23600531 [100]
Observational study in family members	n=1 male who developed SJS.	n=1 the brother of the case, allopurinol-tolerant.	NA	NA	Gout and essential hypertension.	Self-described Han Chinese.	4-digit, high resolution DNA sequencing.	PMID: 23280169 [101]
Case/control study	n=20 (SJS, DRESS, TEN, EMM).	n=30 allopurinol-tolerant, treated for at least 1 year (not matched to cases).	123.5 (12.8–1195.1) (OR was higher when EMM case was excluded).	$<1 \times 10^{-4}$	NA	Han Chinese (Hong Kong).	Sequence-based typing.	PMID: 22348415 [102]
Case-control study	n=51 patients with allopurinol-induced SCAR (SJS, TEN or HSS).	n=135 allopurinol-tolerant (at least 6 months of treatment).	580.3 (34.4–9780.9)	4.7×10^{-24}	Hyperuricemia. Chronic renal insufficiency was significantly higher in cases vs controls, and gouty arthritis was the converse.	Han Chinese residing in Taiwan.	Sequence-specific oligonucleotide reverse lineblot.	PMID: 15743917 [24]
Comparison of allele frequencies in a population.	n=31 patients with allopurinol-induced SJC or TEN.	NA	61 (32–118) for the allele frequency of cases compared to the allele frequency found in the general European population.	$<10^{-8}$	Mostly hyperuricemia.	Mixed population, mostly European.	OLERSUP SSP HLA-B kit, sequencing in three cases.	PMID: 18192896 [103]
Comparison of allele frequencies in a population.	n=10 patients with allopurinol-induced SJS, TEN (one also treated with carbamazepine, another also treated with phenytoin).	NA	40.83 (10.53–158.9) allele frequency compared to the frequency in n=493 healthy Japanese subjects.	<0.0001	NA	Japanese.	Sequencing.	PMID: 19018717 [104]
Case-control	n=27 patients with allopurinol-induced SJS or TEN (within 3 months of treatment).	n=54 allopurinol-tolerant patients (>6 months treatment) from the same hospitals.	348.3 (19.2–6336.9)	1.6×10^{-13}	Hyperuricemia, some patients with gouty arthritis.	Self-identified Thai or Thai-Chinese.	PCR with sequence specific primers, and sequence-based typing.	PMID: 19696695 [105]
Case/control	n=25 patients with allopurinol-induced SCARs (20 with DIHS, 5 with SJS/TEN).	n=57 allopurinol-tolerant patients.	97.8 (18.3–521.5) (cases verses tolerant control).	2.45×10^{-11}	Cases = patients with gouty arthritis or hyperuricemia related to chronic renal failure. Controls = patients with chronic renal failure.	Korean.	Direct DNA sequencing analysis.	PMID: 21301380 [28]
Comparison of allele frequency in healthy individuals.	n=7 allopurinol-induced SJS/TEN patients.	n=115 healthy individuals.	13.625 (2.774–69.448)	0.248 after correction for	NA	Caucasian, Northern Italy.	4-digit allele level within the antigen binding domain. PCR-SSP.	PMID: 21545408 [29]

Study Type	Cases	Controls	OR (95% C.I.)	P value	Patient Population	Race/ethnicity	Typing and genotyping method	Reference
Case/control	n=16 patients with an allopurinol hypersensitivity reaction (9 had SCARs, 7 had simple rashes).	n=432 allopurinol-tolerant patients (60 days).	179.24 (10.19–3151.74) SCARs patients vs tolerant.	<0.001	Patients with chronic renal insufficiency who took allopurinol.	Korean.	Serologic HLA typing by microlymphocytotoxicity method for HLA-B*58.	PMID: 21393610 [106]
Case/control	n=38 allopurinol-induced MPE, DRESS, SJS/TEN (within first 2 months of exposure).	n=63 allopurinol-tolerant (treated for >3 months with no cutaneous manifestations).	580.07 (32.18–10456.80)	7.01×10^{-18}	Hyperuricemia and gouty arthritis. (A higher frequency of chronic renal insufficiency was seen in cases).	Cases = from the Southern region of China, control = all Han Chinese.	Direct DNA sequencing.	PMID: 22909208 [107]
Case report	n=1, an 8-year old girl who developed TEN.	NA	NA	NA	Developed asymptomatic hyperuricemia due to anti-TB treatment and was treated with allopurinol.	German, Kenyan parents.	Not described.	PMID: 19483528 [108]
Case report	n=1, a 65-year old male who developed DRESS 1 month after allopurinol treatment initiation.	NA	NA	NA	Hyperuricemia.	Han Chinese.	Method not described.	PMID: 22901319 [109]
Study identified patients across Australia with allopurinol hypersensitivity and genotyping.	N=11 patients with allopurinol hypersensitivity including SJS/TEN and DRESS/DIHS, n=12 patients with MPE.	NA	NA	NA	Not described.	Australian, mixed population: Caucasian and South-East Asian.	Four-digit high resolution DNA sequence-based HLA typing.	PMID: 21790926 [110]
Case report	n=1, a 57-year old male who was diagnosed with SJS 10 days after allopurinol treatment.	NA	NA	NA	Not described.	Not described.	Reverse sequence-specific oligonucleotide with PCR for serological HLA typing.	PMID: 17587850 [111]
Case report	n=1, a 77 year-old male who was diagnosed with allopurinol-induced DIHS.	NA	NA	NA	Not described.	Not described.	Not described.	PMID: 17587850 [111]
Case report	n=1, a 93-year old male diagnosed with Allopurinol-induced SJS/TEN (a year earlier he had previously experienced maculopapular-type eruption and fever within 1 month of allopurinol treatment).	NA	NA	NA	Not described.	Not described.	Not described.	PMID: 17587850 [111]

Study Type	Cases	Controls	OR (95% C.I.)	P value	Patient Population	Race/ethnicity	Typing and genotyping method	Reference
Drug-surveillance programme assessing Allopurinol cutaneous ADRs	n=84 cases, including maculopapular eruptions, SJS, TEN and DRESS. Testing for HLA-B*5801 was only done in a subgroup of patients with SJS/TEN.	Allele frequency in a general European population of 0.015 was compared.	18/18 cases of SJS/TEN in whom the assay was performed carried HLA-B*5801. OR=65.07 (30.66–138.09) compared to the general European population allele frequency.	<0.0000.	Asymptomatic hyperuricemia, gout or secondary hyperuricemia (many also with hypertensive heart disease and renal failure).	Southern Sardinia, Italian, European.	PCR-SSO/PCR-SSP.	PMID: 22017528 [112]

Abbreviations

ADRs = adverse drug reactions
 DIHS = drug-induced hypersensitivity syndrome
 DRESS = drug reaction with eosinophilia and systemic symptoms
 EMM = erythema multiforme major
 HS/SJS = hypersensitivity syndrome
 NA = not applicable
 MPE = maculopapular exanthema
 PCR = polymerase chain reaction
 PCR-rSSO = PCR- reverse sequence-specific oligonucleotide
 PCR-SBT = PCR-sequence based typing
 SJS = Steven's Johnson Syndrome
 SSP = sequence-specific primers
 TEN = toxic epidermal necrolysis
 OR = odds ratio
 CI = confidence interval
 HLA = human leukocyte antigen

Table 2

Urate oxidase/rasburicase-induced adverse reactions associated with G6PD deficiency.

Patient details	Reason for urate oxidase/rasburicase treatment	Consequence of urate oxidase/rasburicase treatment	Genetic or enzyme screening	Reference
16 year-old African American male.	Hyperuricemia due to Burkitt's lymphoma.	Developed methemoglobinemia. This was reversed by discontinuation of rasburicase, blood transfusion and oxygen delivery.	Diagnosed with G6PD deficiency because of known sensitivity - no screening to confirm was carried out and no genetic information was provided.	PMID: 22190578 (Ng et al. 2011) [113]
Adult case report.	Cancer patients at high risk of developing TLS.	Patients with known G6PD deficiency were excluded from the study, however one patient developed methemoglobinemia and hemolytic anemia after the first dose of rasburicase, which was discontinued. Methylene blue treatment exacerbated hemolysis, and the patient was identified as having G6PD deficiency.	Diagnosis method not reported and no genetic information provided.	PMID: 22015451 (Vadhan-Raj et al. 2011) [114]
Male adult case report	A male with Burkitt's lymphoma prescribed rasburicase before initiating chemotherapy.	Developed acute intravascular hemolysis.	The initial assay obtained soon after hemolysis was normal, however A- G6PD deficiency was later confirmed by a subsequent assay.	PMID: 20196170 (Bain et al. 2010) [115]
12 year old Laotian male with T-cell ALL.	Hyperuricemia.	Developed methemoglobinemia and was treated with methylene blue. This did not improve methemoglobin levels or oxygen saturation levels and an exchange transfusion was undertaken to remove methemoglobin.	G6PD activity assay revealed a deficiency (genotyping not reported).	PMID: 18561168 (Bhat et al. 2008) [116]
African American male adult.	Acute renal failure secondary to hyperuricemia.	Developed methemoglobinemia and hemolytic anemia. Treated with daily packed red blood cell transfusions for 3 days, with resolution of methemoglobinemia and hemolysis. Rasburicase was thought to be the probable cause, as indicated by the Naranjo probability scale.	G6PD deficiency was confirmed by G6PD activity assay (no genotyping reported).	PMID: 16204390 (Browning and Kruse, 2005) [49]
Male adult.	Long term treatment with an i.v. of urate oxidase every other day for hyperuricemia several months following a kidney transplant.	9 months later treated for 3 consecutive days with urate oxidase and subsequently diagnosed with hemolytic anemia, for which the patient received hemodialysis and recovered.	G6PD deficiency was later confirmed. The patient was classified as having the Mediterranean variant because of ethnic origin (born in Italy), although this was not confirmed by electrophoresis or genotyping.	PMID: 2019023 (Ducros et al. 1991) [117]
Pediatric case (mentioned in the discussion as an unpublished observed case).	Undergoing chemotherapy.	Hemolytic anemia.	Not detailed.	PMID: 2019023 (Ducros et al. 1991) [117]
A 12 year old African American male with ALL.	Patients with known G6PD deficiency were excluded from the study.	Developed methemoglobinemia after administration of non-recombinant urate oxidase (Uricozyme) and was later diagnosed with G6PD deficiency.	No test for diagnosis or genotyping reported.	PMID: 9369411 (Pui et al. 1997) [34]

Patient details	Reason for urate oxidase/rasburicase treatment	Consequence of urate oxidase/rasburicase treatment	Genetic or enzyme screening	Reference
A single case reported in the cohort of n=410.	A retrospective study of medical records of patients with B-cell lymphoma or ALL.	A single patient developed hemolysis with urate-oxidase treatment, 'revealing a previously unknown G6PD deficiency'.	No tests confirming the diagnosis of G6PD deficiency were mentioned.	PMID: 12075750 (Patte et al, 2002) [118]
African American adult male with multiple myeloma admitted for chemotherapy.	Hyperuricemia and acute kidney injury.	Methemoglobinemia. As G6PD status was unknown, ascorbic acid was administered to treat the methemoglobinemia rather than methylene blue. The patient developed hemolysis, and required red blood cell transfusion.	Test results on day 3 revealed the patient was G6PD deficient (by enzyme activity level, measured in U/g Hb). Both methemoglobinemia and hemolysis were attributed to G6PD deficiency (genotyping not reported).	PMID: 22573495 (Sonbol et al, 2012) [119]
A 14 year old Cambodian male diagnosed with Burkitt's lymphoma.	Received allopurinol for hyperuricemia, and furosemide and calcitonin for hypercalcemia. Rasburicase was administered before induction of chemotherapy.	Developed methemoglobinemia and subsequent hemolysis and required 3 red blood cell transfusions.	On day 3, G6PD deficiency was confirmed by quantitative assay (prior to the first transfusion).	PMID: 17387701 (Borinstein et al, 2007) [120]
A pediatric case in a cohort of n=278 pediatric and adult patients.	Rasburicase was administered in patients at risk of tumor lysis during initiation of chemotherapy in a compassionate use study. Patients with known G6PD deficiency were excluded.	A pediatric patient developed methemoglobinemia and was subsequently diagnosed with G6PD deficiency.	Testing method was not reported.	PMID: 12942574 (Bosly et al, 2003) [121]
A newborn male who was born at 30 weeks gestation by cesarean.	Among other complications, he was treated with rasburicase for a high uric acid level.	Hemolysis developed and he subsequently died.	A postmortem blood analysis showed a deficiency in G6PD enzyme, and genetic analysis revealed he was hemizygous for the G6PD Mediterranean variant.	PMID: 23209099 (Zaramella et al, 2012) [122]
46-year old man, mixed Mauritian-Chinese background.	Treated for chronic lymphocytic leukemia.	12 hours after rasburicase administration methemoglobinemia and hemolytic anemia developed. He was transfused with packed red blood cells, fluids and ascorbic acid.	Screening test revealed he had abnormal G6PD deficiency (variant not described).	PMID: 23860572 (Cheah et al, 2013) [123]
Case report of an adult male.	Part of a chemotherapy protocol.	A deficiency in G6PD was revealed.	Mediterranean variant determined by genotyping.	PMID: 19654083 (article in French) (Joly et al, 2009) [124].

Abbreviations

ALL = acute lymphoblastic leukemia; G6PD = glucose-6-phosphate dehydrogenase; TLS = tumor Lysis Syndrome.