Genetic variants of **UDP-glucuronosyltransferase 1A** genes are associated with disease presentation and outcome in primary sclerosing cholangitis

Tobias J. Weismüller1 | Taotao Zhou1 | Sandra Kalthoff1 | Henrike Lenzen2,3 | Michael P. Manns3 | Christian P. Strassburg1

**Abstract**

**Background and aims:** Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease without a curative medical therapy. The human UDP-glucuronosyltransferases 1A play a major role in the detoxification and elimination of bilirubin, bile acids and xenobiotics. Whether genetic UGT1A variants determine course and outcome of PSC has not yet been described.

**Methods:** A large cohort of German PSC patients with a long-term-follow-up was genotyped for UGT1A variants including **UGT1A1*28**, **UGT1A3-66 T>C** and **UGT1A7 p.N129K/p.R131K** using TaqMan 5’-nuclease assays. Results were correlated with clinical characteristics and transplant-free survival.

**Results:** About 331 patients with PSC were included in the study (69.9% male, mean age at diagnosis 32.6 years). Median transplant-free survival was 14.9 years. Patients with wild-type alleles of all three UGT1A genes had a longer transplant-free survival (17.2 vs. 14.4 years, \( P = .048 \)) than patients carrying a homozgyous or heterozygous SNP variant in at least one of the **UGT1A1**, **UGT1A3** or **UGT1A7** genes. Additionally, we found that patients carrying wild-type alleles of all three **UGT1A** genes had lower serum bilirubin (25 vs. 38 \( \mu \)mol/L, \( P = .02 \)) and serum cholesterol (195 vs. 223 mg/dL), \( P = .035 \) at first presentation. Furthermore, inflammatory bowel disease was found to be associated with wild-type **UGT1A1** alleles (82.2% vs. 68.4%, \( P = .046 \)).

**Conclusions:** This large cohort shows an association with single nucleotide polymorphisms of the **UGT1A1**, **UGT1A3** and **UGT1A7** genes and outcome in PSC. Thus, **UGT1A1** variants may represent a tool for the prognostic stratification of PSC patients and establish a link between disease progression and the regulation of detoxification by glucuronidation in PSC.

**Abbreviations:** AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCA, cholangiocarcinoma; CRC, colorectal carcinoma; CRP, C-reactive protein; gGT, gamma-glutamyl transferase; IBD, inflammatory bowel disease; LT, liver transplantation; NSAID, non-steroidal anti-inflammatory drug; PSC, primary sclerosing cholangitis; SNP, single nucleotide polymorphism; UDCA, ursodeoxycholic acid; UGT, UDP-glucuronosyltransferases; WBC, white blood cell.

TJW and TZ equally share position as first author.

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1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic progressive cholestatic liver disease with a strong clinical association with inflammatory bowel diseases (IBD). Patients with PSC suffer from recurrent episodes of cholangitis resulting in biliary cirrhosis, and are at a high risk to develop hepatobiliary or colorectal malignancies. At present, there is no curative medical therapy available and therefore liver transplantation (LT) remains the only definitive treatment.

The pathogenesis of PSC is still poorly understood. Multifactorial genesis is presumed, including a proposed genetic susceptibility for PSC. Genome-wide association studies have enabled researchers to look into a wide array of genetic variants to identify patterns of risk loci. Additionally, published data suggest that single nucleotide polymorphisms (SNPs) in PSC patients are associated with genes coding for certain phenotypes in cholangiocyte biology or tumour formation, and can also represent pivotal proteins in fibrogenesis and immunology, which includes IL-2-R or HLA-complex.

Stasis of bile is a known driver of inflammation and ultimately hepatic fibrosis. During cholestasis, individual bile acids and other xenobiotic compounds present in bile expose biliary epithelial cells to a constant stimulus for inflammation, cellular stress and proliferation. The UDP-glucuronosyltransferase (UGT)1A family of proteins plays a major role in the detoxification and elimination of bilirubin, bile acids and a broad array of potentially cytotoxic xenobiotics, which are linked to inflammation. To date, the relationship between the functionally important UGT1A proteins and their naturally occurring genetic variants and the course and outcome of PSC has not yet been established.

The UGT1A gene locus encodes nine active protein isoforms, which are expressed in a tissue specific fashion in many organs. Although UDP-glucuronosyltransferases are very abundantly expressed in the liver (eg UGT1A1 and UGT1A3), extrahepatic glucuronidation is specifically enabled by, for example, the exclusively extrahepatic UGT1A7 in the upper gastrointestinal tract. Genetic variations of the UGT1A genes are frequent and alter the function of the affected genes. Most prominently, polymorphisms of the UGT1A genes are known to cause hyperbilirubinaemia syndromes such as Gilbert-Meulengracht and Crigler-Najjar syndromes. Other genetic variants are associated with the occurrence of different types of carcinomas, for example in bladder, breast, oesophagus, colorectal tract and lung. The risk to develop cholangiocarcinoma (CCA) is significantly higher in patients with PSC. Whether specific UGT1A variants are associated with a higher risk for CCA or contribute to this risk is presently unknown.

Clinical observation has shown that the phenotype and risk for colorectal malignancy in individuals with IBD in PSC have been found to differ from those without PSC. A milder clinical course is usually observed in PSC-IBD and bile acid and microbiota appear to differ from those of regular IBD patient, indicating gut-liver-axis-related factors. Altered glucuronidation of bilirubin or xenobiotics would represent an intriguing hypothesis for the development of IBD in PSC.

Therefore, cholestasis and the associated toxicity of bile components represent an important factor for PSC progression to cirrhosis or CCA. UGT1A is a key process determining the elimination and detoxification of pro-inflammatory and carcinogenic compounds. We thus analysed UGT1A variants in healthy blood donors and in patients with PSC to compare clinical presentation, outcome and association with IBD in carriers of UGT1A variants and wild-type genes in order to establish marker for the course and presentation of PSC.

2 | PATIENTS AND METHODS

Patients

Blood samples were collected from 331 consecutive patients with a well-documented diagnosis of PSC attending the Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, between September 2009 and January 2012. All patients were of German Caucasian ancestry. The diagnosis of PSC was made according to the EASL criteria and based on elevated cholestatic serum enzymes and on typical cholangiographic findings or, in case of small-duct PSC, on a typical histology. Patients with a sclerosing cholangitis owing to secondary causes were excluded. All patients agreed to participate in the prospective study ‘clinical course, management and risk factors in primary sclerosing cholangitis’ [Approval by the Ethics committee of Hannover Medical School (356/2008)]. Written informed consent was obtained from all patients prior to blood sampling.

Control blood samples were obtained from a total of 249 anonymous healthy blood donors from the Department of Transfusion Medicine/Blood Bank of Hannover Medical School, Germany.
2.1 | Data collection

At study entry the following clinical characteristics at date of diagnosis of PSC were recorded from the patient charts: Biochemical blood tests (including haemoglobin level, platelet count, white blood cell (WBC) count, partial thromboplastin time, prothrombin time, C-reactive protein (CRP), creatinine, cystatine C, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (gGT), direct bilirubin, cholesterol), type of PSC (small duct vs. classical PSC), diagnosis of IBD, diagnosis of autoimmune hepatitis (AIH) and serum levels of IgG4.

Furthermore, autoimmune comorbidities comprising diabetes mellitus type 1, thyroiditis, celiac disease, rheumatoid arthritis, sarcoidosis, nephritis, vitiligo, fibrosing alveolitis, Sjögren’s syndrome, systemic sclerosis and myasthenia gravis were documented.

All patients were followed up until June 2016 or until reaching one of the study end points (death and LT). Secondary clinical end points such as hepatobiliary malignancy or colorectal carcinoma (CRC) were also recorded.

2.2 | Genotyping of UGT1A variants

Genomic DNA was isolated from whole blood samples by the NucleoSpin Blood L Kit according to the recommendations of the manufacturer (Machery and Nagel). Concentrations were determined by spectrophotometry at 260 nm and samples were stored in 10 mM Tris/EDTA buffer (pH 8.0) at 4°C until analysis.

Approximately 10 ng of genomic DNA was used as a template in Taqman 5′-nuclease assays to screen for the following UGT1A SNP: UGT1A1*28, UGT1A3-66 T>C and UGT1A7 p.N129K/p.R131K. Primers and probes specific for each SNP were designed with Primer Express software (Applied Biosystems) and labelled with either 6-FAM or VIC as reporter dyes and MGB-NFQ (Applied Biosystems) as a quencher as described previously. All assays were performed as 25-µL reactions using qPCR Mastermix Plus (Eurogentec), 600 nM primer and 200 nM MGB-probe (Applied Biosystems) on 96-well plate. Each run consisted of a hot start at 95°C for 10 min and 35 cycles of 94°C for 15 s and 61°C for 1 min. Fluorescent signals of the reporter dyes were detected using an ABI 7000 instrument (Applied Biosystems).

2.3 | Statistical analyses

Data were analysed using the SPSS 22.0 software package for Windows (SPSS Inc.). Continuous variables are presented as means or medians and were compared by Mann-Whitney U-test. Categorical variables were compared by chi-squared test. The actuarial survival free of LT rate was estimated by Kaplan-Meier survival analysis. Patients were grouped according to their different UGT1A variants and the differences between the actuarial estimates were analysed using the log-rank test. All tests were two-tailed and a P-value of .05 or less was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics and outcome

About 331 patients with well-characterized and documented PSC and 249 healthy blood donors were included in the study. The two groups were gender matched with 69.9% male PSC patients and 67.9% male controls. Mean age at time of PSC diagnosis was 32.6 years. Concomitant IBD was documented in 68.7% of the cases. PSC-AIH-phenotype was diagnosed in 13.9% of the patients (see Table 1). For the outcome analysis of the PSC cohort, we excluded three patients with an unclear follow-up status so that 328 patients remained. The median follow-up time after first diagnosis of PSC was 13.7 ± 8.3 years (range 0-38.2 years). Owing to LT in 131 patients and death before LT in 21 patients, the median transplant-free survival time after PSC diagnosis was 14.9 ± 0.73 years.

3.2 | Prevalence of UGT1A variants

Frequency of UGT1A1*28, UGT1A3-66 and UGT1A7 N129K/R131K variants were comparable between PSC patients and healthy blood donors (see Table 2).

3.3 | Biochemical parameters and UGT1A variants

Direct serum bilirubin of PSC cohort was compared between UGT wild types and variants. Patients carrying either a heterozygous or homozygous UGT1A1*28 variant showed significantly lower direct bilirubin levels than subjects with UGT1A1 wild type (P = .002; see Table 3).
In contrast, patients showing at least one polymorphism in all of the three genes showed significantly higher bilirubin concentrations than wild type (P = .02). There was a trend towards higher bilirubin levels in patients carrying the UGT1A7 N129K/R131K variant compared to the UGT1A7 wild-type cohort (P = .089; see Table 3).

There was no statistically significant difference regarding the other cholestasis parameters ALP and gGT or transaminases (AST, ALT) between wild types and variants of UGT1A1, UGT1A3 or UGT1A7. Mean concentrations of parameters reflecting renal function (creatinine, cystatine C), liver synthesis (albumin, prothrombine time) or inflammation (CRP, WBC) were within normal range in each group.

Serum cholesterol was found to be higher in every tested polymorphism compared to wild type (see Table 3).

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**TABLE 2** Frequency of wild type and variants of UGT1A1, UGT1A3 and UGT1A7 in the PSC study population and in a control cohort of healthy blood donors are given in percent.

|                  | PSC (n = 331) | Healthy blood donors (n = 249) |
|------------------|---------------|-------------------------------|
|                  | WT Heteroz Homoz. | WT Heteroz Homoz. | WT Heteroz Homoz. |
| UGT1A1*28        | 45.2% 41.2% 13.6% | 39.4% 48.6% 12.0% |
| UGT1A3-66T>C     | 33.0% 47.0% 20.0% | 28.9% 53.4% 17.7% |
| UGT1A7 N129K/R131K | 17.0% 40.9% 42.1% | 16.1% 42.3% 41.5% |
| UGT1A1*28, UGT1A3-66T>C and UGT1A7 N129K/R131K | 13.6% – 11.5% | 14.9% – 10.9% |

**TABLE 3** Mean direct serum bilirubin and cholesterol values at first presentation in PSC patients carrying either wild-type alleles or at least one variant allele of UGT1A1, UGT1A3 and UGT1A7. P-values were calculated with Mann-Whitney U-test.

|                  | Direct serum bilirubin (µmol/L) | Serum cholesterol (mg/dL) |
|------------------|-------------------------------|----------------------------|
|                  | WT Variant P                   | WT Variant P |
| UGT1A1*28        | 39.9 33.6 .002                 | 200.7 233.7 .003 |
| UGT1A3-66T>C     | 42.3 33.6 .126                 | 201.9 227.9 .046 |
| UGT1A7 N129K/R131K | 28.4 38.1 .089               | 194.4 224.26 .014 |
| UGT1A1*28, UGT1A3-66T>C and UGT1A7 N129K/R131K | 25.1 38.2 .02 | 195.1 223.1 .035 |

**FIGURE 1** Frequency of IBD subtypes in patients with wild-type alleles only, at least one allele for UGT1A1*28 or UGT1A3-66T>C or UGT1A7 N129K/R131K and patients with homozygous variants in all three genes. P-values were assessed using chi-squared test.
3.4 | UGT1A1, UGT1A3 and UGT1A7 wild types are associated with a higher incidence of IBD

Ulcerative colitis and Crohn’s disease were present significantly more often in patients carrying wild-type alleles for all three genes than in patients with at least one haplotype (P = .046) or homozygous variants (P = .022; see Figure 1). The least prevalent wild type of the three tested genes in patients without IBD was UGT1A7 (12.9%). Among patients with IBD, UGT1A7 wild type was more common in patients with ulcerative colitis (20.4%) than in cases of Crohn’s disease (14.8%), but this difference was not significant (P = .436).

3.5 | Risk of CRC in PSC-IBD with homozygous UGT1A3-66T>C

In the large subgroup of 226 patients with PSC and concomitant IBD, the frequency of colorectal carcinoma was 13.3% in 44 patients carrying homozygous alleles for the UGT1A3-66T>C polymorphism, while in cases of UGT1A3 wild type or heterozygous haplotype CRC was diagnosed in only 5.0% (P = .044). The two other analysed UGT1A variants showed no significant association with the incidence of CRC in PSC.

3.6 | UGT1A variants are not associated with PSC-AIH-phenotype or IgG4 levels

About 13.9% of our patient cohort was diagnosed with PSC-AIH-phenotype. Prevalence of UGT1A variants or wild types, respectively, did not differ between patients with concomitant AIH and patients suffering from PSC only (see Table S2). Transplant-free survival of patients with PSC-AIH-phenotype did not differ from the rest of the cohort (P = .21).

IgG4 levels at the beginning of follow-up were available in 153 cases. IgG4 levels did not differ between genotypes (see Table S2). Patients who reached end point death or LT showed significantly higher IgG4 levels (P = .029). In multivariate Cox-regression analyses, IgG4 (P = .001) and UGT1A7 (P = .022) or UGT1A1 and 3 and 7 (P = .028) respectively proved to be independent risk factors for survival.

About 25.1% of the cases was found to suffer from other autoimmune diseases that are described above. Frequencies of autoimmune comorbidities were comparable between variants and wild types of UGT1A1 and 3 and 7 (see Table S2). Comorbidities were not associated with transplant-free survival (P = .44).

3.7 | UGT1A7 N129/131 K is associated with risk for LT

To analyse the impact of different UGT1A variants on clinical outcome, the Kaplan-Meier estimates of transplant-free survival using the combined end point LT or death were compared by log-rank test. The median transplant-free survival in PSC patients was 14.9 years. Patients showing a homozygous or heterozygous variant in at least one of the UGT1A1, UGT1A3 or UGT1A7 genes had a significantly shorter transplant-free survival than PSC patients with wild-type alleles for all three UGT1A genes (14.4 ± 0.9 years vs. 17.2 ± 3.7 years, P = .048; Figure 2). Furthermore, patients carrying the UGT1A7 N129K/R131K polymorphism alone had a significantly lower transplant-free survival (P = .048).
**FIGURE 3** Kaplan-Meier estimates of cumulative transplant-free survival after PSC diagnosis for UGT1A7 wild-type carriers and patients with heterozygous or homozygous UGT1A7 N129K/R131K alleles. P-value is calculated using log-rank test.

**FIGURE 4** Kaplan-Meier estimates of cumulative transplant-free survival after PSC diagnosis for UGT1A1 wild-type carriers and patients with heterozygous or homozygous UGT1A1*28 alleles. P-value is calculated using log-rank test.
inferior outcome with a shorter transplant-free survival than the wild-type cohort (14.0 ± 0.9 years vs. 17.2 ± 3.6 years, \( P = .034 \); Figure 3). Variants in UGT1A1*28 (\( P = .198 \)) and UGT1A3-66T>C (\( P = .831 \)) had no significant impact on transplant-free survival (Figures 4 and 5).

3.8 Malignancy-free survival does not differ between genetic variants and wild type

Hepatobiliary malignancy, defined as cholangiocellular carcinoma (n = 23), gallbladder cancer (n = 5) or hepatocellular carcinoma (n = 1), developed in 8.76% of the PSC patients. The prevalence of these malignancies was not associated with any of the studied genotypes.

4 DISCUSSION

The UGT1A1*28 polymorphism is well established to cause one of the most frequent genetic syndromes, namely Gilbert disease by a reduction of bilirubin conjugation. This variant has been shown to be associated with a number of other additional UGT1A variants, which are also characterized by an altered enzymatic activity\(^2\) and have been associated with cytotoxicity and genotoxicity as well as cancer disposition. However, in our initial assessment the overall prevalence of polymorphisms did not differ between healthy controls and our large cohort of patients with well-defined PSC, which is in line with findings of the recent genome-wide association studies, which identified various risk loci but did not point to the UGT1A gene locus on chromosome 11. However, in a more detailed analysis, UGT1A1*28 was associated with significantly lower levels of direct serum bilirubin at first diagnosis of the disease compared to wild type. The most likely explanation is a lower inflammatory activity leading to lower levels of conjugated bilirubin. UGT1A1*28 leads to fluctuating elevated levels of unconjugated (indirect) bilirubin (levels not given in the study), which has been described to lead to antioxidant activity, less inflammation and protection against diseases such as coronary heart disease.\(^{25}\) The data indicate that UGT1A1*28 could be viewed as a protective genetic trait in PSC. But the more detailed analysis of a complex haplotype of variants also indicates that UGT1A variants are associated with an increased risk disposition.

Carriers of the UGT1A7 N129K/R131K allele showed a trend to higher conjugated bilirubin concentrations, likely reflecting a more severe clinical course of PSC. Therefore, because early LT and death represent clinical end points indicative of a more progressive course of PSC, we compared transplant-free survival. In this analysis carriers of at least one variant UGT1A allele are characterized by an inferior outcome that carriers of wild-type UGT1A alleles.

In combination, our data suggest that UGT1A variant is likely to exert a differential effect on the course of PSC, UGT1A7 N129K/R131K reflecting a negative marker regarding survival, and UGT1A1*28 associated with milder cholestasis.
Apart from overall survival the association with IBD is a prominent feature of PSC, which may also be influenced by variations of glucuronidation. The overall analysis suggests that in the studied large cohort of PSC patients, for carriers of wild-type alleles of UGT1A1, UGT1A3 and UGT1A7, the risk for IBD is increased. Interestingly, it has been reported previously that patients with Crohn's disease were less likely to be homozygous for UGT1A1*28 than healthy controls. Protective effects have been attributed to the anti-oxidant capabilities of unconjugated bilirubin, as evidenced by patients with Gilbert syndrome exhibiting a lower risk for cardiovascular diseases. Our results support these findings regarding lower levels of conjugated bilirubin and a lower likelihood of developing IBD. A possible explanation for this finding is that local metabolism of bilirubin and other xenobiotics by UGT1A expressed in the intestinal tract contributes to the disposition for inflammatory disease involving the mucosa of the gastrointestinal tract. Along this line it has been demonstrated that unconjugated bilirubin is capable of suppressing TLR4/NFκB signalling, which indicates a role for xenobiotic metabolism in the liver-gut axis.

The findings reported here are in line with previously published associations in another German cohort. In that study UGT1A7 wild type was found significantly more often in patients with ulcerative colitis than in controls and in patients with Crohn's disease. Since UGT1A7 is involved in eliminating aromatic hydrocarbons and smoking does not affect ulcerative colitis as much as Crohn's disease, it was hypothesized that wild-type alleles can serve as a protective factor. Although not statistically significant patients with ulcerative colitis carried UGT1A7 wild-type alleles more frequently than Crohn's disease patients or patients without IBD.

Increased serum levels of IgG4 have been reported in 9%-15% of PSC patients and according to recent descriptions this subgroup might be associated with a faster disease progression. A multicentre study from Norway, Sweden and from the United States found an association between levels of IgG4 above the upper reference limit and specific HLA haplotypes. In our patient cohort we could confirm this distinct phenotype and found that patients who died or needed LT had higher IgG4 levels than patients who reached neither of the end points. However, we found no evidence of a genetic association, since UGT1A genetic variants did not differ in serum levels of IgG4. Accordingly, IgG4 proved to be an independent risk factor for survival in multivariate Cox-regression analyses.

Serum bilirubin as well as serum cholesterol were significantly lower in a cohort of all wild-type carriers. The higher levels of direct serum bilirubin in PSC patients with the UGT1A7 N129K/R131K variant and the higher serum cholesterol levels in all UGT1A variants are likely to be the result of the presence of a higher degree of cholestasis and therefore a higher PSC activity. It is possible that direct effects of conjugation also contribute to this finding. A lower degree of inflammation may also be associated with differences of bile composition and may additionally contribute to lower degrees of mucosal inflammation in the colon.

To further characterize the IBD component of PSC, the development of CRC was studied. In the IBD group the risk for CRC was significantly higher in the 44 patients carrying the homozygous UGT1A3 variant (but not the UGT1A1 and the UGT1A7 polymorphism). This finding is especially interesting since UGT1A3 has an important role for the glucuronidation of primary amines, carboxylic acids, oxosterones and is reportedly expressed in the colon mucosa. Reduced enzyme activity could render inflammatory epithelia susceptible for malignant transformation by hormonal influences, exogenous carcinogens or xenobiotics. Furthermore, UGT1A3 glucuronidates salicylic acid, an anti-inflammatory substance that reduces the risk for colorectal neoplasia and has been studied in chemoprevention studies for colon polyps. The UGT1A3 Thr78Thr (rs17868336; A>G) polymorphism for example was linked with a higher risk for CRC than wild type, and individuals were more likely to develop CRC without non-steroidal anti-inflammatory drug (NSAID) therapy.

In conclusion, our analysis does not support the hypothesis that an individual genetic variant of a UGT1A gene is associated with increased risk to develop PSC. However, our data suggest that course and outcome of PSC are indeed influenced by the presence of UGT1A gene variants. Evidence is presented that variants of the UGT1A1, UGT1A3 and UGT1A7 genes might modify the clinical phenotype and are associated with the disease course of PSC. Carriers of the UGT1A7 variant haplotype N129K/R131K, present as a homozygous trait in 10% of the population and leading to impaired glucuronidation of xenobiotics, exhibit more severe PSC at first diagnosis, reflected by higher levels of direct bilirubin, and show a more progressive course of PSC leading to earlier transplantation or death. Thus, UGT1A variants may represent a tool for the prognostic stratification of PSC patients and link disease progression in PSC to the regulation of detoxification by glucuronidation. Currently, in many centres the medical therapy of PSC is mainly based on ursodeoxycholic acid (UDCA), a bile acid that is also glucuronidated by UGT1A3. Other bile acids like nor-UDCA or obeticholic acid are under investigation as new treatment strategies. Against this background, our findings illustrate the need to further elucidate the role of UGT1A variants as disease modifier in PSC and the role of inducers not only of nuclear receptors but also of detoxification enzymes such as UGT1A proteins and their specific activators.

**CONFLICT OF INTEREST**

The authors don’t have any disclosure to report.

**ORCID**

Tobias J. Weismüller https://orcid.org/0000-0001-9736-1483
Taotao Zhou https://orcid.org/0000-0002-8043-5818
Christian P. Strassburg https://orcid.org/0000-0001-7870-5359

**REFERENCES**

1. Karlsen TH, Folseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis - a comprehensive review. *J Hepatol*. 2017;67(6):1298-1323. https://doi.org/10.1016/j.jhep.2017.07.022
2. Weismüller TJ, Lankisch TO. Medical and endoscopic therapy of primary sclerosing cholangitis. *Best Pract Res Clin Gastroenterol*. 2011;25(6):741-752. https://doi.org/10.1016/j.bpg.2011.10.003
35. Scherer D, Koepl LM, Poole EM, et al. Genetic variation in UGT genes modify the associations of NSAIDs with risk of colorectal cancer: colon cancer family registry. Genes Chromosom Cancer. 2014;53(7):568–578. https://doi.org/10.1002/gcc.22167

36. Zhou D, Kong L, Jiang Y, et al. UGT-dependent regioselective glucuronidation of ursodeoxycholic acid and obeticholic acid and selective transport of the consequent acyl glucuronides by OATP1B1 and 1B3. Chem Biol Interact. 2019;310:108745. https://doi.org/10.1016/j.cbi.2019.108745

37. Kalthoff S, Winkler A, Freiberg N, Manns MP, Strassburg CP. Gender matters: Estrogen receptor alpha (ERα) and histone deacetylase (HDAC) 1 and 2 control the gender-specific transcriptional regulation of human uridine diphosphate glucuronosyltransferases genes (UGT1A). J Hepatol. 2013;59(4):797–804. https://doi.org/10.1016/j.jhep.2013.05.028

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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