# Impact of the interaction between 3'-UTR SNPs and microRNA on the expression of human xenobiotic metabolism enzyme and transporter genes

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Genetic variation in the expression of human xenobiotic metabolism enzymes and transporters (XMETs) leads to inter-individual variability in metabolism of therapeutic agents as well as differed susceptibility to various diseases. Recent expression quantitative traits loci (eQTL) mapping in a few human cells/tissues have identified a number of single nucleotide polymorphisms (SNPs) significantly associated with mRNA expression of many XMET genes. These eQTLs are therefore important candidate markers for pharmacogenetic studies. However, questions remain about whether these SNPs are causative and in what mechanism these SNPs may function. Given the important role of microRNAs (miRs) in gene transcription regulation, we hypothesize that those eQTLs or their proxies in strong linkage disequilibrium (LD) altering miR targeting are likely causative SNPs affecting gene expression. The aim of this study is to identify eQTLs potentially regulating major XMETs via interference with miR targeting. To this end, we performed a genome-wide screening for eQTLs for 409 genes encoding major drug metabolism enzymes, transporters and transcription factors, in publically available eQTL datasets generated from the HapMap lymphoblastoid cell lines and human liver and brain tissue. As a result, 308 eQTLs significantly ( $p < 10^{-5}$ ) associated with mRNA expression of 101 genes were identified. We further identified 7,869 SNPs in strong LD ( $r^2 > 0.8$ ) with these eQTLs using the 1,000 Genome SNP data. Among these 8,177 SNPs, 27 are located in the 3'-UTR of 14 genes. Using two algorithms predicting miR-SNP interaction, we found that almost all these SNPs (26 out of 27) were predicted to create, abolish, or change the target site for miRs in both algorithms. Many of these miRs were also expressed in the same tissue that the eQTL were identified. Our study provides a strong rationale for continued investigation for the functions of these eQTLs in pharmacogenetic settings.

Keywords: eQTL, xenobiotic metabolism enzyme and transporter, microRNA, pharmacogenetics, 3'-UTR

#### **INTRODUCTION**

Xenobiotic metabolizing enzymes and transporters (XMETs) are involved in biotransformation and detoxification of carcinogens, environmental toxins, and therapeutic drugs (Carlsten et al., 2008; Korkina et al., 2009). In humans, the process of biotransformation and detoxification of xenobiotics by XMETs can be divided into three phases: modification (phase I) primarily by enzymes of the cytochromes P450 superfamily; conjugation (phase II), e.g., glucuronidation by UDP-glucuronosyl transferase; and excretion (phase III) mainly by membrane transporters. XMETs are expressed in almost all tissue types, centrally and locally protecting the entire body against the damages caused by various natural and synthetic compounds. XMETs are highly expressed in digestive tract and especially in the liver, the most important organ for central metabolism (Conde-Vancells et al., 2010). Variations in the expression and activity of these XMETs lead to significant inter-individual difference in the disposition of exogenous chemicals including absorption, distribution, metabolism, and excretion (ADME) of pharmaceutical drugs. On the other hand, many XMETs are also found to be very abundant in non-digestive tract tissues/cells, e.g., brain, lung, bladder, and blood (Pavek and Dvorak, 2008). These XMETs could affect the local response to certain drugs at the site of action. Meanwhile, due to the crucial role of XMETs in detoxification of carcinogens and toxins, genetic variation in XMETs function in specific tissues/organs is also an important mechanism underlying genetic susceptibility to certain diseases, e.g., those XMETs expressed in lung and bladder may modify cancer risk. Recent genome-wide association studies have identified polymorphisms at the *UGT1A* locus strongly associated with urinary bladder cancer risk (Selinski et al., 2012). XMETs are sensitively regulated by various nuclear receptors (NRs) and transcription factors (TFs). These trans-acting regulators play a pivotal role in mediating cellular response to exposure to xenobiotics by modulating the transcription of XMETs, thus significantly contributing to the variability in the function of XMETs (Bourgine et al., 2012).

Identifying the DNA polymorphisms leading to the variations in XMET function is a major area of interest in pharmacogenetic and genomic research. To date, numerous studies focused on individual XMET genes have discovered a large number of sequence variations, many of which alter protein coding sequence and consequently affecting the activity of XMETs (Adjei et al., 2003; Hildebrandt et al., 2004; Ji et al., 2005; Moyer et al., 2007; Mrozikiewicz et al., 2011). Meanwhile, even more variants were suggested to quantitatively modulate gene transcription (Pavek and Dvorak, 2008). Recently, genome-wide mapping for gene expression quantitative trait loci (eQTLs) in a few human tissues/cells offered unprecedented opportunities to identify the most influential single nucleotide polymorphisms (SNPs) determining gene expression level of XMETs (Gamazon et al., 2010). However, unlike the variants located in the protein coding sequences for which the causality for altered enzyme activity can be more easily understood, how eQTLs affect gene transcription is largely unknown. Understanding the underlying mechanisms will lead to identification of novel causative DNA variants for XMET function as well as reliable pharmacogenetic markers.

MicroRNAs (miRs) are single stranded, about 22-nucleotides (nt) long, evolutionarily conserved, and function as important posttranscriptional regulators of mRNA expression by binding to the 3'-UTR of target mRNAs (Ambros, 2004; Bartel, 2004). MiRs are involved in various developmental and physiological processes by negatively regulating gene expression (Zhang et al., 2007). Over 30% of all protein-coding genes were estimated to be regulated by miRs (Brennecke et al., 2005; Krek et al., 2005; Lewis et al., 2005; Lim et al., 2005). Due to the conservation of the miR target site, SNPs located in 3'-UTR sequences may abolish or create a miR target, thus significantly affecting the mRNA expression (Saunders et al., 2007). Previous studies have suggested that many XMETs are regulated by miRs (Tsuchiya et al., 2006; Takagi et al., 2010; Patron et al., 2012). Several studies also demonstrated that SNPs in XMET gene 3'-UTRs led to different levels of enzyme activity (Saunders et al., 2007; Chin et al., 2008). Hence, we hypothesized that it may be an important mechanism that common SNPs or their linkage disequilibrium (LD) proxies located in the XMET gene 3'-UTR sequences alter mRNA expression via interference with miR targeting. In order to identify these candidate SNPs that may significantly modulate XMET expression, in this study we used multiple published human eQTL datasets to perform an in silico screening for SNPs that highly correlated with mRNA level of 409 major XMET genes. The significant SNPs and/or their LD proxies located in the gene 3'-UTRs were selected to predict a potential interference with miRs. We found that 27 SNPs located in the 3'-UTR of 14 XMET genes are likely associated with gene expression via altering miR binding.

### MATERIALS AND METHODS

**SELECTION OF eQTLs** 

The general strategy for the data analysis was presented in Figure 1. We used the published eQTLs datasets generated from the HapMap lymphoblastoid cell lines (LCLs; Montgomery et al., 2010), human liver (Schadt et al., 2008), and human brain (Gibbs et al., 2010). Although additional eQTL datasets in human LCLs are also available, we chose to use the one by Montgomery et al. (2010) which utilized high-throughput sequencing for the quantification of gene expression, as this technology has been suggested to produce more accurate gene expression data. To our knowledge, all datasets were collected from tissue/cells derived from individuals of Caucasian in origin. We used the online tool<sup>1</sup> to search statistically significant eQTLs. As our study was focused on cis-acting eQTLs, we used a cut-off of  $p = 10^{-5}$  for significance, considering the window for genomic region (500 kb) of each gene and the potential number of SNPs (1 in every 100–1,000 bp).

#### **SEARCH FOR SNPs IN LD WITH eQTLs**

To search SNPs in LD with significant eQTLs, we used the SNAP<sup>2</sup> program to screen the 1,000 Genome SNP data within 500 kb range of the eQTLs of interest in the CEU population with a LD level cut-off of  $R^2 = 0.8$ . Annotation for the location of eQTLs and their proxies relative to the gene structure was also collected with

<sup>&</sup>lt;sup>2</sup> http://www.broadinstitute.org/mpg/snap/ldsearch.php



<sup>&</sup>lt;sup>1</sup> http://www.ncbi.nlm.nih.gov/gtex/GTEX2/gtex.cgi

the program. Only SNPs and/or their proxies located within the 3'-UTR of the studied genes of interest were retained for further analyses.

#### PREDICTION OF SNP-miR INTERACTION

In order to predict the potential SNP-miR interaction, two programs, MicroSNiPer<sup>3</sup> and PolymiRTS<sup>4</sup> were used. The major difference between the two programs is the algorithm used to predict the target site of miRs. The PolymiRTS program used the TargetScan<sup>5</sup>; Lewis et al., 2005; Friedman et al., 2009) algorithm (Bao et al., 2007). In contrast, the MicroSNiPer program used the FASTA (Pearson and Lipman, 1988) alignment program to determine if a change in a nucleotide in 3'-UTR sequence would change the miR binding capability, based on the requirement of perfect Watson– Crick match to the seed 2–7 nt of miRs (Lewis et al., 2005). To be conservative, we used 7-mers match as the cut-off value for a positive prediction.

#### RESULTS

#### **GENOME-WIDE eQTL ANALYSIS OF XMETs**

Expression quantitative traits loci were screened for all 409 major XMET genes, including 144 phase I, 85 phase II and 111 phase III genes, 48 NRs, and transcription factor genes as well as another 21 genes related to drug ADME (**Table A1** in Appendix). As a result, a total of 308 significant ( $p < 10^{-5}$ ) eQTLs were identified from 101 XMET genes. These include nine in LCL, 83 in liver, and 221 in brain tissues. Five SNPs were found as eQTLs shared in two tissue types: rs1023252 in both LCL and brain tissues, rs11101992, rs156697, rs2071474, and rs241440 in both liver and brain tissues (**Figure 2**). Among the total of 308 eQTLs, 20 SNPs were found to be located in the 3'-UTR region; 3 SNPs were in the 5'-UTRs;

<sup>3</sup> http://cbdb.nimh.nih.gov/microsniper

<sup>4</sup> http://compbio.uthsc.edu/miRSNP/

<sup>5</sup> http://www.TargetScan.org/



171 SNPs were intronic; 8 and 6 SNPs were synonymous and nonsynonymous coding variants, respectively; and 12 and 15 SNPs were located in the upstream and downstream flanking region of the genes, respectively. The remaining 73 SNPs were located in intergenic regions.

#### eQTLs AND THEIR LD PROXIES

We chose to screen the 1,000 Genome SNP dataset as this would produce the most comprehensive coverage for the SNPs that may be in LD with a given eQTL. A total of 7,869 SNPs with significant LD with 260 eQTLs were identified. Combined with the remaining 48 eQTLs which had no reliable proxies in the 1,000 Genome dataset, a total of 8,177 SNPs (308 eQTLs and 7,869 proxy SNPs) were included in the subsequent analyses.

#### **PREDICTION OF miR-SNPs INTERACTION**

Of the 112 eQTLs and proxies located in the 3'-UTR sequences, 27 SNPs were found in the 3'-UTR of 14 genes of interest. The remaining SNPs were located in nearby genes thus were excluded from the subsequent analysis. These SNPs were all common SNPs with their minor allele frequency (MAF)  $\geq$ 0.067. Among the 27 SNPs, 12 were found in liver, and 15 were identified in brain tissue. More detailed information for these SNPs was listed in **Table A2** in Appendix.

We focused our study on the association between miRs and these 27 SNPs in the 14 genes. After screened with the two algorithms, MicroSNiPer (Barenboim et al., 2010) and PolymiRTs (Gong et al., 2012), all the 27 SNPs apart from rs11807 (which is not predicted to be in a target site in PolymiRTs database) were found to potentially create, abolish, or alter the target site for miRs in both algorithms. Notably, 34 miRs were predicted by both algorithms to interact with 19 of these SNPs (**Table A2** in Appendix). Of these 34 overlap miRs, except for rs2480256 of CYP2E1 which is not located in the seed sequence of hsa-miR-570-3p, all the remaining SNPs were found to be located in the seed sequence of miR targets.

To further validate the interaction between miRs and SNPs, we investigated whether the identified miRs were expressed in the same tissue as the identified eQTL. We used the GEO datasets (GSE21279 and GSE26545) to screen miR expression in liver and brain tissues, respectively (Hou et al., 2011; Hu et al., 2011). Since many predicted miRs were new and not probed by the published platforms, we thus only concentrate on the list of miRs probed in the platforms. Overall, over 74% (20 out of 27) of the identified miR-SNPs were found to have at least one predicted miR co-expressed with the gene of interest in the same tissue.

We further aimed to investigate whether these 27 SNPs are more likely to be targeted by miRs especially by the co-expressed miR in liver and brain tissues, compared to random-selected 3'-UTR SNPs with similar MAF. No statistical significance were found, possibly due to the limited power caused by the small number (n = 27) of SNPs involved (data not shown).

#### DISCUSSION

Although a large number of DNA variants affecting the function of XMETs have been identified, and many of them have been well linked with clinical response to pharmacotherapy or disease susceptibility (Motsinger-Reif et al., 2010), genetic variations in the activity of most XMETs remain incompletely explained. Recent studies continue to discover novel functional variants in XMET genes (Ramsey et al., 2012). Meanwhile, genome-wide association studies have found a number of XMET SNPs without previously known function significantly associated with different phenotypes in humans (Teichert et al., 2009; Estrada et al., 2012). These studies consistently suggested that additional sequence variants with fundamental role in XMET function have not been identified. Recent eQTL mapping in human tissues provided an opportunity to discover functional XMET polymorphisms at the genome-wide level. However, questions remain whether the identified eQTLs are causal for the altered gene expression and via what mechanism. Our study provides a comprehensive evaluation for this question in major human XMET genes, and generated a list of candidate SNPs that may modulate XMET genes via interference with miR targeting in multiple human tissue types.

Single nucleotide polymorphisms located in the gene 3'-UTRs could have great impact on miR targeting. It has been demonstrated that the entire 3'-UTR sequence could play important roles in miR function in addition to miR target sites (Hu and Bruno, 2011). In particular, negative selection in humans is stronger on computationally predicted conserved miR binding sites than on other conserved sequence motifs in 3'-UTRs, and polymorphisms in predicted miR binding sites are highly likely to be deleterious (Chen and Rajewsky, 2006). Gong et al. (2012) mapped SNPs to the 3'-UTRs of all human protein coding genes. Their results showed that among the 225,759 SNPs identified in 3'-UTRs, over 25% of SNPs potentially abolished 90,784 original miR target sites, while another 25% created a similar number of putative miRNA target sites. Besides these in silico studies, a number of SNPs altering miR targeting have been experimentally demonstrated to be associated with multiple diseases as well as drug metabolism and environmental procarcinogen detoxification (Abelson et al., 2005; Tan et al., 2007; Yu et al., 2007; Yokoi and Nakajima, 2011). Although the seed sequences for miR binding are critical and highly conserved, recent studies have also suggested that 3'-UTR sequences outside of the seed sequences, e.g., flanking sequences may be equally important for miR targeting by controlling the accessibility of the miR or local RNA structure (Grimson et al., 2007). For example, a SNP (829C > T) located 14 bp downstream of a miR-24 binding site in the 3'-UTR of

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human dihydrofolate reductase gene (*DHFR*) was demonstrated to affect *DHFR* expression by interfering with miR-24 function, resulting in *DHFR* over expression and methotrexate resistance (Mishra et al., 2007). By using two algorithms predicting potential SNP-miR interaction, we suggested that 27 eQTLs or their proxies in high LD for 14XMET genes may function through interference with one or more miRs, with most of the SNPs located in the seed sequences. Meanwhile, the majority (20 out of 27) of the identified miR-SNPs were found to have predicted miR co-expressed with the gene of interest in the same tissue. Although no statistically significant enrichment of miR targeting for these SNPs, the strong trends observed here warrants further experimental validations.

Our findings may also provide useful information in addition to the previous observations on the function of these SNPs. Previous studies demonstrated that SNP rs2480256 in the *CYP2E1* gene was significantly associated with systemic lupus erythematosus (Liao et al., 2011). Another study showed that cyclosporine A concentration in serum was significantly correlated with the genotype of the *CYP3A5* rs15524 polymorphism (Onizuka et al., 2011). In addition, a *GSTM3* haplotype including rs1537236 was significantly associated with a decreased growth for maximum mid-expiratory flow rate (MMEF) in a large population-based lung function study (Breton et al., 2009). SNP rs11807 in the 3' region of *GSTM5* was found to be associated with hypertension (Delles et al., 2008). Our results thus may help further elucidate the mechanism(s) by which the SNPs are involved in the susceptibility to these specific phenotypes.

In conclusion, our study summarized the potentially interacting SNP-miRs that may affect the expression of major XMET gene, which may ultimately facilitate to elucidate the mechanism how these genes are regulated as well as how they are involved in the genetic variations in drug metabolism and disease pathogenesis. Further investigations are necessary to corroborate the hypotheses generated in this study.

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#### **APPENDIX**

Table A1 | Major XMETs and related genes investigated in this study.

Phase I	I Phase II Phase III Nuclear receptors and		Miscellaneous	
( <i>n</i> = 144)	( <i>n</i> = 85)	( <i>n</i> = 111)	transcription factors ( $n = 48$ )	genes ( <i>n</i> = 21)
AADAC	AANAT	ABC1	AHR	CRABP1
ABP1	ACSL1	ABCA1	AHRR	CRABP2
ADH1A	ACSL3	ABCA2	AIP	CYB5A
ADH1B	ACSL4	ABCA3	ARNT	GZMA
ADH1C	ACSM1	ABCA7	ARNT2	GZMB
ADH4	ACSM2B	ABCA8	CREBBP	MT1A
ADH5	ACSM3	ABCB1	EP300	MT1B
ADH6	AGXT	ABCB10	ESR1	MT1F
ADH7	AS3MT	ABCB11	ESR2	MT1H
ADHFE1	ASMT	ABCB4	FOXA2	MT1M
AKR1A1	BAAT	ABCB5	FOXO1	MT1X
AKR1B1	CCBL1	ABCB6	HIF1A	MT2A
AKR1B10	CES5A	ABCB7	HIF3A	MT3
AKR1C1	COMT	ABCB8	HNF4A	MT4
AKR1C2	DDOST	ABCB9	HSP90AA1	MTHFR
AKR1C3	GAMT	ABCC1	KEAP1	POR
AKR1C4	GGT1	ABCC10	NCOA1	RBP1
AKR1CL1	GLYAT	ABCC11	NCOA2	RBP2
AKR1D1	GNMT	ABCC12	NCOA3	TP53
AKR1E2	GSTA1	ABCC12	NCOR1	TXN
AKR7A2	GSTA2	ABCC2	NCOB2	TXN2
AKR7A3	GSTA3	ABCC3	NFF2L2	
AKR7I	GSTA4	ABCC4	NB0B2	
ALDH16A1	GSTA5	ABCC5	NB1H2	
ALDH18A1	GSTK1	ABCC6	NB1H3	
ALDH1A1	GSTM1	ABCC8	NR1H4	
ALDH1A2	GSTM2	ABCC9	NB112	
ALDH1A3	GSTM3	ABCD4	NB113	
ALDH1B1	GSTM4	ABCG2	NB3C1	
ALDH1L1	GSTM5	ABCG8	NB3C2	
ALDH2	GST01	ALD	NR5A2	
ALDH3A1	GSTO2	AOP1	PPARA	
ALDH3A2	GSTP1		PPARD	
	GSTT1		PPARG	
ALDH3B2	GSTT2	ATP6V0C	PPARGC1A	
	GSTT2B	ΔΤΡ7Δ	PPARGC1B	
	GST71	ATP7R	PPBC1	
	HNIMT	KCNK9	PTGES3	
	INIMT	MARCKSI 1	BABA	
	MGST1		BABB	
	MGST2	MBP	BARG	
	MGST2 MGST3	MVP	BXBA	
A0C3	MEGTO	ΟΔΒΡ	BXBB	
	ΝΔΔ2Ο		BXBG	
BCHE	ΝΔΤ1	SI C10A1	ТНВА	
CBR1	NAT2		THRB	
CBR3	NINIMT		TRIP11	
CBR4	PNMT			
CEL	PTGES		VUII	
ULL	TULS	SECTORT		

(Continued)

#### Table A1 | Continued

In-144)(n=85)(n=11)transcription factors (n=48)genes (n=21)CES1SAT1SLC18a2CES2SULT1A1SLC18a2CES3SULT1A2SLC19a2CES4SULT1A3SLC1042CES7SULT1A3SLC1043CVP11A1SULT1C2SLC1A2CVP11A1SULT1C2SLC1A6CVP11A1SULT1C3SLC1A6CVP11A1SULT1C3SLC1A6CVP1A1SULT21SLC2A1CVP1A1SULT21SLC2A1CVP1A1SULT21SLC2A1CVP1A1SULT21SLC2A1CVP1A1SULT21SLC2A1CVP1A1SULT21SLC2A1CVP1A2TPMTSLC2A24CVP2A41TSTSLC2A3CVP2A51UGT1A1SLC2A4CVP2A61UGT1A6SLC2A4CVP2A61UGT1A6SLC2A4CVP2A61UGT1A6SLC2A4CVP2A61UGT1A6SLC2A4CVP2A61UGT1A6SLC2A4CVP2A61UGT1A6SLC2A4CVP2A61UGT1A6SLC2A4CVP2A71UGT1A6SLC2A4CVP2A61UGT2A1SLC2A4CVP2A71UGT2A4SLC3A1CVP2A61UGT2A1SLC3A1CVP2A71UGT2A4SLC3A1CVP2A72UGT2B4SLC3A4CVP2A73UGT2A4SLC3A4CVP2A74UGT2A4SLC3A4CVP2A74UGT3A4SLC3A4CVP2A74UGT3A4SLC3A4CVP2A74	Phase I	Phase II	Phase III	Nuclear receptors and	Miscellaneous
CIS1         SATI         SLC18A2           CES2         SULTIA1         SLC19A1           CES3         SULTIA2         SLC19A2           CES4         SULTIA3         SLC19A2           CES7         SULTIA4         SLC19A2           CFFA         SULTIA5         SLC1A3           CVP1IA1         SULTIC3         SLC1A4           CVP1IA1         SULTIC3         SLC1A5           CVP1A1         SULTIC3         SLC1A6           CVP1A1         SULTA1         SLC2A1           CVP1A1         SULT2A1         SLC2A11           CVP1A1         SULT2A1         SLC2A12           CVP1A1         SULT61         SLC2A12           CVP1A1         SULT61         SLC2A12           CVP2A2         TPMT         SLC2A12           CVP2A1         TST         SLC2A12           CVP2A1         TST         SLC2A43           CVP2A1         UGT1A1         SLC2A4           CVP2A1         UGT1A3         SLC2A4           CVP2A21         UGT1A4         SLC2A4           CVP2A24         UGT1A5         SLC2A4           CVP2A5         UGT1A6         SLC2A4           CVP2A6	(n = 144)	(n = 85)	(n = 111)	transcription factors ( $n = 48$ )	genes $(n = 21)$
CLS1SAITSLC1842CES2SULTA1SLC19A1CES3SULTA2SLC19A2CES4SULTA3SLC19A3CES7SULTA3SLC1A1CYP11A1SULTC3SLC1A2CYP11B1SULTC2SLC1A3CYP11B2SULTC4SLC2A1CYP17A1SULTC4SLC2A1CYP1A1SULT21SLC2A1CYP1A1SULT21SLC2A1CYP1A2SULT61SLC2A16CYP2A1SULT61SLC2A2CYP2A1TSTSLC2A4CYP2A1TSTSLC2A4CYP2A1UGT1A1SLC2A4CYP2A1UGT1A1SLC2A4CYP2A1UGT1A3SLC2A6CYP2A2UGT1A3SLC2A6CYP2A3UGT1A4SLC2A8CYP2A4UGT1A5SLC2A6CYP2A5UGT1A6SLC2A8CYP2A6UGT1A6SLC2A8CYP2A7UGT1A6SLC2A8CYP2A7UGT1A6SLC2A8CYP2A7UGT1A6SLC2BA1CYP2A6UGT2A5SLC3BA1CYP2A7UGT2B1SLC3BA1CYP2A6UGT2B1SLC3BA2CYP2A7UGT2B1SLC3BA1CYP2A6UGT2B1SLC3BA1CYP2A7UGT2B1SLC3BA1CYP2A6UGT2B1SLC3BA1CYP2A7UGT2B1SLC3BA1CYP2A6UGT2B1SLC3BA2CYP2A7UGT2B1SLC3BA2CYP2A6UGT3A1SLC3BA2CYP2A7UGT3A1 <td< td=""><td>0501</td><td>CAT1</td><td>CI C10A0</td><td></td><td></td></td<>	0501	CAT1	CI C10A0		
CL23SUCHASUCHACES3SUCHASUCHACES4SULTASUCHACCF7SULTASUCHACYPHASULTASUCHACYPHASULTC3SUCHACYPHASULTC3SUCTACYPHASULTC3SUCTACYPHASULTC3SUCTACYPHASULTC4SUCTACYPHASULTC4SUCTACYPHASULTASUCZACYPHASULTASUCZACYPA2SULTASUCZACYPA2SULTASUCZACYPA4SULTASUCZACYPA4SULTASUCZACYPA4SULTASUCZACYP2A1SULTASUCZACYP2A2TMTSUCZACYP2A3UGTA1SUCZAACYP2A4UGTA4SUCZAACYP2A5UGTA5SUCZAACYP2A6UGTA4SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA7SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A7UGTA6SUCZAACYP2A6UGTA7SUCZAACYP2A7UGTA6SUCZAAC	CESI		SLC18AZ		
CESASUC1742SUC1943CESFSUC1743SUC1943CES7SUUT161SUC142CYP1181SUUT162SUC142CYP1182SUUT163SUC146CYP1741SUUT164SUC147CYP1941SUUT164SUC2416CYP142SUUT281SUC22412CYP143SUUT81SUC2416CYP144SUUT81SUC2416CYP145SUUT81SUC2416CYP146SUUT81SUC2416CYP247TPMTSUC246CYP2481UGT141SUC2436CYP2691UGT141SUC246CYP2691UGT143SUC246CYP2691UGT145SUC246CYP2691UGT145SUC246CYP2791UGT145SUC246CYP2791UGT145SUC246CYP2791UGT145SUC246CYP2791UGT145SUC246CYP2791UGT145SUC246CYP2791UGT145SUC246CYP2792UGT145SUC246CYP2793UGT145SUC246CYP2794UGT145SUC246CYP2795UGT2817SUC246CYP2794UGT2810SUC246CYP2795UGT2817SUC246CYP2794UGT2817SUC341CYP2795UGT2816SUC342CYP2796UGT2817SUC341CYP2797UGT342SUC341CYP2791SUC342CYP2791SUC342CYP2791SUC342CYP2794UGT341<	CESZ	SULITAT	SLC 19A1		
CEA4SUCI INASUCI INACFS7SULT INASUCI AICYPII EISULT INASUCI AICYPII EISULT IC2SUCI AICYPI IB2SULT IC3SUCI AICYPI IB1SULT IC4SUCI AICYPI AISULT IC1SUCI AICYPI AISULT IC1SUCI AICYPI AISULT AISUCI AICYPI AISULT BISUC2 AICYP2 AITFM SUC2 AICYP2 AIGTI AISUC2 AICYP2 AIUGT IAISUC2 AICYP2 AIUGT IAISUC3 AI<	CES3	SULITAZ	SLC 19A2		
CES7SUG TIANSUC TACYP1161SUT TE3SUC TA2CYP1162SUT TC3SLC TA3CYP1751SUT TC3SLC TA3CYP19741SUT TC3SLC 22 TA3CYP19741SUT TC4SLC 22 TA1CYP19741SUT TC4SLC 22 TA1CYP1742SUT TC4SLC 22 TA1CYP1743SUT TC4SLC 22 TA1CYP1744SUT TC4SLC 22 TA1CYP2745SUT TC4SLC 22 TA2CYP2741SUT TC4SLC 22 TA2CYP2741TFMTSLC 22 TA2CYP2741UGT TA4SLC 22 TA3CYP2751UGT TA4SLC 22 TA3CYP2761UGT TA5SLC 22 TA3CYP2763UGT TA4SLC 22 TA3CYP2764UGT TA4SLC 27 TA3CYP2765UGT TA4SLC 27 TA3CYP2764UGT TA4SLC 27 TA3CYP2765UGT TA4SLC 27 TA3CYP2767UGT TA4SLC 27 TA3CYP2768UGT TA4SLC 27 TA3CYP2769UGT TA4SLC 27 TA3CYP2760UGT TA4SLC 27 TA3CYP2761UGT TA4SLC 27 TA4CYP2761UGT TA4SLC 27 TA4CYP2761UGT TA4SLC 27 TA4CYP27	CES4	SULITA3	SLC 19A3		
CH11M1SULT162SULT162CYP11B1SULT162SULT64CYP17A1SULT164SULT67CYP17A1SULT161SUL747CYP1A1SUL7211SUL7214CYP1A1SUL7211SUL7211CYP20A1SUL741SUL7221CYP20A1SUL741SUL7241CYP22681UGT1A1SUL72A1CYP27281UGT1A0SUL72A1CYP27281UGT1A1SUL72A1CYP27211UGT1A1SUL72A1CYP27211UGT1A2SUL72A1CYP27211UGT1A4SUL72A1CYP27211UGT1A5SUL72A3CYP27211UGT1A6SUL72A3CYP27213UGT1A7SUL72A1CYP27214UGT1A6SUL72A3CYP27215UGT1A7SUL72A1CYP27216UGT1A9SUL72A3CYP27218UGT1A9SUL72A3CYP27219UGT1A9SUL72A3CYP27210UGT1A9SUL72A3CYP27210UGT2A3SUL72A3CYP27210UGT2A4SUL72A3CYP27210UGT2B15SUL72A3CYP27210UGT2B14SUL72A3CYP27210UGT2B2SUL73A1CYP27211UGT2B4SUL73A1CYP2721UGT3A2SUL73A1CYP2731UGT3A1SUL73A1CYP2743UGT3A1SUL73A1CYP2744UGT3A2SUL73A1CYP2741UGT3A2SUL73A1CYP2743UGT3A1SUL73A1CYP374SUL73A1SUL73A1 <td>CVD11A1</td> <td>SULLIA4</td> <td>SLCIAT</td> <td></td> <td></td>	CVD11A1	SULLIA4	SLCIAT		
CHP1161         SUC11C3         SUC1A3           CYP1152         SUC11C3         SUC1A3           CYP13A1         SULT1C4         SUC3A5           CYP13A1         SULT2A1         SUC2A11           CYP1A2         SULT2A1         SUC2A11           CYP1A1         SULT2A1         SUC2A11           CYP2A2         SULT6B1         SUC2A12           CYP2A4         TFMT         SUC2A16           CYP2A41         TST         SUC2A16           CYP2A51         UGT1A1         SUC2A6           CYP2A61         UGT1A1         SUC2A6           CYP2A61         UGT1A3         SUC2A6           CYP2A7         UGT1A4         SUC2A6           CYP2A61         UGT1A5         SUC2A6           CYP2A7         UGT1A6         SUC3A1           CYP2A7         UGT2A1         SUC3A1           CYP2		SULLIBI	SLUTAZ		
CHP11A1         SULT1C4         SULT1C4           CYP17A1         SULT21         SULT214           CYP1A1         SULT21         SUC22A1           CYP1A1         SULT21         SUC22A1           CYP1A2         SULT41         SUC22A1           CYP1A3         SULT41         SUC22A1           CYP2A4         TPMT         SUC22A2           CYP2A41         TST         SUC22A3           CYP26B1         UGT1A1         SUC22A4           CYP26B1         UGT1A1         SUC22A5           CYP26B1         UGT1A3         SUC2A4           CYP27C1         UGT1A4         SUC2A7           CYP27B1         UGT1A5         SUC2A8           CYP27C1         UGT1A6         SUC2A8           CYP27C1         UGT1A5         SUC2A8           CYP27C1         UGT1A5         SUC2A8           CYP27C1         UGT1A6         SUC2A8           CYP27C2         UGT1A8         SUC2A8           CYP27A7         UGT1A8         SUC2A8           CYP27A8         UGT2A1         SUC28A3           CYP27A9         UGT2A1         SUC28A3           CYP27A1         UGT2A1         SUC28A3		SULLICZ	SLCTA3		
CPP1PA1         SULT PA1         SULT PA1           CPP1PA1         SULT PA1         SULC2A1           CPP1A2         SULT PA1         SULC2A1           CPP1A2         SULT PA1         SULC2A1           CPP2A3         SULT PA1         SULC2A1           CPP2A41         SULT PA1         SULC2A16           CPP2A41         TST         SUC22A3           CPP2A41         UGT PA1         SUC22A4           CPP2A5B1         UGT PA1         SUC22A4           CPP2A61         UGT PA1         SUC22A4           CPP2B61         UGT PA1         SUC22A4           CPP2B61         UGT PA1         SUC22A6           CPP2B61         UGT PA1         SUC2A6           CPP2D61         UGT PA1         SUC2BA1           CPP2D61         UGT PA1         SUC2BA2           CPP2D61         UGT PA1         SUC3BA1           CPP2D61         UGT PA1         SUC3BA1           CPP2D61         UGT PA1 <t< td=""><td></td><td>SULTIC3</td><td>SLC1A5</td><td></td><td></td></t<>		SULTIC3	SLC1A5		
CHP IsAI         SULT PA1         SULT PA1         SULT PA1           CYP IA1         SULT PA1         SUC22A1           CYP IA2         SULT PA1         SUC22A12           CYP PA1         SULT PA1         SUC22A12           CYP PA1         SULT PA1         SUC22A12           CYP PA1         TFWT         SUC22A3           CYP P2A4         TFWT         SUC22A3           CYP P2B1         UGT 1A1         SUC22A6           CYP P2B1         UGT 1A3         SUC22A6           CYP P2B1         UGT 1A3         SUC22A6           CYP P2B1         UGT 1A5         SUC22A6           CYP P2B1         UGT 1A5         SUC22A9           CYP P2B1         UGT 1A5         SUC2A9           CYP P2A6         UGT 1A5         SUC2BA1           CYP P2A6         UGT 1A5         SUC2BA1           CYP P2A6         UGT 1A5         SUC2BA1           CYP P2A6         UGT 2A1         SUC2BA1           CYP P2A6         UGT 2B10         SUC2BA1           CYP P2A6         UGT 2B11         SUC2BA1           CYP P2A6         UGT 2B15         SUC2BA1           CYP P2A6         UGT 2B17         SUC2BA1           C		SULTIC4	SLUTA7		
CHP1A1         SULT2A1         SULT2A1           CYP1B1         SULT2B1         SLC22A12           CYP2DA1         SULT8B1         SLC22A16           CYP2DA1         TST         SLC22A3           CYP2DA2         TPMT         SLC22A3           CYP2DA3         UGT1A1         SLC22A4           CYP2B61         UGT1A1         SLC22A4           CYP2B61         UGT1A3         SLC22A6           CYP2B61         UGT1A4         SLC22A6           CYP2B61         UGT1A4         SLC22A6           CYP2B61         UGT1A6         SLC22A6           CYP2B7         UGT1A6         SLC22A9           CYP2A1         UGT1A6         SLC2A9           CYP2A6         UGT1A7         SLC2BA1           CYP2A7         UGT1A9         SLC2BA1           CYP2A6         UGT2B10         SLC2BA1           CYP2A7         UGT2B10         SLC2BA1           CYP2A6         UGT2B10         SLC2BA1           CYP2C19         UGT2B15         SLC2BA1           CYP2C3         UGT2B15         SLC2BA1           CYP2C4         UGT2B10         SLC2BA1           CYP2C5         UGT2B15         SLC2BA1		SULITER	SLCZTA5		
CYP1A2         SULT2A1         SLC2A1           CYP20A1         SULT6B1         SLC22A16           CYP20A1         TST         SLC22A2           CYP26A1         UGT1A1         SLC2A3           CYP26A1         UGT1A1         SLC2A4           CYP26A1         UGT1A1         SLC2A4           CYP26A1         UGT1A3         SLC2A6           CYP27A1         UGT1A4         SLC2A7           CYP27A1         UGT1A5         SLC2A8           CYP27A1         UGT1A5         SLC2A9           CYP27A1         UGT1A7         SLC2A1           CYP27A1         UGT1A7         SLC2A13           CYP27A1         UGT1A5         SLC2A9           CYP27A1         UGT1A7         SLC2A13           CYP27A1         UGT3A1         SLC2A1           CYP27A3         UGT2A1         SLC2A3           CYP27A4         UGT2A1         SLC2A1           CYP27A5         UGT2A1         SLC2A1           CYP27A6         UGT2A13         SLC2A1           CYP27A1         UGT2A1         SLC2A1           CYP27A1         UGT2A1         SLC2A1           CYP27A1         UGT2A1         SLC2A1		SULIZAT	SLCZZAT		
CYP1A1SULTA1SL22A12CYP2A1TPMTSLC22A16CYP2A41TSTSLC22A3CYP2A61UGT1A1SLC22A6CYP26B1UGT1A1SLC22A6CYP2CA1UGT1A3SLC22A6CYP2CA1UGT1A6SLC22A7CYP2A7UGT1A6SLC22A7CYP2A61UGT1A7SLC2A8CYP2A7UGT1A6SLC2A9CYP2A6UGT1A7SLC2A1CYP2A7UGT1A6SLC2A9CYP2A7UGT1A9SLC2BA1CYP2A7UGT2A1SLC2BA1CYP2A7UGT2B10SLC2BA2CYP2A6UGT2B10SLC2BA2CYP2C9UGT2B10SLC2BA1CYP2C9UGT2B10SLC2BA1CYP2C9UGT2B10SLC2BA2CYP2C9UGT2B10SLC2BA2CYP2D6UGT2B10SLC2BA1CYP2D7UGT2B10SLC2BA1CYP2D8UGT2B17SLC2BA1CYP2D9UGT2B17SLC3BA1CYP2D1UGT2B2SLC3BA1CYP2D2UGT2B1SLC3BA1CYP2D1UGT2B1SLC3BA1CYP2D1SLC3BA1CYP2D1SLC3A1CYP2D3UGT3A1SLC3BA1CYP2D4SLC3A1CYP3D41SLC3A1CYP3D41SLC3A1CYP3D41SLC3A1CYP3D41SLC3A4CYP3D41SLC3A4CYP3D42SLC3A4CYP3D43SLC3A4CYP3D44SLC3A4CYP3D45SLC3A4CYP3	CYPIA2	SULIZB1	SLC22A11		
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CYP2C9         UGT2B15         SLC29A4           CYP2D6         UGT2B17         SLC2A1           CYP2E1         UGT2B28         SLC31A1           CYP2F1         UGT2B4         SLC38A1           CYP2J2         UGT2B7         SLC38A2           CYP2S1         UGT3A1         SLC3A4           CYP2V1         SLC3A2         SLC47A1           CYP39A1         SLC47A2         SLC47A2           CYP3A5         SLC6A3         SLC6A4           CYP3A7         SLC6A4         SLC7A11           CYP46A1         SLC7A5         SLC7A5           CYP4A22         SLC7A6         SLC7A6	CYP2C8	UGT2B11	SLC29A3		
CYP2D6         UGT2B17         SLC2A1           CYP2E1         UGT2B28         SLC31A1           CYP2F1         UGT2B4         SLC38A1           CYP2J2         UGT2B7         SLC38A2           CYP2R1         UGT3A1         SLC38A5           CYP2S1         UGT3A2         SLC3A1           CYP2V1         UGT3A2         SLC3A1           CYP2V1         UGT3A2         SLC3A1           CYP2V1         SLC3A2         SLC47A1           CYP39A1         SLC47A2         SLC47A2           CYP3A43         SLC6A3         SLC6A3           CYP3A5         SLC6A4         SLC7A11           CYP46A1         SLC7A5         SLC7A5           CYP4411         SLC7A6         SLC7A6	CYP2C9	UGT2B15	SLC29A4		
CYP2E1         UGT2B28         SLC31A1           CYP2F1         UGT2B4         SLC38A1           CYP2J2         UGT2B7         SLC38A2           CYP2R1         UGT3A1         SLC38A5           CYP2S1         UGT3A2         SLC3A1           CYP2V1         SLC3A1         SLC3A2           CYP2V1         SLC3A2         SLC3A1           CYP2V1         SLC47A1         SLC47A1           CYP39A1         SLC5A4         SLC6A3           CYP3A43         SLC6A3         SLC6A4           CYP3A5         SLC6A4         SLC7A11           CYP46A1         SLC7A5         SLC7A5           CYP4A22         SLC7A6         SLC7A6	CYP2D6	UGT2B17	SLC2A1		
CYP2F1         UGT2B4         SLC38A1           CYP2J2         UGT2B7         SLC38A2           CYP2R1         UGT3A1         SLC38A5           CYP2S1         UGT3A2         SLC3A1           CYP2U1         SLC3A2         SLC47A1           CYP39A1         SLC47A2         SLC47A2           CYP3A43         SLC6A3         SLC6A3           CYP3A5         SLC6A4         SLC7A11           CYP46A1         SLC7A5         SLC7A5           CYP4A22         SLC7A6         SLC7A6	CYP2E1	UGT2B28	SLC31A1		
CYP2J2         UGT2B7         SLC38A2           CYP2R1         UGT3A1         SLC38A5           CYP2S1         UGT3A2         SLC3A1           CYP2U1         SLC3A2         SLC7A2           CYP39A1         SLC47A1         SLC47A2           CYP3A4         SLC5A4         SLC6A3           CYP3A5         SLC6A3         SLC6A4           CYP3A7         SLC6A4         SLC7A11           CYP46A1         SLC7A5         SLC7A5           CYP4A22         SLC7A6         SLC7A6	CYP2F1	UGT2B4	SLC38A1		
CYP2R1         UGT3A1         SLC38A5           CYP2S1         UGT3A2         SLC3A1           CYP2U1         SLC3A2         SLC47A1           CYP39A1         SLC47A1         SLC47A2           CYP3A4         SLC5A4         SLC5A4           CYP3A5         SLC6A3         SLC6A4           CYP3A7         SLC6A4         SLC7A11           CYP46A1         SLC7A5         SLC7A5           CYP4A22         SLC7A6         SLC7A6	CYP2J2	UGT2B7	SLC38A2		
CYP2S1         UGT3A2         SLC3A1           CYP2U1         SLC3A2           CYP2W1         SLC47A1           CYP39A1         SLC47A2           CYP3A4         SLC5A4           CYP3A5         SLC6A3           CYP3A7         SLC7A11           CYP4A11         SLC7A5           CYP4A22         SLC7A6	CYP2R1	UGT3A1	SLC38A5		
CYP2U1       SLC3A2         CYP2W1       SLC47A1         CYP39A1       SLC47A2         CYP3A4       SLC5A4         CYP3A5       SLC6A3         CYP3A7       SLC7A11         CYP4A11       SLC7A5         CYP4A22       SLC7A7	CYP2S1	UGT3A2	SLC3A1		
CYP2W1         SLC47A1           CYP39A1         SLC47A2           CYP3A4         SLC5A4           CYP3A5         SLC6A3           CYP3A7         SLC7A11           CYP4A11         SLC7A5           CYP4A22         SLC7A7	CYP2U1		SLC3A2		
CYP39A1         SLC47A2           CYP3A4         SLC5A4           CYP3A43         SLC6A3           CYP3A5         SLC6A4           CYP3A7         SLC7A11           CYP46A1         SLC7A5           CYP4A11         SLC7A6           CYP4A22         SLC7A7	CYP2W1		SLC47A1		
CYP3A4         SLC5A4           CYP3A43         SLC6A3           CYP3A5         SLC6A4           CYP3A7         SLC7A11           CYP46A1         SLC7A5           CYP4A11         SLC7A6           CYP4A22         SLC7A7	CYP39A1		SLC47A2		
CYP3A43       SLC6A3         CYP3A5       SLC6A4         CYP3A7       SLC7A11         CYP46A1       SLC7A5         CYP4A11       SLC7A6         CYP4A22       SLC7A7	CYP3A4		SLC5A4		
CYP3A5       SLC6A4         CYP3A7       SLC7A11         CYP46A1       SLC7A5         CYP4A11       SLC7A6         CYP4A22       SLC7A7	CYP3A43		SLC6A3		
CYP3A7         SLC7A11           CYP46A1         SLC7A5           CYP4A11         SLC7A6           CYP4A22         SLC7A7	CYP3A5		SLC6A4		
CYP46A1         SLC7A5           CYP4A11         SLC7A6           CYP4A22         SLC7A7	CYP3A7		SLC7A11		
CYP4A11         SLC7A6           CYP4A22         SLC7A7	CYP46A1		SLC7A5		
CYP4A22 SLC7A7	CYP4A11		SLC7A6		
	CYP4A22		SLC7A7		
CYP4B1 SLC7A8	CYP4B1		SLC7A8		
CYP4F11 SLCO1A2	CYP4F11		SLCO1A2		
CYP4F12 SLCO1B1	CYP4F12		SLCO1B1		
CYP4F2 SLCO1B3	CYP4F2		SLCO1B3		
CYP4F22 SLC01C1	CYP4F22		SLCO1C1		

#### Table A1 | Continued

Phase I	Phase II	Phase III	Nuclear receptors and	Miscellaneous
( <i>n</i> = 144)	( <i>n</i> = 85)	( <i>n</i> = 111)	transcription factors ( $n = 48$ )	genes ( <i>n</i> = 21)
CYP4E3		SI CO2A1		
CYP4F8		SLCO2B1		
CYP4V2		SI CO3A1		
CYP4X1		SI CO4A1		
CYP471		SI CO4C1		
CYP51A1		SLCO5A1		
CYP7A1		SLCO6A1		
CYP7B1		TAP1		
CYP8B1		TAP2		
DHRS2		VDAC2		
DHRS4		VDAC3		
DHRS9				
DPYD				
EPHX1				
EPHX2				
ESD				
FMO1				
FMO2				
FMO3				
FMO4				
FMO5				
HSD17B10				
KCNAB1				
KCNAB2				
KCNAB3				
KDM1A				
KDM1B				
MAOA				
MAOB				
NQO1				
NQO2				
PAOX				
PON1				
PON2				
PON3				
PTGIS				
PTGS1				
PTGS2				
SPR				
SUOX				
TBXAS1				
UCHL1				
UCHL3				
XDH				

#### Table A2 | Putative miRNAs associated with SNPs in the 3'-UTR region.

Gene	Classification	SNP	Tissue		Putative miRNAs	
				microSNiPer	PolymiRTs	Overlap
ALDH16A1	Phase I	rs1055637	Liver	hsa-miR-4265	hsa-miR-3151	hsa-miR-4669
				hsa-miR-3120-5n	hsa-miR-4447	
				hsa-miR-4322	hsa-miR-491-5n	
				hsa-miR-4669	hsa-miB-132-5n	
				hsa-miR-4726-3p	hsa-miR-4669	
CYP2E1	Phase I	rs2480256	Liver	hsa-miR-570	hsa-miR-570-3p	hsa-miR-570-3p
CYP2E1	Phase I	rs2480257	Liver	hsa-miR-4762-5p	hsa-miR-5582-3p	
					hsa-miR-570-3p	
CYP2U1	Phase I	rs8727	Liver	<b>hsa-miR-549</b> hsa-miR-125b-2*	hsa-miR-549	hsa-miR-549
CYP3A5	Phase I	rs15524	Liver	hsa-miR-562	hsa-miR-500a-5p	hsa-miR-500a-5p
				hsa-miR-501-5p	hsa-miR-5680	
				hsa-miR-500b		
				hsa-miR-500a		
				hsa-miR-4668-3p		
				hsa-miR-3973		
				hsa-miR-362-5p		
CYP3A7	Phase I	rs10211	Liver	N/A	hsa-miR-125a-5p	
					hsa-miR-125b-5p	
					hsa-miR-345-3p	
					hsa-miR-3920	
					hsa-miR-4319	
					hsa-miR-4732-3p	
					hsa-miR-670	
EPHX2	Phase I	rs1042032	Brain	hsa-miR-4476	hsa-miR-183-5p	hsa-miR-2392
				hsa-miR-4533	hsa-miR-2392	hsa-miR-183-5p
				hsa-miR-2392		
				hsa-miR-432*		
				hsa-miR-761		
				hsa-miR-183		
				hsa-miR-3665		
EDU IVO		1010001		hsa-miR-32390	D 4000	D 4000
EPHX2	Phase I	rs1042064	Brain	hsa-miR-31	hsa-miK-4696	hsa-miR-4696
				nsa-miR-576-3p		
				hsa miP 4606		
GSTM3	Phase II	re1109138	Brain	hsa-miR-4090	N/A	
G211VI3	1 11036 11	131100100	Drain	hsa-miR-2964a-3n		
				hsa-let-7i*		
GSTM3	Phase II	rs1537236	Brain	hsa-miB-4762-5n	hsa-miR-182-5n	hsa-miR-4470
Gormo	1 11030 11	131007200	Diam	hsa-miR-4470	hsa-miR-4470	
GSTM3	Phase II	rs1537235	Brain	hsa-miR-4790-3p	hsa-miR-409-5p	
GSTM3	Phase II	rs3814309	Brain	hsa-miR-4421	hsa-miB-3130-3p	
				hsa-miR-3182	hsa-miR-4793-3p	hsa-miR-4793-3p
				hsa-miR-1237		
				hsa-miR-486-5p		
				hsa-miR-4793-3p		
				hsa-miR-3120-5p		
				hsa-miR-4527		
				hsa-miR-29b		

(Continued)

#### Table A2 | Continued

Gene	Classification	SNP	Tissue		Putative miRNAs	
				microSNiPer	PolymiRTs	Overlap
GSTM5	Phase II	rs11807	Liver	hsa-miR-1202	N/A	
				hsa-miR-1227		
				hsa-miR-1973		
MGST3	Phase II	rs8133	Liver	hsa-miR-875-3p	hsa-miR-582-3p	hsa-miR-582-3p
				hsa-miR-582-3p	hsa-miR-875-3p	hsa-miR-875-3p
				hsa-miR-4698	hsa-miR-224-3p	hsa-miR-3688-3p
				hsa-miR-4694-3p	hsa-miR-3688-3p	hsa-miR-4694-3p
				hsa-miR-4495	hsa-miR-4694-3p	
				hsa-miR-411*	hsa-miR-522-3p	
				hsa-miR-3688-3p		
ATP7B	Phase III	rs928169	Liver	hsa-miR-4734	hsa-miR-4447	hsa-miR-4472
				hsa-miR-4430	hsa-miR-4472	hsa-miR-4481
				hsa-miR-4481	hsa-miR-4481	hsa-miR-4745-5p
				hsa-miR-4472	hsa-miR-4745-5p	hsa-miR-4785
				hsa-miR-3652	hsa-miR-4785	
				hsa-miR-3135b	hsa-miR-4787-5p	
				hsa-miR-4745-5p		
				hsa-miR-3944-3p		
				hsa-miR-1275		
				hsa-miR-491-5p		
				hsa-miR-4446-3p		
				hsa-miR-4498		
				hsa-miR-194*		
				hsa-miR-122		
				hsa-miR-4734		
				hsa-miR-4430		
				hsa-miR-3652		
				hsa-miR-4309		
				hsa-miR-4785		
				hsa-miR-3198		
				hsa-miR-1298		
SLC31A1	Phase III	rs10759637	Liver	hsa-miR-4448	hsa-miR-3672	
				hsa-miR-3119	hsa-miR-4524a-3p	
				hsa-miR-4461		
TAP2	Phase III	rs13501	Brain	hsa-miR-3198	hsa-miR-1289	hsa-miR-1289
				hsa-miR-1289	hsa-miR-3198	hsa-miR-3198
				hsa-miR-4309	hsa-miR-4294	hsa-miR-4309
				hsa-miR-3127-5p	hsa-miR-4309	
					hsa-miR-5702	
TAP2	Phase III	rs17034	Brain	hsa-miR-4772-3p	hsa-miR-1271-3p	
					hsa-miR-4763-5p	
					hsa-miR-550a-3-5p	
					hsa-miR-550a-5p	
					hsa-miR-4327	
					hsa-miR-636	
TAP2	Phase III	rs241451	Brain	hsa-miR-1260	hsa-miR-4684-5p	hsa-miR-4684-5p
				hsa-miR-4758-3p		
				hsa-miR-4684-5p		
TAP2	Phase III	rs241452	Brain	hsa-miR-1206	hsa-miR-1206	hsa-miR-1206
				hsa-miR-1		
				hsa-miR-4789-5p		
				·		

(Continued)

#### Table A2 | Continued

Gene	Classification	SNP	Tissue		Putative miRNAs	
				microSNiPer	PolymiRTs	Overlap
TAP2	Phase III	rs241453	Brain	hsa-miR-4298	hsa-miR-1302	hsa-miR-1302
				hsa-miR-1302	hsa-miR-4298	hsa-miR-4298
TAP2	Phase III	rs241454	Brain	hsa-miR-4476	hsa-miR-4476	hsa-miR-4476
				hsa-miR-4779	hsa-miR-4533	hsa-miR-4779
					hsa-miR-3173-3p	
					hsa-miR-4779	
TAP2	Phase III	rs241455	Brain	hsa-miR-130a*	hsa-miR-2116-3p	hsa-miR-130a-5p
				hsa-miR-323-3p	hsa-miR-130a-5p	
					hsa-miR-23a-3p	
					hsa-miR-23b-3p	
					hsa-miR-23c	
					hsa-miR-3680-5p	
					hsa-miR-4798-3p	
TAP2	Phase III	rs241456	Brain	hsa-miR-3940-5p	hsa-miR-2110	hsa-miR-4450
				hsa-miR-4507	hsa-miR-3150a-3p	
				hsa-miR-92a-1*	hsa-miR-4450	
				hsa-miR-4450	hsa-miR-450a-3p	
					hsa-miR-1270	
					hsa-miR-3676-5p	
					hsa-miR-4531	
					hsa-miR-4683	
					hsa-miR-620	
TAP2	Phase III	rs2857101	Brain	hsa-miR-944	hsa-miR-126-5p	hsa-miR-944
				hsa-miR-4795-3p	hsa-miR-4795-3p	hsa-miR-4795-3p
				hsa-miR-183*	hsa-miR-944	
UGT2A1	Phase II	rs4148312	Liver	hsa-miR-548t	hsa-miR-3662	hsa-miR-3662
				hsa-miR-548ah	hsa-miR-548c-3p	hsa-miR-3609
				hsa-miR-3662	hsa-miR-3609	hsa-miR-548ah-5p
				hsa-miR-3646	hsa-miR-548ah-5p	hsa-miR-548t-5p
				hsa-miR-3609	hsa-miR-548n	
				hsa-miR-340	hsa-miR-548t-5p	
				hsa-miR-1245		
				hsa-miR-106a		
ARNT	Nuclear receptors	rs11552229	Liver	hsa-miR-4716-5p	hsa-miR-4717-3p	

The miRs expressed in the tissue where the eQTL was identified are highlighted in bold.