UGT1A3 and Sex Are Major Determinants of Telmisartan Pharmacokinetics—A Comprehensive Pharmacogenomic Study

Päivi Hirvensalo1,2, Aleksi Tornio1,2, Terhi Launiainen1,2, Maria Paile-Hyvärinen1,2, Tuija Tapaninen1,2, Mikko Neuvonen1,2, Janne T. Backman1,2 and Mikko Niemi1,2,*

To investigate how variability in multiple pharmacokinetic genes associates with telmisartan exposure, we determined telmisartan single-dose (40 mg) pharmacokinetics and sequenced 379 genes in 188 healthy volunteers. Intronic UGT1A variants showed the strongest associations with the area under the plasma concentration-time curve from zero hours to infinity (AUC_{0–∞}) and peak plasma concentration (C_{max}) of telmisartan. These variants were strongly linked with the increased function UGT1A3*2 allele, suggesting that it is the causative allele underlying these associations. In addition, telmisartan plasma concentrations were lower in men than in women. The UGT1A3*2 was associated with a 64% and 63% reduced AUC_{0–∞} of telmisartan in UGT1A3*2 heterozygous and homozygous men, respectively (P = 1.21 × 10^{-16} and 5.21 × 10^{-8}). In women, UGT1A3*2 heterozygosity and homozygosity were associated with 57% (P = 1.54 × 10^{-11}) and 72% (P = 3.31 × 10^{-15}) reduced AUC_{0–∞}, respectively. Furthermore, a candidate gene analysis suggested an association of UGT1A3*3 and the SLCO1B3 c.767G>C missense variant with telmisartan pharmacokinetics. A genotype score, which reflects the effects of sex and genetic variants on telmisartan AUC_{0–∞}, associated with the effect of telmisartan on diastolic blood pressure. These data indicate that sex and UGT1A3 are major determinants and suggest a role for OATP1B3 in telmisartan pharmacokinetics.

Study Highlights

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

☑️ High interindividual variability exists in the pharmacokinetics of telmisartan. There are no comprehensive studies evaluating how variability in multiple pharmacokinetic genes associates with telmisartan exposure.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

☑️ This study investigated how genetic variants associate with telmisartan single-dose pharmacokinetics in healthy volunteers.

**WHAT THIS STUDY ADD TO OUR KNOWLEDGE?**

☑️ This study shows that the UGT1A3*2 and *3 alleles are associated with reduced telmisartan exposure and the SLCO1B3 c.767G>C missense variant with increased telmisartan exposure. Based on the results, genotype scores were generated to predict telmisartan pharmacokinetics in men and women with different combinations of UGT1A3 and SLCO1B3 variants.

**HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**

☑️ This knowledge might aid in identifying individuals with increased risk of insufficient telmisartan exposure and impaired blood pressure-lowering response with the 40 mg dose. This may aid in individualizing antihypertensive therapy.

Telmisartan is an angiotensin II receptor antagonist for treatment of hypertension.1 Uridine diphosphate-glucuronosyltransferase (UGT) 1A3 metabolizes telmisartan extensively to an acyl-glucuronide metabolite, which is the only telmisartan metabolite found in humans.2,3 UGT1A1, 1A7, 1A8, and 1A9 may also contribute to telmisartan glucuronidation.3 Furthermore, in vitro studies have suggested the involvement of OATP1B3 (encoded by SLCO1B3) and 2B1 (encoded by SLCO2B1) transporters in the cellular uptake and P-gp/MDR1 (encoded by ABCB1) in the cellular efflux of telmisartan.4–7 Telmisartan acyl-glucuronide is a substrate of OATP1B3 and it is eliminated mainly by biliary excretion.2,8,9

High interindividual variability exists in the pharmacokinetics of telmisartan and low exposure to telmisartan is associated with poor blood pressure-lowering effect.10–12 Telmisartan is usually effective with a 40 mg daily dose, but a significant proportion of patients require a higher dose or combination treatment to achieve sufficient blood pressure control.13 For optimal therapy, it would be important to understand the sources of variability in the response to antihypertensive medication.

1Department of Clinical Pharmacology, University of Helsinki and HUS Diagnostic Center, Helsinki University Hospital, Helsinki, Finland; 2Individualized Drug Therapy Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland. *Correspondence: Mikko Niemi (mikko.niemi@helsinki.fi)

Received April 1, 2020; accepted May 19, 2020. doi:10.1002/cpt.1928
There are few previous studies on the associations of genetic variants on the pharmacokinetics of telmisartan with relatively small sample sizes, but comprehensive studies are lacking. In two of the studies, either the UGT1A3*2 or the UGT1A1*28 allele was associated with significantly reduced plasma concentrations of telmisartan. In addition, one small study suggested an association of the c.-24C>T (rs717620) single nucleotide variation (SNV) and telmisartan peak plasma concentration (C_{max}).

On the other hand, variants in, for example, CYP2C8, CYP2C9, UGT2B7, SLC01B3, ABCB1, and ABCG2 have not been associated with telmisartan pharmacokinetics. The aim of this study was to evaluate how variations in 379 pharmacokinetic genes associate with telmisartan pharmacokinetics.

**METHODS**

A total of 188 healthy unrelated white Finnish volunteers participated in the study after giving written informed consent. Their health was confirmed by medical history, clinical examination, and laboratory tests. Participants were not on any continuous medication nor were tobacco smokers. The study was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (record number 267/13/03/00/2011 and the Finnish Medicines Agency Fimea (EudraCT number 2011-0046-45-40). Of the participants, 91 were women and 97 men. Their mean ± SD age was 24 ± 4 years, height 174 ± 9 cm, body weight 69 ± 12 kg, and body mass index 22.8 ± 2.6 kg/m².

**Telmisartan pharmacokinetics and pharmacodynamics**

After an overnight fast, each participant ingested a 40 mg dose of telmisartan (Micardis tablet; Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany) with 150 mL of water at 8 AM. Standardized meals were served at 4, 7, and 10 hours after telmisartan ingestion. Timed blood samples (4–9 mL each) were collected to light-protected EDTA tubes prior to and 0.5, 1, 1.5, 2, 3, 4, 5, 7, 9, 12, 24, and 48 hours after telmisartan administration. Tubes were immediately placed on ice. Plasma was separated within 30 minutes and stored at −70°C until analysis. Systolic and diastolic blood pressures were measured in a sitting position with an automatic oscillometric blood pressure monitor (Omron Healthcare Europe BV, Hoofddorp, The Netherlands) before and at 4, 12, and 24 hours after telmisartan ingestion. The pharmacodynamic variables, the average change in diastolic and systolic blood pressure, were calculated by dividing the incremental area under the blood pressure-time curve from time 0 to 24 hours with 24 hours.

Telmisartan and telmisartan acyl-β-D-glucuronide plasma concentrations were quantified using a Nexera X2 ultra-high-performance liquid chromatograph (Shimadzu, Kyoto, Japan) coupled to a Qtrap 5500 mass spectrometer (ABSciex, Foster City, CA). Plasma samples were pretreated using a Phece phospholipid removal plate (Phenomenex, Torrance, CA) according to the manufacturer’s instructions. In brief, plasma and acetonitrile containing the internal standards were mixed in a ratio of 1:5 (v/v), and the mixture was allowed to incubate for 10 minutes at room temperature. The sample mixture was then filtered through the cartridge, diluted with mobile phase (A), and delivered to the ultra-high-performance liquid chromatography system. Telmisartan and telmisartan acyl-glucuronide were separated on a Kinetex Biphenyl (2.6 µm, 2.1 mm × 100 mm; Phenomenex) using a gradient elution. Mobile phase consisted of 10 mM ammonium formate (pH 3.2, adjusted with formic acid) (A) and acetonitrile (B). The mobile phase gradient was a linear ramp from 30% B to 97% B over 1 minute, followed by 0.5 minutes at 97% B on hold, and an equilibration step back to the starting composition. The flow rate and the column temperature were maintained at 350 μL/min and 30°C, and the injection volume was 5 μL. Isotope-labeled analogs served as internal standards for both analytes. The mass spectrometer was operated in a positive polarity mode and the targeted mass-to-charge ratio (m/z) ion transitions were 515→276 and 691→515 for telmisartan and telmisartan acyl-glucuronide. The lower limits of quantification were 0.3 ng/mL and 0.1 ng/mL, respectively. The day-to-day precision values (coefficients of variation) for both compounds were below 15% and accuracy within ±15%, except for the lower limits of quantification, for which both precision and accuracy were within 20%.

The areas under the plasma concentration-time curve from 0 hours to infinity (AUC_{0→∞}), C_{max}, and the elimination half-life (t_{1/2}) values were calculated for telmisartan and telmisartan acyl-glucuronide with standard noncompartmental methods using Phoenix WinNonlin, version 6.3 (Cerrara, Princeton, NJ).

**DNA sequencing and genotyping**

Genomic DNA was extracted from EDTA blood samples using the Maxwell 16 LEV Blood DNA Kit on a Maxwell 16 Research automated nucleic acid extraction system (Promega, Madison, WI). A total of 379 pharmacokinetic genes, comprising phase I and II metabolizing enzymes, influx and efflux drug transporters, and regulatory proteins, were selected to be studied. These genes ± 20 bp, were completely sequenced in the study participants using targeted massive parallel sequencing at the Technology Centre at Institute for Molecular Medicine Finland (Helsinki, Finland). NEBNext DNA Sample Prep protocol (New England BioLabs, Ipswich, MA) was used for library preparation and the NimbleGen SeqCap EZ Choice protocol (Roche Sequencing, Pleasanton, CA) for target enrichment capture. Sequencing was done on the Illumina HiSeq2000 platform with 100 bp paired-end reads (Illumina, San Diego, CA). Quality control, short read alignment, and variant calling and annotation were carried out using an in-house developed pipeline. Mean coverage depth was 37.2X. Coverage depth ± 10X, Hardy–Weinberg equilibrium P < 3.15 × 10−7 (Bonferroni correction), and proportion missing ≤ 0.05 were used as quality thresholds. A total of 46,064 SNVs with minor allele frequency (MAF) ≥ 0.05 passed these criteria and were included in the statistical analysis. In order to verify genotype calls and to supplement missing data, all study participants were genotyped with TaqMan genotyping assays on a Quantstudio 12K Flex Real-Time PCR System for the UGT1A rs13401281, rs3821242, rs4663969, rs6715325, rs6431625, rs45449995, rs4148323, and rs306474 sequence variations (Thermo Fisher Scientific, Waltham, MA). Call identity with sequencing data was 99.5% for rs6715325 and 100% for all other SNVs. In case of discordant results, genotypes obtained by sequencing were used in the statistical analysis.

**Statistical analysis**

The number of participants was estimated to be sufficient to detect an effect size of ω² larger than 0.2 with two predictors in multiple linear regression analysis, with a power > 80% (Bonferroni corrected at level 1.09 × 10−6). The data were analyzed with the statistical programs JMP Genomics 8.2 (SAS Institute, Cary, NC) and IBM SPSS 22.0 for Windows (Armonk, NY). The pharmacokinetic variables were logarithmically transformed before analysis. Sex and body weight were tested as demographic covariates for pharmacokinetic data using stepwise linear regression analysis, with P value thresholds of 0.05 for entry and 0.10 for removal. Possible associations of genetic variants with pharmacokinetic variables were investigated using linear regression analysis fixed for significant demographic covariates with a stepwise approach. A Bonferroni corrected P value threshold of 1.09 × 10−6 was used for the 379 gene and thresholds of 0.05 for entry and 0.10 for removal for the candidate gene analysis. Additive coding was used for genetic variants in the 379 gene analysis and both additive and dummy variable coding in the candidate gene analysis. Haploview computations for UGT1A gene were performed with PHASE version 2.1.1. Statistical comparisons of proportions were done using the Fisher’s exact test. Possible correlation of telmisartan
AUC with the change in blood pressure during 24 hours was investigated using partial correlation analysis controlling for baseline blood pressure. Comparison of the change in blood pressure during 24 hours between genotype scores was investigated with analysis of variance, with baseline blood pressure as a covariate and P value < 0.05 considered statistically significant. Pharmacokinetic data are given as geometric means with geometric coefficients of variation and ranges, geometric SDs, or 90% confidence intervals (CIs). Pharmacodynamic data are given as arithmetic means with 95% CIs and proportions with 95% CIs.

RESULTS

Telmisartan pharmacogenomics

Among the 188 healthy volunteers, the AUC\(_{0–\infty}\) and C\(_{\text{max}}\) of telmisartan varied 49-fold and 31-fold, respectively, and those of telmisartan acyl-glucuronide 18-fold and 17-fold, respectively (Table 1). Both telmisartan AUC\(_{0–\infty}\) and C\(_{\text{max}}\) were larger in women than in men. In addition, body weight was a significant covariate for telmisartan C\(_{\text{max}}\). When entering both sex and body weight as independent variables in the regression analysis for telmisartan AUC\(_{0–\infty}\), sex (P = 0.005) but not body weight (P = 0.405) remained significantly associated. This indicates that the association of sex is independent of the weight.

In a stepwise linear regression analysis, which tested the associations of 46,064 SNVs with MAF of at least 0.05, the rs6715325 SNV, located between the UGT1A4 and UGT1A3 first exons, showed the strongest association with the AUC\(_{0–\infty}\) of telmisartan (Table 2, Figure 1). The AUC\(_{0–\infty}\) was 46% (P = 1.81 \times 10^{-22}) smaller per copy of the variant allele. Furthermore, the rs2361501 SNV, located after UGT1A3 first exon, showed the strongest association with telmisartan C\(_{\text{max}}\), which was 26% (P = 4.00 \times 10^{-7}) smaller per copy of the variant allele. After adjusting for the rs6715325 or rs2361501 variant, no other variants remained associated with telmisartan AUC\(_{0–\infty}\) or C\(_{\text{max}}\) at the Bonferroni corrected significance level. The investigated genetic variants were not significantly associated with the \(t_{1/2}\) of telmisartan.

Similar to parent telmisartan, telmisartan acyl-glucuronide C\(_{\text{max}}\) was significantly associated with intronic SNVs located around UGT1A3 first exon. The strongest association was observed with four SNVs (rs13401281, rs11891311, rs7564935, and rs11888459) in complete linkage disequilibrium with each other. The C\(_{\text{max}}\) was 39% (P = 6.25 \times 10^{-11}) higher per copy of the variant allele (Table 2). After adjusting for any one of these variants, no other variants remained statistically significantly associated with the C\(_{\text{max}}\). The investigated variants were not significantly associated with the AUC\(_{0–\infty}\) or \(t_{1/2}\) of telmisartan acyl-glucuronide. The telmisartan acyl-glucuronide/telmisartan AUC\(_{0–\infty}\) ratio also showed the strongest association with a UGT1A variant (Table 2).

Linkage disequilibrium and haplotype analysis

In order to identify the causative SNVs underlying the association of the top noncoding UGT1A SNVs (rs6715325, rs2361501, rs13401281, and rs4663969) with telmisartan pharmacokinetic variables, we next investigated the linkage disequilibrium profile and computed haplotypes across the UGT1A gene. This was done for the top noncoding SNVs and the missense and functional variants (MAF ≥ 0.01) of the UGT1As, which metabolize telmisartan in vitro (UGT1A1, UGT1A3, UGT1A7, and UGT1A9; Figure 2). All the top noncoding SNVs were strongly linked with each other as well as with the two UGT1A3 c.31T>C (p.Trp11Arg, rs3821242) and c.140T>C (p.Val47Ala, rs6431625) missense SNVs, which define the UGT1A3*2 allele (Figure 2a). The top SNVs were also in a relatively strong linkage disequilibrium with the UGT1A1*28 allele (rs3064744, c.-54_-53insTA, TA6>TA7) and with the UGT1A7 c.622T>C (p.Trp208Arg, rs11692021) missense SNV.

Altogether, 25 haplotypes were inferred in the haplotype computation (Figure 2b). The top noncoding SNVs were present in

Table 1 Pharmacokinetic variables of telmisartan and telmisartan acyl-glucuronide in 188 healthy volunteers and the effects of significant demographic covariates on these variables

| Variable | Geometric mean | CV | Range | Demographic covariate | Effect (90% CI) | P value | Adjusted R² |
|----------|----------------|----|-------|-----------------------|-----------------|---------|-------------|
| Telmisartan | | | | | | | |
| C\(_{\text{max}}\), ng/mL | 35 | 80% | 5.2–165 | Body weight | Sex | -14.2% (-18.7%, -9.5%) | 4.01 \times 10^{-6} | 0.25 |
| T\(_{\text{max}}\), hour | 1.5 | — | 0.5–9 | — | — | — | 0.8 |
| AUC\(_{0–\infty}\), ng·hour/mL | 308 | 84% | 37–1797 | Sex | — | 55.9% (31.7%, 84.6%) | 2.26 \times 10^{-5} | 0.09 |
| t\(_{1/2}\), hour | 18 | 41% | 6.7–83 | Body weight | Sex | -4.2% (-6.8%, -1.6%) | 9.41 \times 10^{-3} | 0.03 |
| Telmisartan acyl-glucuronide | | | | | | | |
| C\(_{\text{max}}\), ng/mL | 4.4 | 58% | 1.2–19.4 | Body weight | Sex | -10.7% (-13.8%, -7.5%) | 2.54 \times 10^{-7} | 0.13 |
| T\(_{\text{max}}\), hour | 0.75 | — | 0.5–12 | — | — | — | 0.8 |
| AUC\(_{0–\infty}\), ng·hour/mL | 74 | 50% | 18–318 | Body weight | Sex | -7.7% (-10.5%, -4.7%) | 3.76 \times 10^{-5} | 0.08 |
| t\(_{1/2}\), hour | 20 | 58% | 7.9–94 | Sex | — | 18.5% (4.3%, 34.7%) | 0.0296 | 0.02 |
| Telmisartan acyl glucuronide/ telmisartan AUC\(_{0–\infty}\) ratio | 0.24 | 73% | 0.05–1.4 | Sex | — | -20.1% (-31.7%, -6.7%) | 0.018 | 0.03 |

AUC\(_{0–\infty}\), area under the plasma concentration-time curve from 0 hour to infinity; CI, confidence interval; CV, geometric coefficient of variation; C\(_{\text{max}}\), peak plasma concentration; T\(_{\text{max}}\), concentration peak time; t\(_{1/2}\), elimination half-life.

aPer 10% increase in body weight; sex: women vs. men. bT\(_{\text{max}}\) data given as median.
Table 2 Results of the stepwise forward linear regression analysis of the effects of 46,064 SNVs in 379 genes on telmisartan pharmacokinetics

| Pharmacokinetic variable | Effect | Gene | Location | Nucleotide change | MAF | dbSNP ID | Average | 90% CI | Adjusted P value |
|--------------------------|--------|------|----------|------------------|-----|----------|---------|--------|-----------------|
| Telmisartan AUC<sub>0-∞</sub> | variable | rs6715325 | UGT1A4 | Intron 1 | c.867+6908T>C | 0.46 | −45.6% | −50.3%, −40.5% | 1.81 × 10<sup>−22</sup> | 0.45 |
| Telmisartan AUC<sub>0-∞</sub> | per copy of the minor allele | rs13401281 | UGT1A3 | Intron 1 | c.867+51A>T | 0.47 | −26.0% | −32.7%, −18.7% | 4.00 × 10<sup>−7</sup> | 0.36 |
| Telmisartan acyl-glucuronide AUC<sub>0-∞</sub> | ratio | rs4663969 | UGT1A4 | Intron 1 | c.867+346T>G | 0.40 | 39.2% | 28.6%, 50.6% | 6.25 × 10<sup>−11</sup> | 0.30 |
| Telmisartan acyl-glucuronide/telmisartan AUC<sub>0-∞</sub> ratio | per copy of the minor allele | rs2361501 | UGT1A3*2 | Intron 1 | c.867+16674C>A | 0.46 | 91.7% | 78.1%, 106.3% | 1.02 × 10<sup>−32</sup> | 0.55 |

Pharmacokinetic variable: Telmisartan AUC<sub>0-∞</sub>, area under the plasma concentration-time curve from 0 hour to infinity; CI, confidence interval; C<sub>max</sub>, peak plasma concentration; dbSNP, database-single-nucleotide polymorphism (National Center for Biotechnology Information Short Genetic Variations database); MAF, minor allele frequency; SNV, single nucleotide variation; 

Effect<sup>a</sup>, effect of a copy of the minor allele; Location<sup>b</sup>, includes the effect of significant demographic covariant and the top SNV; dbSNP ID<sup>c</sup>, rs13401281 is in complete linkage disequilibrium with rs11891311, rs7564935, and rs11888459.

Candidate gene analysis

Due to the risk of false negative associations with the conservative Bonferroni correction in the primary analysis, we next carried out a candidate gene analysis for telmisartan AUC<sub>0-∞</sub> without correction for multiple testing. In this analysis, we included missense and functional variants with MAF of ≥ 0.01 in genes suggested to be involved in telmisartan pharmacokinetics (UGT1A3, UGT1A1, UGT1A7, UGT1A8, UGT1A9, SLC01B3, SLC01B2, ABCB1, and ABCC2, Table S1). In the analysis, UGT1A3*2 was associated with a 48% (P = 3.82 × 10<sup>−22</sup>) and UGT1A3*3 with a 28% (P = 7.01 × 10<sup>−3</sup>) reduced AUC<sub>0-∞</sub> per copy of the allele, and SLC01B3 c.767G>C (p.Gly256Ala, rs60140950) with a 22% (P = 0.0392) increased telmisartan AUC<sub>0-∞</sub> per copy of the minor allele (Table 3). Because of linkage disequilibrium throughout the whole UGT1A locus, we repeated the candidate gene analysis using the inferred UGT1A8-A9-A7-A3-A1 haplotypes with MAF ≥ 0.01 (Figure 2b). All the haplotypes, which contained UGT1A3*2, were associated with reduced AUC<sub>0-∞</sub> of telmisartan (Table S2).

Interestingly, the UGT1A3*2 allele lacked gene-dose effect especially in men and thus the log-additive regression model seemed to overestimate the AUC<sub>0-∞</sub> of heterozygous UGT1A3*2 carriers. We, therefore, repeated the candidate gene analysis with UGT1A3*2 divided to four dummy variables representing the heterozygous and homozygous men and women. In this analysis, UGT1A3*2 heterozygosity and homozygosity in men were associated with a 64% (P = 1.21 × 10<sup>−16</sup>) and 63% (P = 1.19 × 10<sup>−21</sup>) increased telmisartan acyl-glucuronide/telmisartan AUC<sub>0-∞</sub>, respectively (Table 3). Heterozygosity and homozygosity were associated with a 177% (P = 2.25 × 10<sup>−18</sup>) increased telmisartan AUC<sub>0-∞</sub> in 4, and 0.061 (P = 8.59 × 10<sup>−16</sup>) increased telmisartan acyl-glucuronide/telmisartan AUC<sub>0-∞</sub>, respectively. Entering body weight as a covariate in addition to sex did not change the results.

To further investigate the roles of UGT variants in telmisartan glucuronidation, we next carried out a candidate gene analysis for telmisartan acyl-glucuronide/telmisartan AUC<sub>0-∞</sub> ratio with UGT1A3*2 dummy variables and other UGT1A3 and UGT1A1, UGT1A7, UGT1A8, and UGT1A9 variants. UGT1A3*2 heterozygosity and homozygosity in men were associated with a 177% (P = 3.13 × 10<sup>−22</sup>) and 293% (P = 2.25 × 10<sup>−18</sup>) increased telmisartan acyl-glucuronide/telmisartan AUC<sub>0-∞</sub> ratio, respectively (Table S3). In women, the UGT1A3*2 heterozygosity and homozygosity were associated with 116% (P = 1.19 × 10<sup>−21</sup>) increased telmisartan acyl-glucuronide/telmisartan AUC<sub>0-∞</sub> ratio, respectively.

To predict telmisartan AUC<sub>0-∞</sub> in men and women with different combinations of UGT1A3 and SLC01B3 genotypes, we calculated genotype scores (GS) using the UGT1A3*2 dummy
variable candidate gene linear regression model with the following equation:

\[ G_{\text{telmisartan}} = 1.47^{(M)} \text{ or } 1^{(F)} \times UGT1A3 \times 2 \text{ factor} \times 0.74^{(UGT1A3\ast3)} \times 1.23^{(SCL01B3\ast767G\astC)} \]

Where M is male and F is female, UGT1A3\ast2 factor is 0.36 for heterozygous men, 0.37 for homozygous men, 0.42 for heterozygous women, 0.28 for homozygous women, and 1 for noncarriers of UGT1A3\ast2, and \( n \) is the number of variant alleles (0, 1, or 2) of UGT1A3\ast3 and SCL01B3 c.767G\astC (Figures 3 and 4). The GS is 1.00 in men who do not carry any of the variants. For others, the score shows the fold difference in telmisartan AUC\(_{0\rightarrow\infty}\) compared with 1.00.

**Pharmacodynamics**

A total of 65% and 23% of individuals with GS of below 0.5 and between 0.5 and 0.8 had AUC\(_{0\rightarrow\infty}\) values below 229 ng\cdot hour/mL, which was found in a previous study to be the AUC \(_{0\rightarrow\infty}\) value giving 50% of telmisartan maximum effect (Figure 3). The respective percentages in individuals with GS between 0.8 and 1.25, and above 1.25 were 6% and 3%. Diastolic blood pressure decreased 1.3 mmHg (95% CI, 0.05, 2.5 mmHg) less in individuals
The MAFs (minor allele frequencies) and SNV (single-nucleotide variation) data presented in this figure are important for understanding the genetic basis of drug metabolism. Telmisartan, a commonly used antihypertensive drug, is metabolized by the UGT1A isoenzymes. The top SNVs identified in the study include rs13401281, rs11891311, rs7564935, and rs11888459. These SNVs are completely linked to the *15 allele of UGT1A7, which is associated with a lower activity of the enzyme.

The linkage disequilibrium (LD) observed among these SNVs and other missense and functional variants of the UGT1A isoenzymes is depicted in the figure. The LD is quantified using the linkage disequilibrium coefficient (r²), which is a measure of the degree of association between two loci. The figure shows the LD between the top SNVs and other variants, indicating the extent to which they are inherited together.

In summary, the data highlight the importance of genetic variation in predicting the metabolism of telmisartan and the potential for individual differences in drug response.

**Figure 2** (a) Linkage disequilibrium of the top noncoding SNVs and missense and functional variants of the UGT1A isoenzymes, which metabolize telmisartan in vitro. (b) UGT1A haplotypes inferred with missense and functional variants, and top noncoding UGT1A SNVs. Intronic variations are depicted in blue and missense variations in red. The *alleles are defined on the basis of missense variations within each UGT1A enzyme. The UGT1A7 allele containing the c.352G>T (p.Asp118Tyr, rs140814031) SNV together with c.387G>T (p.Trp208Arg, rs11692021), and c.622T>C SNVs has not been named before and is here given tentatively the name UGT1A7*15.49,50 For clarity, only rs13401281 of the four completely linked telmisartan acyl-glucuronide peak plasma concentration (C_{max}) top SNVs (rs13401281, rs11891311, rs7564935, and rs11888459) is presented in this figure. MAF, minor allele frequency; SNV, single-nucleotide variation.
with GS below 0.8 than in those with GS above 0.8 ($P = 0.042$; Figure 3). The average change in systolic blood pressure was not significantly associated with the GS (data not shown). Telmisartan AUC$_{0-\infty}$ correlated negatively with the average change in diastolic blood pressure ($r = -0.16$; $P = 0.034$) and systolic blood pressures ($r = -0.19$; $P = 0.008$).

Table 3 Results of the candidate gene analyses on telmisartan AUC$_{0-\infty}$

| Pharmacokinetic variable | Covariate/SNV                                                        | Effect$^a$ | 90% CI                  | $P$ value | Adjusted $R^2$ for each step |
|--------------------------|---------------------------------------------------------------------|------------|-------------------------|-----------|-----------------------------|
| Telmisartan AUC$_{0-\infty}$ | Sex                                                                | Average (%) | 90% CI                  | $P$ value | Adjusted $R^2$ for each step |
| (Log-additive model)     | UGT1A3*2                                                            | -48.5      | -53.2, -43.2            | $3.82 \times 10^{-22}$ | 0.447 |
|                          | UGT1A3*3                                                            | -28.2      | -41.2, -12.2            | $7.01 \times 10^{-3}$  | 0.464 |
|                          | SLCO1B3 c.767G>C (rs60140950)                                      | 21.7       | 4.1, 42.4               | $0.0392$  | 0.475 |
| Telmisartan AUC$_{0-\infty}$ | Sex                                                                | 47.2       | 20.6, 79.7              | $1.58 \times 10^{-2}$  | 0.087 |
| (UGT1A3*2 dummy variables) | UGT1A3*2 heterozygous men                                          | -63.6      | -69.6, -56.3            | $1.21 \times 10^{-16}$ | 0.227 |
|                          | UGT1A3*2 homozygous women                                          | -71.6      | -77.7, -63.9            | $3.31 \times 10^{-15}$ | 0.321 |
|                          | UGT1A3*2 heterozygous women                                        | -57.3      | -64.9, -48.1            | $1.54 \times 10^{-11}$ | 0.439 |
|                          | UGT1A3*2 homozygous men                                            | -63.2      | -72.5, -50.8            | $5.21 \times 10^{-8}$  | 0.505 |
|                          | SLCO1B3 c.767G>C (rs60140950)                                      | 23.1       | 6.7, 42.0               | $0.0172$  | 0.532 |

AUC$_{0-\infty}$, area under the plasma concentration-time curve from zero hour to infinity; CI, confidence interval; SNV, single nucleotide variation

$^a$Per minor allele copy or per dummy variable; sex: women vs. men.

Figure 3 (a) The geometric mean ± geometric SD area under the plasma telmisartan concentration-time curve from zero hours to infinity (AUC$_{0-\infty}$) values grouped by genotype scores (GS). The UGT1A3*1 allele includes all other UGT1A3 alleles than UGT1A3*2 and *3. (b) GS for individuals with different genotype combinations. UGT1A3 and SLCO1B3 reference genotypes are depicted with white, heterozygous with gray, and homozygous variant genotypes with black rectangles. The estimated population frequencies of the genotype combinations were obtained from the 1000 Genomes Project Data. $^{18,48}$ (c) The percentage of individuals (95% confidence interval (CI)) with AUC$_{0-\infty} < 229$ ng·hour/mL in different GS groups. (d) The average change (95% CI) in diastolic blood pressure during 24 hours after telmisartan administration in GS groups < 0.8 and ≥ 0.8.
In the candidate gene analysis, also the UGT1A3*3 allele was associated with decreased telmisartan AUC. The effect of this allele was, however, smaller than that of UGT1A3*2 and explained only 1–2% of the interindividual variability in telmisartan exposure. In previous studies with relatively small numbers of UGT1A3*3 carriers, the allele has not affected UGT1A3 mRNA or protein expression in human liver samples.\textsuperscript{18,27} In vitro studies on the effects of UGT1A3*3 on glucuronidation activity have been inconsistent, with studies showing either reduced or unchanged enzyme activity.\textsuperscript{29–31} Given the low allele frequency of UGT1A3*3 and the relatively weak association with telmisartan exposure, the result needs confirmation in future studies.

In accordance with the associations with parent telmisartan, the UGT1A3*2 allele was associated with increased telmisartan acyl-glucuronide C\textsubscript{max} and telmisartan acyl-glucuronide/telmisartan AUC ratio. In theory, the increased metabolite/parent compound AUC ratio could be explained by either increased formation or reduced elimination of the metabolite, or both. Given that the UGT1A3*2 allele was associated with a reduced AUC and thus an increased oral clearance of telmisartan, increased metabolite formation is the most probable explanation. The increased C\textsubscript{max} of telmisartan acyl-glucuronide in association with the UGT1A3*2 allele is likely explained by formation of the metabolite during the first pass. Despite a strong association with the AUC of parent telmisartan, the UGT1A3*2 allele was not associated with the AUC of the acyl-glucuronide metabolite. This indicates that UGT1A3*2 increases the rate of glucuronidation of telmisartan, but that the total amount of glucuronide formed is not changed. This is consistent with glucuronidation being the exclusive route of telmisartan elimination.

In addition to UGT1A3, which metabolizes telmisartan with the highest affinity in vitro, telmisartan is a substrate of UGT1A1, UGT1A7, UGT1A8, and UGT1A9.\textsuperscript{3} All UGT1A enzymes are encoded by the UGT1A gene in chromosome 2.\textsuperscript{32} They share exons 2–5, but have unique first exons. Strong linkage disequilibrium patterns span the entire UGT1A gene.\textsuperscript{18} In the present study, we fully sequenced the whole UGT1A gene. Of the variants in the other candidate UGT1A genes, the UGT1A1*28 and UGT1A7*3 alleles are strongly linked with UGT1A3*2. The UGT1A1*28 allele has been associated with decreased glucuronidation of UGT1A1 substrates due to significantly decreased UGT1A1 protein expression.\textsuperscript{33–35} Moreover, the UGT1A7*3 allele has been associated with decreased function of UGT1A7 in vitro.\textsuperscript{36} After adjusting for the UGT1A3 effect, no other UGT1A variants, including UGT1A1*28 and UGT1A7*3, were significantly associated with telmisartan AUC. Similarly, in the haplotype-based analysis, the UGT1A1*28 and UGT1A7*3 alleles did not associate independently with telmisartan pharmacokinetics (Table S2). Taken together, these data indicate that genetic variability in UGT1A enzymes other than UGT1A3 is of major importance for telmisartan pharmacokinetics.

In this study, the UGT1A3*2 allele seemed to lack a clear gene-dose effect on telmisartan AUC and C\textsubscript{max}. That is, men showed no difference and women showed only a relatively small difference between UGT1A3*2 homozygotes and heterozygotes. No obvious explanation exists for these findings. However, linkage between
GT1A3*2 and GT1A1*28 and a role of GT1A1 in intestinal telmisartan metabolism may play a role. It is notable, that the effects of the GT1A1*28 allele are generally much more pronounced in homozygotes than in heterozygotes,18–20 whereas those of GT1A3*2 are usually seen already in heterozygotes.21,22 In theory, the effects of GT1A1*28 might thus counteract the effects of GT1A3*2 on telmisartan pharmacokinetics in GT1A3*2/GT1A1*28 homozygotes.

Considering that telmisartan pharmacokinetics strongly depends on GT1A3 activity, it could be susceptible to GT1A3-mediated drug-drug interactions. Interestingly, nisoldipine has increased the AUC of telmisartan by 132%.37 In human liver microsomes, nisoldipine inhibits the glucuronidation of estradiol,38 mediated by GT1A1, GT1A3, GT1A8, GT1A10, and GT2B7.39 Further studies are required to determine whether nisoldipine inhibits GT1A3. Telmisartan could be a useful index substrate for GT1A3-mediated drug-drug interactions.

Telmisartan has been suggested to be a relatively selective substrate of OATP1B3, an influx transporter expressed on the basolateral membrane of hepatocytes.2 In the candidate gene analysis, the SLCO1B3 c.767G>C missense SNV was associated with increased telmisartan AUC, with a 22% increase per minor allele copy. However, this SNV explained only 1% of the interindividual variability in telmisartan exposure. There seems to be no previous studies investigating the associations of this SNV with telmisartan or other OATP1B3 substrate pharmacokinetics in humans. The SIFT and PolyPhen in silico prediction tools suggest the c.767G>C SNV to be deleterious.40,41 In one in vitro study, however, this SNV did not significantly affect the uptake of the OATP1B3 substrate cholecytokinin-8.42 A recent in vitro study suggested that OATP2B1 would play a more important role than OATP1B3 in the hepatic uptake of telmisartan.5 In our study, SNVs in SLCO2B1 were not, however, associated with telmisartan pharmacokinetics. The analysis included, for example, the c.601G>A SNP associated previously with 3S,5R-fluvastatin and the c.1457C>T SNP associated previously with 3S,5R-fluvastatin, fexofenadine, and celineprolol pharmacokinetics.43–45

In accordance with previous studies,10,16,26 the AUC and Cmax of telmisartan were significantly lower in men than in women. Body size did not explain this difference. Our finding that the telmisartan acyl-glucuronide/telmisartan AUC ratio was higher in men than in women suggests that the difference could be due to higher telmisartan glucuronidation capacity in men. Interestingly, no sex difference seemed to exist in telmisartan AUC and Cmax in individuals homozygous for GT1A3*2.

Telmisartan plasma concentration–time profiles are characterized by a biexponential decline after the Cmax, with a rapid initial distribution followed by a prolonged terminal elimination phase.10 Of note, no appreciable drug accumulation occurs during multiple dosing. This suggests that our pharmacokinetic results after a single telmisartan dose can be extrapolated to continuous treatment. However, advanced age, concomitant diseases, and other medications may increase variability in telmisartan pharmacokinetics in patients with hypertension as compared with the healthy volunteers of the present study. Nevertheless, the effects of GT1A variants seem to be similar in patients with hypertension and healthy volunteers.26 This suggests that the effects of genetic variants on telmisartan pharmacokinetics in healthy volunteers can be extrapolated to patients with hypertension.

The maximum antihypertensive effect of telmisartan is usually attained within 4–8 weeks after the start of treatment, but some effect can be seen already 3 hours after the first dose in patients with hypertension.11 In general, the antihypertensive effect of telmisartan is much more pronounced in hypertensive than in normotensive individuals. Nevertheless, in our study in normotensive healthy volunteers, the average change in diastolic and systolic blood pressures correlated negatively with telmisartan AUC. Moreover, a low GS was associated with the weak diastolic blood pressure-lowering effect of telmisartan. One should keep in mind, however, that these pharmacodynamic results should not be directly extrapolated to patients with hypertension. The finding that the average change in systolic blood pressure was not significantly associated with the GS may be explained by greater variation in systolic than diastolic blood pressure.

A previous angiotensin II challenge study in healthy volunteers showed that telmisartan efficacy is concentration-dependent. The telmisartan AUC0–∞ value giving 50% of the maximum effect was estimated to be 229 ng × hour/mL.12 In the present study, the proportion of individuals having AUC0–∞ values below 229 ng·hour/mL after a 40 mg dose increased along with a decreasing GS. In the treatment of hypertension, the effective dose of telmisartan is usually 40 mg once daily, but a significant proportion of patients require 80 mg daily due to poor efficacy.13 Because the effect of telmisartan is dose-dependent and concentration-dependent, and there is large variability in telmisartan exposure, it is probable that inadequate efficacy with the 40 mg dose may, in some cases, be due to insufficient plasma concentrations. On the other hand, although telmisartan is usually well-tolerated,46,47 it is possible that increased exposure predisposes to hypotension or other adverse effects. The GS might aid in finding the right telmisartan doses for patients with hypertension.

The participants of this study were white Finnish volunteers, among whom the allele frequency of GT1A3*2 was 0.39. The GT1A3*2 allele is generally very common in European (0.32), Sub-Saharan African (0.56), and South-Asian (0.42) populations, but less common in East Asians (0.12).18 On the contrary, GT1A3*3 is more common in South and East Asians (MAF 0.20 and 0.18) as compared with Europeans (0.07) and Sub-Saharan Africans (0.086). These interethnic differences in GT1A3 allele frequencies lead to differences in the distributions of telmisartan GSs among populations (Figure 3).18,48 In previous studies in Asian individuals, the GT1A3*2 allele or linked GT1A4 variants have been associated with a similar effect on telmisartan pharmacokinetics, as was seen in the present study.3,14,26 This suggests that our findings can be extrapolated to other populations.

In conclusion, these results indicate that genetic variants of GT1A3 associate strongly with the pharmacokinetics of telmisartan. Due to lower plasma concentrations, carriers of GT1A3*2 may be at an increased risk of poor blood pressure-lowering efficacy of telmisartan. The results also suggest an association of SLCO1B3 c.767G>C variant with telmisartan
exposure. The generated GS may aid in individualizing treat-
ment with telmisartan.

**SUPPORTING INFORMATION**
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

**ACKNOWLEDGMENTS**
The authors thank Ms. Katja Halme, Ms. Hanna Hyvärinen, Ms. Satu Karjalainen, Mr. Jouko Laitila, Ms. Eija Mäkinen-Pulli, Ms. Rajia Nevala, and Ms. Lisbet Partanen for skillful assistance in conducting the clinical pharmacokinetic study, and Mr. PekkaEllonen and Ms. Majia Lepistö, M.Sc., for the massive parallel sequencing.

**FUNDING**
This study was supported by grants from the European Research Council (Grant agreement 282106). State funding for university-level health research, the Sigrid Jusélius Foundation (Helsinki, Finland), the Biomedicum Helsinki Foundation (Helsinki, Finland), and the Orion Research Foundation sr (Espoo, Finland).

**CONFLICT OF INTEREST**
All authors declared no competing interests for this work.

**AUTHOR CONTRIBUTIONS**
P.H. and M.Ni. wrote the manuscript. P.H., A.T., J.T.B., and M.Ni. designed the research. P.H., A.T., T.L., M.Ne., T.T., M.P.-H., J.T.B., and M.Ni. performed the research. P.H. and M.Ni. analyzed the data.

© 2020 The Authors. Clinical Pharmacology & Therapeutics published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

1. Frampton, J.E. Telmisartan: a review of its use in cardiovascular disease prevention. *Drugs* 71, 651–677 (2011).
2. Stangier, J. et al. Absorption, metabolism, and excretion of intravenously and orally administered [14C]telmisartan in healthy volunteers. *J. Clin. Pharmacol.* 40, 1312–1322 (2000).
3. Yamada, A. et al. The impact of pharmacogenetics of metabolic enzymes and transporters on the pharmacokinetics of telmisartan in healthy volunteers. *Pharmacogenet. Genomics* 21, 523–530 (2011).
4. Ishiguro, N. et al. Predominant contribution of OATP1B3 to the hepatic uptake of telmisartan, an angiotensin II receptor antagonist, in humans. *Drug Metab. Dispos.* 34, 1109–1115 (2006).
5. Izumi, S. et al. Relative activity factor (RAF)-based scaling of uptake clearance mediated by organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 in human hepatocytes. *Mol. Pharm.* 15, 2277–2288 (2018).
6. Chang, C., Bahadduri, P.M., Polli, J.E., Swaan, P.W. & Ekins, S. Rapid identification of P-glycoprotein substrates and inhibitors. *Drug Metab. Dispos.* 34, 1976–1984 (2006).
7. Kataoka, M. et al. Dynamic analysis of GI absorption and hepatic distribution processes of telmisartan in rats using positron emission tomography. *Pharm. Res.* 29, 2419–2431 (2012).
8. Ishiguro, N. et al. Establishment of a set of double transfectants coexpressing organic anion transporting polypeptide 1B3 and hepatic efflux transporters for the characterization of the hepatobiliary transport of telmisartan acyclouridine. *Drug Metab. Dispos.* 36, 796–805 (2008).
9. Maeda, K. et al. Quantitative investigation of hepatobiliary transport of [11C]telmisartan in humans by PET imaging. *Drug Metab. Pharmacokinet.* 34, 293–299 (2019).
10. Stangier, J., Su, C.A. & Roth, W. Pharmacokinetics of orally and intravenously administered telmisartan in healthy young and elderly volunteers and in hypertensive patients. *J. Int. Med. Res.* 28, 149–167 (2000).
11. Smith, D.H., Matzek, K.M. & Kempthorne-Rawson, J. Dose response and safety of telmisartan in patients with mild to moderate hypertension. *J. Clin. Pharmacol.* 40, 1380–1390 (2000).
12. Stangier, J. et al. Inhibitory effect of telmisartan on the blood pressure response to angiotensin II challenge. *J. Cardiovasc. Pharmacol.* 38, 672–685 (2001).
13. Giles, T.D., Bakris, G.L., Smith, D.H., Davidai, G. & Weber, M.A. Defining the antihypertensive properties of the angiotensin receptor blocker telmisartan by a practice-based clinical trial. *Am. J. Hypertens.* 16, 460–466 (2003).
14. Ieiri, I. et al. Pharmacokinetic and pharmacogenomic profiles of telmisartan after the oral microdose and therapeutic dose. *Pharmacogenet. Genomics* 21, 495–505 (2011).
15. Miura, M., Satoh, S., Inoue, K., Saito, M., Habuchi, T. & Suzuki, T. Telmisartan pharmacokinetics in Japanese renal transplant recipients. *Clin. Chim. Acta.* 399, 83–87 (2009).
16. Caballeiro, T. et al. Evaluation of the relationship between sex, polymorphisms in CYP2C8 and CYP2C9, and pharmacokinetics of angiotensin receptor blockers. *Drug Metab. Dispos.* 41, 224–229 (2013).
17. Guo, X. et al. No effect of MDR1 C3435T polymorphism on oral pharmacokinetics of telmisartan in 19 healthy Chinese male subjects. *Clin. Chem. Lab. Med.* 47, 38–43 (2009).
18. Hirvensalo, P. et al. Comprehensive pharmacogenomic study reveals an important role of UGT1A3 in montelukast pharmacokinetics. *Clin. Pharmacol. Ther.* 104, 158–168 (2018).
19. PharmaADME.org <http://pharmaadme.org>. Accessed May 8, 2020.
20. Morrissey, K.M., Wen, C.C., Johns, S.J., Zhang, L., Huang, S.M. & Giacomini, K.M. The UCSF-FDA TransPortal: a public drug transporter database. *Clin. Pharmacol. Ther.* 92, 545–546 (2012).
21. Sulonen, A.M. et al. Comparison of solution-based exome capture methods for next generation sequencing. *Genome Biol.* 12, R94 (2011).
22. Ehmer, U. et al. Rapid allelic discrimination by TaqMan PCR for the detection of the Gilbert’s syndrome marker UGT1A1*28. *J. Mol. Diagn.* 10, 549–552 (2008).
23. Clinical Pharmacology & Therapeutics Editorial Team. Statistical guide for Clinical Pharmacology & Therapeutics. *Clin. Pharmacol. Ther.* 88, 150–152 (2010).
24. Stephens, M., Smith, N.J. & Donnelly, P. A new statistical method for haplotype reconstruction from population data. *Am. J. Hum. Genet.* 68, 978–989 (2001).
25. Stephens, M. & Donnelly, P. A comparison of Bayesian methods for haplotype reconstruction from population genotype data. *Am. J. Hum. Genet.* 73, 1162–1169 (2003).
26. Pei, Q. et al. Effects of genetic variants in UGT1A1, SLC01B3, ABCB1, ABC21, ABC22, ABCG2, ORM1 on PK/PD of telmisartan in Chinese patients with mild to moderate essential hypertension. *Int. J. Clin. Pharmacol. Ther.* 55, 659–665 (2017).
27. Riedmaier, S. et al. UDP-glucuronosyltransferase (UGT) polymorphisms affect atorvastatin lactonization in vitro and in vivo. *Clin. Pharmacol. Ther.* 87, 65–73 (2010).
28. Lin, M. et al. Effects of UDP-glucuronosyltransferase (UGT) polymorphisms on the pharmacokinetics of febuxostat in healthy Chinese volunteers. *Drug Metab. Pharmacokinet.* 32, 77–84 (2017).
29. Caillier, B. et al. A pharmacogenomics study of the human estrogen glucuronosyltransferase UGT1A3. *Pharmacogenet. Genomics* 17, 481–495 (2007).
30. Chen, Y., Chen, S., Li, X., Wang, X. & Zeng, S. Genetic variants of human UGT1A3: functional characterization and frequency distribution in a Chinese Han population. *Drug Metab. Dispos.* 34, 1462–1467 (2006).
31. Iwai, M., Maruo, Y., Ito, M., Yamamoto, K., Sato, H. & Takeuchi, Y. Six novel UDP-glucuronosyltransferase (UGT1A3)
polymorphisms with varying activity. J. Hum. Genet. 49, 123–128 (2004).
32. Guillemette, C., Lévesque, É. & Rouleau, M. Pharmacogenomics of human uridine diphospho-glucuronosyltransferases and clinical implications. Clin. Pharmacol. Ther. 96, 324–339 (2014).
33. Monaghan, G., Ryan, M., Seddon, R., Hume, R. & Burchell, B. Genetic variation in bilirubin UDP glucuronosyltransferase gene promoter and Gilbert’s syndrome. Lancet 347, 578–581 (1996).
34. Ando, Y., Saka, H., Asai, G., Sugiura, S., Shimokata, K. & Kamataki, T. UGT1A1 genotypes and glucuronidation of SN-38, the active metabolite of irinotecan. Ann. Oncol. 9, 845–847 (1998).
35. Bhatt, D.K. et al. Age- and genotype-dependent variability in the protein abundance and activity of six major uridine diphosphate-glucuronosyltransferases in human liver. Clin. Pharmacol. Ther. 105, 131–141 (2019).
36. Guillemette, C., Ritter, J.K., Auyeung, D.J., Kessler, F.K. & Housman, D.E. Structural heterogeneity at the UDP-glucuronosyltransferase 1 locus: functional consequences of three novel missense mutations in the human UGT1A7 gene. Pharmacogenetics 10, 629–644 (2000).
37. Bajcetic, M. et al. Pharmacokinetics of oral doses of telmisartan and nisoldipine, given alone and in combination, in patients with essential hypertension. J. Clin. Pharmacol. 47, 295–304 (2007).
38. Satoh, T., Tomikawa, Y., Takanashi, K., Itoh, S., Itoh, S. & Yoshizawa, I. Studies on the interactions between drugs and estrogen. III. Inhibitory effects of 29 drugs reported to induce gynecomastia on the glucuronidation of estradiol. Biol. Pharm. Bull. 27, 1844–1849 (2004).
39. Lépine, J. et al. Specificity and regioselectivity of the conjugation of estradiol, estrone, and their catecholestrogen and methoxyestrogen metabolites by human uridine diphospho-glucuronosyltransferases expressed in endometrium. J. Clin. Endocrinol. Metab. 89, 5222–5232 (2004).
40. Sim, N.L., Kumar, P., Hu, J., Henikoff, S., Schneider, G. & Ng, P.C. SIFT web server: predicting effects of amino acid substitutions on proteins. Nucleic Acids Res. 40, W452–W457 (2012).
41. Adzhubei, I.A. et al. A method and server for predicting damaging missense mutations. Nat. Methods 7, 248–249 (2010).
42. Schwarz, U.I. et al. Identification of novel functional organic anion-transporting polypeptide 1B3 polymorphisms and assessment of substrate specificity. Pharmacogenet. Genomics 21, 103–114 (2011).
43. Hirvensalo, P. et al. Enantiospecific pharmacogenomics of fluvastatin. Clin. Pharmacol. Ther. 106, 668–680 (2019).
44. Imanaga, J. et al. The effects of the SLCO2B1 c.1457C > T polymorphism and apple juice on the pharmacokinetics of fexofenadine and midazolam in humans. Pharmacogenet. Genomics 21, 84–93 (2011).
45. Ieiri, I. et al. Microdosing clinical study: pharmacokinetic, pharmacogenomic (SLCO2B1), and interaction (grapefruit juice) profiles of celiprolol following the oral microdose and therapeutic dose. J. Clin. Pharmacol. 52, 1078–1089 (2012).
46. Stangier, J., Su, C.A., Schöndorfer, G. & Roth, W. Pharmacokinetics and safety of intravenous and oral telmisartan 20 mg and 120 mg in subjects with hepatic impairment compared with healthy volunteers. J. Clin. Pharmacol. 40, 1355–1364 (2000).
47. Manolis, A.J., Reid, J.L., de Zeeuw, D., Murphy, M.B., Seewaldt-Becker, E., Köster, J. & on behalf of the ARAMIS Study Group. Angiotensin II receptor antagonist telmisartan in isolated systolic hypertension (ARAMIS) study: efficacy and safety of telmisartan 20, 40 or 80 mg versus hydrochlorothiazide 12.5 mg or placebo. J. Hypertens. 22, 1033–1037 (2004).
48. Clarke, L. et al. The international genome sample resource (IGSR): a worldwide collection of genome variation incorporating the 1000 Genomes Project data. Nucleic Acids Res. 45, D854–D859 (2017).
49. Whirl-Carrillo, M. et al. Pharmacogenomics knowledge for personalized medicine. Clin. Pharmacol. Ther. 92, 414–417 (2012).
50. PharmGKB UGT1A7 haplotypes <https://www.pharmgkb.org/gene/PA37182/haplotype>. Accessed March 10, 2020.