Table S1 | Common functional genetic variants in drug disposition genes

<table>
<thead>
<tr>
<th>Protein name (Gene name)</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aryl hydrocarbon receptor (AHR)</td>
<td>Variants lead to reduced in vitro inducibility by polycyclic aromatic hydrocarbons.</td>
<td>1</td>
</tr>
<tr>
<td>β-glucuronidase (GUSB)</td>
<td>Ex vivo enzyme activity in plasma was 60-90% higher in carriers of two intronic variants.</td>
<td>2</td>
</tr>
<tr>
<td>Carbonyl reductase 3 (CBR3)</td>
<td>A variant has increased in vitro activity for menadione.</td>
<td>3</td>
</tr>
<tr>
<td>Carboxylesterase 2 (CES2)</td>
<td>Intrinsic variants have been associated with decreased mRNA levels in colon tumors or liver, but not with enzyme activity. Other variants have not been shown to be functional. Uncommon loss-of-function variants were observed in a Japanese population.</td>
<td>4-7</td>
</tr>
<tr>
<td>Concentrative nucleoside transporter 1 (SLC28A1)</td>
<td>A variant has reduced in vitro affinity for gemcitabine. Two uncommon variants are deficient for thymidine uptake.</td>
<td>8</td>
</tr>
<tr>
<td>Cytochrome P450 1A1 (CYP1A1)</td>
<td>Promoter variants have been associated with altered inducibility by aryl hydrocarbons but not with differences of basal enzyme levels.</td>
<td>1, 9, 10</td>
</tr>
<tr>
<td>Cytochrome P450 1B1 (CYP1B1)</td>
<td>Variants have reduced in vitro activity toward estradiol.</td>
<td>11</td>
</tr>
<tr>
<td>Cytochrome P450 2A13 (CYP2A13)</td>
<td>A nonsense polymorphism has been observed. An uncommon variant has reduced in vitro activity for several substrates.</td>
<td>12-14</td>
</tr>
<tr>
<td>Cytochrome P450 2E1 (CYP2E1)</td>
<td>A promoter region repeat sequence polymorphism may be associated with enzyme induction. Uncommon non-synonymous SNPs lead to reduced in vitro protein activity</td>
<td>15-17</td>
</tr>
<tr>
<td>Cytochrome P450 2G1 (CYP2G1)</td>
<td>Deletion of exons 4-6 resulting in no functional protein is the most common form of this gene. A functional allele was found in 18% of black individuals but ≤4% of other ethnic groups.</td>
<td>18</td>
</tr>
<tr>
<td>Cytochrome P450 2G2 (CYP2G2)</td>
<td>A nonsense variant in exon 3 resulting in no functional protein is the most common form of this gene. A functional allele was found in 14-46% of individuals of various ethnicities.</td>
<td>18</td>
</tr>
<tr>
<td>Cytochrome P450 2J2 (CYP2J2)</td>
<td>A promoter region and several coding region polymorphisms reduce in vitro expression or function. The promoter variant was associated with reduced arachidonic acid metabolites in vivo.</td>
<td>19-21</td>
</tr>
</tbody>
</table>
Cytochrome P450 3A4 (CYP3A4)  The functionality of a promoter variant has been debated. Coding region variants have been observed, some of which have reduced intrinsic clearance for certain substrates. Together, the coding region variants may be sufficiently common to contribute meaningfully to phenotype.  22-28

Cytochrome P450 3A7 (CYP3A7)  Variants are associated with increased expression.  29, 30

Cytochrome P450 3A43 (CYP3A43)  A frameshift polymorphism that truncates the open reading frame has been observed.  31

Cytochrome P450 4B1 (CYP4B1)  A frameshift polymorphism that truncates the open reading frame has been observed.  32

Cytochrome P450 4F12 (CYP4F12)  Several promoter and coding region polymorphisms affect in vitro expression or enzyme kinetics.  33, 34

Equilibrative nucleoside transporter 1 (SLC29A1)  Promoter region polymorphisms reduce in vitro expression; common coding region variants have not been reported.  35, 36

Flavin monooxygenase 1 (FMO1)  A promoter region polymorphism reduces in vitro expression; coding region variants affect activity but probably occur at low frequencies.  37 and references therein

Flavin monooxygenase 2 (FMO2)  FMO2 is polymorphically expressed due to a nonsense allele; functional alleles have only been observed to date in Africans & Hispanics.  37 and references therein

Glutathione-S-transferase α (GSTA1)  Promoter variants are associated with GSTA1 (and possible GSTA2) expression level in human liver and in vitro.  38, 39

Glutathione-S-transferase α (GSTA2)  A variant leads to diminished enzyme activity toward several substrates. Other variants appear to not alter activity.  40-42

Glutathione-S-transferase μ (GSTM3)  Variants show increased in vitro specific activity toward 1-chloro-2,4-dinitrobenzene.  43

Glutathione-S-transferase ω (GSTO1)  An amino acid deletion leads to diminished enzyme activity toward several substrates. Other variants appear to not alter activity.  44, 45

Glutathione-S-transferase ω (GSTO2)  A variant has high dehydroascorbate reductase activity, but does not affect activity toward other substrates.  44, 45

Glutathione-S-transferase ω (GSTZ1)  Variants have substrate-dependent effect on catalytic activity.  46, 47

Histamine-N-methyltransferase (HNMT)  A variant alters enzyme stability and activity level in kidney biopsies.  48, 49

Monoamine oxidase A (MAOA)  A promoter variant increases transcriptional activity.  50
<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Description</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine oxidase B (MAOB)</td>
<td>Promoter and intronic variants lead to higher transcriptional activity in reporter gene assays.</td>
<td>51</td>
</tr>
<tr>
<td>Multidrug resistance-associated protein 3 (ABCC3)</td>
<td>A promoter variant is associated with reduced hepatic expression levels and altered transcription factor binding. The only common non-synonymous variant reported has not been shown to have functional consequences.</td>
<td>52, 53</td>
</tr>
<tr>
<td>Multidrug resistance-associated protein 8 (ABCC11)</td>
<td>A variant alters excretory activity.</td>
<td>54</td>
</tr>
<tr>
<td>N-acetyltransferase 1 (NAT1)</td>
<td>Variants with decreased expression or catalytic activity have been identified and associated with cancer risk, probably via poor carcinogen deactivation. Association with altered drug disposition has not been reported.</td>
<td>55 and references therein; <a href="http://www.louisville.edu/medschool/pharmacology/NAT1.html">http://www.louisville.edu/medschool/pharmacology/NAT1.html</a></td>
</tr>
<tr>
<td>Oligopeptide transporter 2§ (SLC15A2)</td>
<td>A variant haplotype has altered catalytic activity.</td>
<td>56</td>
</tr>
<tr>
<td>Organic anion transport protein 1A2 (SLCO1A2)</td>
<td>Taken together, coding region variants that result in reduced transport activity have a frequency &gt;5%.</td>
<td>57</td>
</tr>
<tr>
<td>Organic anion transport protein 2B1§ (SLCO2B1)</td>
<td>A variant was shown to have reduced in vitro transport activity.</td>
<td>58</td>
</tr>
<tr>
<td>Organic anion transporter 4-like§ (SLC22A12)</td>
<td>Variants with have been identified and associated with either hyper- and hypouricemia. Association with altered drug disposition has not been reported.</td>
<td>59, 60 and references therein</td>
</tr>
<tr>
<td>Organic cation transporter 1 (SLC22A1)</td>
<td>Coding region variants were shown to have reduced in vitro transport activity.</td>
<td>61-63</td>
</tr>
<tr>
<td>Organic cation transporter N1 (SLC22A4)</td>
<td>Several variants have been identified, two of which have been shown to alter in vitro transporter function.</td>
<td>64-67</td>
</tr>
<tr>
<td>Organic cation transporter N2 (SLC22A5)</td>
<td>A promoter variant eliminates heat-shock transcriptional induction of a heterologous transfected gene. Rare mutations cause primary carnitine deficiency.</td>
<td>65, 66</td>
</tr>
<tr>
<td>Paraoxonase 1 (PON1)</td>
<td>Two non-synonymous SNPs have been shown to decrease serum enzyme activity in ex vivo assays, and a promoter variant has been associated with increased expression. PON1 genotypes have been associated with chemical and toxin sensitivities, but association of PON1 genotypes with the pharmacokinetics of any drug has not been reported.</td>
<td>68 and references therein; 69, 70</td>
</tr>
</tbody>
</table>
Phenylethanolamine-N-methyltransferase (PNMT) | Promoter region haplotypes have decreased *in vitro* transcriptional activity; functional polymorphisms altering activity and protein levels are uncommon. | 71

Pregnane X receptor (NR1I2) | Upstream, intronic and downstream variants have been associated with CYP3A & P-glycoprotein induction levels, although the functional variants have not been clearly identified. Non-synonymous variants are either not common or have not been shown to have functional consequences *in vivo*. | 72, 73

Quinone NADPH dehydrogenase 1 (NQO1) | A coding region variant leads to enzyme instability; homozygotes lack NQO1 activity. | 74 and references therein

Quinone NADPH dehydrogenase 2 (NMOR2) | A promoter variant decreases expression. | 75

Short chain acyl-coA dehydrogenase (ACADS) | Two variants have reduced activity or stability. | 76 and references therein

Sodium-taurocholate cotransporting polypeptide (SLC10A1) | Common variants have reduced activity or cell surface localization. | 77

Sulfotransferase 1A1 (SULT1A1) | Alleles of this enzyme have reduced *in vitro* activity or expression levels, and have been associated with reduced stability. | 78-82

Sulfotransferase 1A2 (SULT1A2) | Alleles of this enzyme have reduced *in vitro* activity. | 78, 79, 82

Sulfotransferase 2A1 (SULT2A1) | Alleles of this enzyme have reduced activity and expression levels. | 83

Uridine glucuronosyltransferase 1A3 (UGT1A3) | Several variants have been identified; one of which has increased intrinsic clearance. | 84, 85

Uridine glucuronosyltransferase 1A4 (UGT1A4) | Two non-synonymous SNPs have substrate-dependent effects on enzyme activity. | 84, 86, 87

Uridine glucuronosyltransferase 1A7 (UGT1A7) | An amino acid change has reduced *in vitro* activity. | 88 and references therein

Uridine glucuronosyltransferase 1A10 (UGT1A10) | Different variants, one of which has reduced activity, have been observed in populations of diverse origin. | 89-91

Uridine glucuronosyltransferase 2B7 (UGT2B7) | A common non-synonymous variant has been observed to be non-functional in most studies, although there is one report of reduced enzyme activity in genotyped human microsomes. In another study, this variant was found to be in complete linkage disequilibrium with a common promoter variant, which may be the functional polymorphism. Another promoter variant has been associated with | 92-97
| Uridine glucuronosyltransferase 2B17 (UGT2B17) | Reduced transcription in a heterologous expression assay. | Low nitrosamine metabolism was observed in human liver microsomes harboring a common deletion of this gene. | 98-100 |

§ Also known as PEPT2.
* Also known as OATP-A.
# Also known as OATP-B.
& Also known as URAT1.
References


