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ORIGINAL ARTICLE Global genetic variation of select opiate metabolism genes in self-reported healthy individuals

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CYP2D6 is a key pharmacogene encoding an enzyme impacting poor, intermediate, extensive and ultrarapid phase I metabolism of many marketed drugs. The pharmacogenetics of opiate drug metabolism is particularly interesting due to the relatively high incidence of addiction and overdose. Recently, trans-acting opiate metabolism and analgesic response enzymes (*UGT2B7*, *ABCB1*, *OPRM1* and *COMT*) have been incorporated into pharmacogenetic studies to generate more comprehensive metabolic profiles of patients. With use of massively parallel sequencing, it is possible to identify additional polymorphisms that fine tune, or redefine, previous pharmacogenetic findings, which typically rely on targeted approaches. The 1000 Genomes Project data were analyzed to describe population genetic variation and statistics for these five genes in self-reported healthy individuals in five global super- and 26 sub-populations. Findings on the variation of these genes in various populations expand baseline understanding of pharmacogenetically relevant polymorphisms for future studies of affected cohorts.

The Pharmacogenomics Journal advance online publication, 11 April 2017; doi:10.1038/tpj.2017.13

HIGHLIGHTS

- An in silico genetic analysis of five opiate metabolism genes (CYP2D6, UGT2B7, ABCB1, OPRM1, and COMT) was performed to identify SNPs, INDELs, and/or copy number variants in general populations.
- Allele frequencies, observed and expected heterozygosities, test results for Hardy Weinberg Equilibrium, and pairwise linkage disequilibria for polymorphisms in the introns, exons, 3' and 5' untranslated regions, and promoter regions of five genes are reported for 2 504 unrelated healthy individuals from five superpopulations and 26 sub-populations.
- Multidimensional scaling plots show substantial inter-superpopulation separation while sub-populations show variable degrees of clustering within super-populations.
- CYP2D6 * alleles were used to determine activity scores for each sample, potentially identifying poor, intermediate, extensive, and ultrarapid metabolizer phenotypes in a cohort of selfreported healthy individuals.
- Principle component analyses of *CYP2D6* extensive metabolizers indicate intra-metabolizer phenotype variation.

INTRODUCTION

Cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) is a clinically significant enzyme responsible for ~ 30% of phase I metabolism of ~ 25% of marketed drugs.^{1,2} Of particular interest is the enzyme's role in the conversion of pain medications to active metabolites, namely morphine.^{3–5} The highly polymorphic nature of *CYP2D6* results in various metabolizer phenotypes (MP; poor (PM), intermediate (IM), extensive (EM) and ultra-rapid (UM)),^{6–8} typically inferred from the diplotype of *CYP2D6* star (*) alleles (a haplotype of one or more polymorphisms along the length of the gene),⁹ that have been associated with lack of therapeutic response, idiosyncratic responses, or even death.^{10–12}

Comprehensive pharmacogenetic studies have shown that single-nucleotide polymorphisms (SNPs) in other opiate metabolism and pain relief pathway genes also confer variable degrees of enzyme activity.^{13–17} These additional genes of interest include uridine diphosphate glucuronosyltransferase, family 1, polypeptide B7 (UGT2B7), adenosine triphosphate-binding cassette, subfamily B, number 1 (ABCB1), opioid receptor mu 1 (OPRM1) and catechol-O-methyltransferase (COMT). UGT2B7 encodes an enzyme that converts morphine to morphine-6glucuronide; these two compounds are the primary cause of the analgesic effect of opiates. ABCB1 encodes p-glycoprotein (or multidrug resistance protein 1), a membrane-associated transporter responsible for the efflux of morphine from various organs. OPRM1 encodes the primary receptor for signal transduction of the analgesic response. Finally, COMT encodes a protein that interacts with the opioid receptor mechanism to modulate pain response through catecholamine breakdown. Polymorphisms within these genes can impact opiate metabolism by altering the performance of their protein products, leading to non-effective treatment or clinical complications following opiate medication administration.14,15

Previous pharmacogenetic studies have focused on identifying common causal polymorphisms using genome-wide association studies (targeted SNP arrays and targeted massively parallel sequencing) to determine the MP of ante- and post-mortem patients.^{17–19} While valuable, these methods fail to assess polymorphisms comprehensively in a target sequence on the individual and population levels. In addition, they hinder discovery of novel polymorphisms that may provide greater insight into phenotypic variability and subsequent resequencing of target loci

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Received 21 September 2016; revised 16 February 2017; accepted 21 February 2017

may be required for confirmation of allele calls.²⁰ Massively parallel sequencing of the full gene region may reveal additional variants, with reliable depth of coverage, which refine the current working knowledge of *CYP2D6* * alleles, for example, those which introduce premature stop codons before the defining polymorphisms of a * allele.

Pharmacogenetic population studies often control for presence of disease phenotype while placing less emphasis on demography and population substructure as contributing factors to variable allele distribution which may confer different metabolic profiles in populations.^{10,21,22} Consequently, false positive associations may arise regarding the relationship between genotype and MP.²³

Herein, an in silico study of the complete gene sequences of CYP2D6, UGT2B7, ABCB1, OPRM1, COMT and their respective promoter regions was performed to identify novel SNPs, insertion/deletion (INDEL) polymorphisms and copy number variants (CNVs), define baseline population genetic variation, and identify potential phenotypic variability in opiate metabolism and pain relief. A summary is provided of population statistics, variant effect predictions, and clustering of super- and sub-populations based on SNPs, INDELs and CNVs in five genes whose protein products are associated with opiate metabolism. Finally, the distribution of CYP2D6 * alleles in five super-populations and 26 sub-populations is shown which provides additional information regarding variability within the population of EMs.²⁴ These findings serve as substantial population genetic data for healthy cohorts which may guide the pharmacogenetics community towards studies involving comprehensive genetic screening.

MATERIALS AND METHODS

Gene and promoter regions were identified using GeneCards Human Gene Database.²⁵ Genotype data were obtained from 2504 unrelated healthy individuals whose sequence data were downloaded from Phase 3 of the 1000 Genomes Project using the University of California Santa Cruz (UCSC) Table Browser^{26,27} and the appropriate hg19 reference genome coordinates for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, *COMT* and their respective promoter regions. The 1000 Genomes Project reports data with sequence depth of coverage $\geq 4 \times$.

Population genetic summary statistics and statistical tests were performed for five super-populations (African (AFR), Ad Mixed American (AMR), East Asian (EAS), European (EUR) and South Asian (SAS)) and 26 subpopulation (Supplementary Table 1). Allele frequencies, observed and expected heterozygosity calculations, and tests for departures from Hardy-Weinberg equilibrium (HWE) and pairwise linkage disequilibrium (LD, assuming HWE) were performed using Genetic Data Analysis Software.²⁸ Allele frequency 95% confidence intervals were estimated using the normal approximation to the binomial method. Tests for HWE departures and pairwise LD were performed for super- and sub-populations due to the potential for loci meeting HWE expectations or pairwise loci linkage equilibrium in sub-populations but deviating from these expectations when pooled into super-populations.²⁹ Due to the size of ABCB1 and OPRM1 and the number of polymorphisms within each gene, computation constraints with software memory were experienced while performing all tests for pairwise LD between these polymorphisms (~17 million and ~23 million pairwise comparisons for ABCB1 and OPRM1, respectively). Consequently, tests for pairwise LD for ABCB1 and OPRM1 polymorphisms were performed between HWE-deviating loci and all other loci. Both tests are sensitive to low frequency alleles and focusing on this subset of loci for pairwise LD testing, under the assumption of HWE, could indicate if the polymorphisms are subject to some selective pressures and/ or genotyping errors as a result of the relatively low coverage of 1000 Genomes Project data.³⁰ Here we use 'linkage disequilibrium block' to describe a cluster of polymorphisms with significant deviations from pairwise LD with all other polymorphisms for a gene. Ensembl Variant Predictor (Release 84, March 2016)³¹ and Sort Intolerant From Tolerant (SIFT)³²⁻³⁶ were used to determine SIFT, Polymorphism Phenotyping v2 (PolyPhen-2),^{37,38} and Protein Variant Effect Analyzer (PROVEAN)^{39–41} variant effect predictions and scores for all identified polymorphisms. Intronic positions within 1000 bases of an exon were further analyzed using Human Splicing Finder (HSF).⁴² Multidimensional scaling (MDS) plots and principal component analysis plots were generated in RStudio.43

CYP2D6 * alleles were assigned according to the presence of causal polymorphisms associated with known phenotype⁹ and were used to assign activity scores and MP to each individual.⁴⁴ Haplotypes producing no amino acid changes and lacking causal intronic polymorphisms were considered *1; haplotypes conferring the combination of R296C and S486T amino acid changes but lacking any other amino acid change and intronic causal polymorphisms were considered *2. Individuals possessing *CYP2D6* * alleles with undetermined effects on activity (*22, *28 and *43, for example), or haplotypes that could not be associated with a * allele, were removed from MP analyses.

RESULTS

CYP2D6

Allele frequencies for 418 polymorphic loci (402 SNPs, 15 INDELs and one CNV) in the *CYP2D6* region for five super-populations and 26 sub-populations are listed in Supplementary Table 2. The average observed heterozygosity for 26 sub-populations was 0.0341 ± 0.102 with a range of 0.0253 ± 0.0836 (CHS) to 0.0439 ± 0.114 (GWD; Table 1 and Supplementary Table 3). When pooled, the average super-population observed heterozygosity was 0.0384 ± 0.0980 for AFR, 0.0337 ± 0.102 for AMR, 0.0281 ± 0.0918 for EAS, 0.0359 ± 0.107 for EUR and 0.0339 ± 0.107 for SAS (Table 1 and Supplementary Table 3). After Bonferroni correction (*P* < 0.000120), one locus in GBR (rs35742686), one locus in EAS (rs374153932) and four loci in AFR (rs78854695, rs28371705, rs28371703 and rs376217512) significantly deviated from HWE, all of which are less than that due to chance alone (that is, ~21; Table 2 and Supplementary Table 4).

After Bonferroni correction, sub-populations exhibited an average of 470 ± 90 significant pairwise LDs with a range of 331 (ASW) to 721 (KHV) significant pairwise LDs and 3693 AFR, 799 AMR, 1048 EAS, 1031 EUR and 933 SAS significant pairwise LDs were observed ($P < 5.74 \times 10^{-7}$), all of which are less than that due to chance alone (~4358 pairwise comparisons; Table 2 and Supplementary Figure 1). LD heat-maps of five super-populations (Supplementary Figure 2) show a cluster of six to seven polymorphisms (rs29001678 (AMR, EUR, SAS only), rs1081000, rs28695233, rs75276289, rs76312385, rs74644586 and rs1080996), which appear to form an LD block. There were an average of 44 ± 14 significant pairwise LDs between these seven polymorphisms and others within the gene, with a range of 33 (AMR) to 71 (AFR) significant pairwise LDs. This group of polymorphisms is found within CYP2D6 intron 1 (hg19 positions 42526524-42526573) and do not alter CYP2D6 function; however, rs1080995, rs74644586 and rs76312385 are part of the CYP2D6*21A haplotype and may be observed in any CYP2D6 * allele with an intron 1 gene conversion with CYP2D7 (CYP2D6*11, *14B, *21B, *63, *73, *84, *88, *98, *102, *103, *104 and *105).⁵

MDS plots (Figure 1) were created using *CYP2D6* polymorphism pairwise genetic distances between super-populations and within super-populations (between sub-populations). There was substantial separation of the AFR and EAS populations from the cluster of AMR, EUR and SAS populations while sub-population clustering is quite diverse within each super-population.

Variant effect prediction for 418 *CYP2D6* polymorphisms was performed using SIFT, PolyPhen-2 and PROVEAN (Table 3 and Supplementary Table 5).^{32–41} Individual polymorphisms were assigned to one of five categories based on their SIFT, PolyPhen-2 and PROVEAN scores: tolerated with no discrepancies (predictions are concordant), discrepancies but most likely tolerated (predictions are discordant but favor tolerance), discrepancies but most likely damaging (predictions are discordant but favor intolerance), damaging with no discrepancies (predictions are concordant) and conflicting results (only two scores are reported and their predictions are discordant). Summaries of their frequencies and distribution across each gene are shown in Table 3 and Figure 2a, respectively. Due to the potential for multiple alternate alleles at the

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EUR 0.0400 ± 0.121 0.0359 ± 0.107 CEU 0.0410 ± 0.122 0.0357 FIN 0.04070 ± 0.123 0.037 FIN 0.0376 ± 0.116 0.035 SAS 0.0374 ± 0.118 0.0339 ± 0.107 GIH 0.0381 ± 0.121 0.038 SAS 0.0374 ± 0.118 0.0339 ± 0.107 GIH 0.0381 ± 0.121 0.038 ST2B7 AFR 0.0573 ± 0.117 0.0582 ± 0.121 RIN 0.0374 ± 0.119 0.030 ST2B7 AFR 0.0573 ± 0.117 0.0582 ± 0.121 RIN 0.0312 0.035 ST2B7 AFR 0.0573 ± 0.117 0.0582 ± 0.121 RIN 0.0530 ± 0.109 0.055 LWK 0.0610 ± 0.125 0.060 RIN 0.0639 ± 0.134 0.055 AFR 0.0675 ± 0.150 0.0613 ± 0.136 MXL 0.0639 ± 0.134 0.055 AGB 0.0603 ± 0.142 0.066 RIN 0.0723 ± 0.161 0.068 AFR 0.0611 ± 0.142 0.0614 ± 0.151 CLM 0.0723 ± 0.161 0.066	2 ± 0.09
57287 AFR 0.0374 ± 0.118 0.0339 ± 0.107 GIR 0.03040 ± 0.121 0.0337 57287 AFR 0.0374 ± 0.118 0.0339 ± 0.107 GIH 0.03040 ± 0.111 0.0338 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0334 ± 0.119 0.0337 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.0553 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.0553 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.0553 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.0552 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.0553 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.0552 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0604 ± 0.125 0.066	53 ± 0.1
5AS 0.0374±0.118 0.0339±0.107 GIR 0.0402±0.121 0.033 GBR 0.0402±0.121 0.033 0.0339±0.107 GIH 0.0381±0.121 0.036 SAS 0.0374±0.118 0.0339±0.107 GIH 0.0340±0.111 0.033 BEB 0.0371±0.1130 0.0311 0.0311 0.031 STU 0.0374±0.119 0.030 ITU 0.0381±0.121 0.037 MR 0.0573±0.117 0.0582±0.121 YRI 0.0610±0.125 0.066 GWD 0.0524±0.110 0.057 0.057 0.0613±0.136 MXL 0.0605±0.125 0.066 GWD 0.0524±0.110 0.050 MSL 0.0605±0.125 0.066 GWD 0.0625±0.125 0.068 ACB 0.0639±0.134 0.055 AFR 0.0675±0.150 0.0613±0.136 MXL 0.0625±0.150 0.044 PUR 0.0741±0.166 0.065 0.014 0.066 0.065 EAS 0.0611±0.142 0.0644±0.151 CHB <td>'3 <u>+</u> 0.1</td>	'3 <u>+</u> 0.1
5AS 0.0374±0.118 0.0339±0.107 GBR 0.0401±0.121 0.038 77287 AFR 0.0573±0.117 0.0582±0.121 YRI 0.0330±0.107 GIH 0.0331±0.1130 0.0311 57287 AFR 0.0573±0.117 0.0582±0.121 YRI 0.0330±0.109 0.0557 57287 AFR 0.0573±0.117 0.0582±0.121 YRI 0.0330±0.109 0.0557 6WD 0.0524±0.110 0.0301 0.0401±0.125 0.066 GWD 0.0524±0.110 0.050 0.041±0.006 0.0406 AMR 0.0675±0.150 0.0613±0.136 MXL 0.0621±0.140 0.069 CLM 0.0741±0.168 0.0741±0.166 0.055 0.0448±0.105 0.044 EAS 0.0611±0.142 0.0644±0.151 CHB 0.0646±0.150	57 <u>±</u> 0.1
SAS 0.0374 ± 0.118 0.0339 ± 0.107 GIH 0.0381 ± 0.121 0.038 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0374 ± 0.119 0.030 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.055 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.055 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.055 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0533 ± 0.109 0.055 57287 MFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0533 ± 0.109 0.055 57287 MFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.103 0.049 57287 MFR 0.0675 ± 0.150 0.0613 ± 0.136 MSL 0.0604 ± 0.125 0.066 AMR 0.0675 ± 0.150 0.0613 ± 0.136 MXL 0.0621 ± 0.140 0.069 EAS 0.0611 ± 0.142 <td>0 ± 0.09</td>	0 ± 0.09
SAS 0.0374±0.118 0.0339±0.107 GIH 0.0381±0.121 0.036 PJL 0.0340±0.111 0.0331 BEB 0.0371±0.1130 0.031 STU 0.0374±0.119 0.0301 STU 0.0374±0.119 0.030 57287 AFR 0.0573±0.117 0.0582±0.121 YRI 0.0553±0.109 0.055 GWD 0.0523±0.103 0.0495 0.0610 0.055 0.066 GWD 0.0524±0.101 0.050 0.0610 0.055 0.0610 0.055 AFR 0.0675±0.150 0.0613±0.136 MXL 0.0604±0.124 0.066 ASW 0.0605±0.150 0.0613±0.136 MXL 0.0621±0.140 0.069 AFR 0.0675±0.150 0.0613±0.136 MXL 0.0621±0.140 0.069 PUR 0.0723±0.161 0.068 0.0741±0.166 0.062 AFR 0.0611±0.142 0.0644±0.151 CHB 0.0636±0.145 0.065 EAS 0.0611±0.142 0.0644±0.151 CHB 0.0646±0.150	36 ± 0.1
57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0374 ± 0.119 0.031 57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.055 LWK 0.0610 ± 0.125 0.066 GWD 0.0524 ± 0.110 0.050 AFR 0.0675 ± 0.150 0.0613 ± 0.136 MXL 0.0604 ± 0.124 0.066 GWD 0.0524 ± 0.110 0.053 0.069 0.134 0.059 AMR 0.0675 ± 0.150 0.0613 ± 0.136 MXL 0.0621 ± 0.140 0.069 PUR 0.0723 ± 0.161 0.068 0.0639 0.134 0.055 EAS 0.0611 ± 0.142 0.0644 ± 0.151 CHB 0.0646 ± 0.150 0.084 JPT 0.0636 ± 0.145 0.065 0.141 0.065 0.141 0.065 EUR 0.0741 ± 0.168 0.0777 ± 0.177 CEU 0.0738 ± 0.169 0.083 FIN 0.0741 ± 0.168 0.0777 ± 0.177 CEU 0.0738 ± 0.169 0.083 GUR 0.0744 ±	52 ± 0.1
57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YRI 0.0530 ± 0.109 0.055 GWD 0.0524 ± 0.110 0.050 0.0660 ± 0.125 0.0660 GWD 0.0524 ± 0.110 0.050 0.0660 ± 0.125 0.0660 GWD 0.0524 ± 0.110 0.050 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.0660 0.	33 ± 0.1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	2 ± 0.09
57287 AFR 0.0573 ± 0.117 0.0582 ± 0.121 YR 0.0530 ± 0.109 0.055 LWK 0.0610 ± 0.125 0.066 GWD 0.0524 ± 0.110 0.050 GWD 0.0524 ± 0.110 0.050 0.066 GWD 0.0524 ± 0.110 0.050 AMR 0.0675 ± 0.150 0.0613 ± 0.136 MXL 0.0605 ± 0.125 0.068 AMR 0.0675 ± 0.150 0.0613 ± 0.136 MXL 0.0621 ± 0.140 0.069 PUR 0.0723 ± 0.161 0.068 PUR 0.0723 ± 0.161 0.068 EAS 0.0611 ± 0.142 0.0644 ± 0.151 CLM 0.0741 ± 0.166 0.065 PEL 0.0448 ± 0.105 0.049 0.049 0.061 0.061 EAS 0.0611 ± 0.142 0.0644 ± 0.151 CHB 0.0665 ± 0.141 0.065 CLN 0.0771 ± 0.177 CEU 0.0738 ± 0.169 0.083 FUR 0.0741 ± 0.168 0.0777 ± 0.177 CEU 0.0738 ± 0.169 0.083 FIN 0.0744 ± 0.168 0.0665	9 ± 0.09
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$'4 \pm 0.1$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	54 ± 0.1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	58 ± 0.1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	03 ± 0.1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	92 ± 0.1
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	53 ± 0.1
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$1^{-}_{\pm}0.1^{-}_{\pm}$
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	51 ± 0.1
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	4 ± 0.1
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	34 + 0.1
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\frac{1}{3} + 0.1$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	20 + 0.1
$EUR \qquad 0.0741 \pm 0.168 \qquad 0.0777 \pm 0.177 \qquad CEU \qquad 0.0745 \pm 0.167 \qquad 0.083 \pm 0.169 \qquad 0.083 \pm 0.167 \qquad 0.083 \pm 0.169 \qquad 0.083 \pm 0.160 \qquad 0.083 \pm 0.066 \pm 0.066 \qquad 0.083 \pm 0.066 = 0.068 \qquad 0.0726 \pm 0.167 \qquad 0.072 \pm 0.072 \pm 0.067 \qquad 0.072 \pm 0.068 = 0.068 \qquad 0.068 \pm 0.068 = 0.068 \pm 0.068 = 0.068 \pm 0.068 \pm 0.068 = 0.068 \pm 0.068 = 0.06$	7 + 0.2
$\begin{array}{c cccc} CHS & 0.0605 \pm 0.141 & 0.069\\ CDX & 0.0595 \pm 0.139 & 0.046\\ KHV & 0.0570 \pm 0.133 & 0.052\\ EUR & 0.0741 \pm 0.168 & 0.0777 \pm 0.177 & CEU & 0.0738 \pm 0.169 & 0.083\\ TSI & 0.0745 \pm 0.167 & 0.083\\ FIN & 0.0744 \pm 0.168 & 0.066\\ GBR & 0.0726 \pm 0.167 & 0.072\\ \end{array}$	$\frac{1}{6}$
EUR 0.0741 ± 0.168 0.0777 ± 0.177 CEU 0.0745 ± 0.169 0.083 TSI 0.0744 ± 0.168 0.0777 ± 0.177 CEU 0.0745 ± 0.167 0.083 FIN 0.0744 ± 0.168 0.072 0.074 0.066 0.072	98 + 0.1
EUR 0.0741 ± 0.168 0.0777 ± 0.177 CEU 0.0738 ± 0.169 0.083 TSI 0.0745 ± 0.167 0.083 FIN 0.0744 ± 0.168 0.072 GBR 0.0726 ± 0.167 0.072	58 + 0.1
EUR 0.0741 ± 0.168 0.0777 ± 0.177 CEU 0.0738 ± 0.169 0.083 TSI 0.0745 ± 0.167 0.083 FIN 0.0744 ± 0.168 0.066 GBR 0.0726 ± 0.167 0.072	9 + 0.1
TSI 0.0745 ± 0.167 0.083 FIN 0.0744 ± 0.168 0.066 GBR 0.0726 ± 0.167 0.072	36 ± 0.1
FIN 0.0744 ± 0.168 0.066 GBR 0.0726 ± 0.167 0.072	34 + 0.1
$GBR 0.0726 \pm 0.167 0.072$	5 ± 0.1
	$\frac{1}{2} = 0.1$
IBS 0.0746 ± 0.168 0.081	4+0.1
SAS 00720+0164 00740+0170 GH 00777+0167 0074	14 ± 0.1
	$10^{+} \pm 0.1$
BEB 0.0701 + 0.159 0.073	1 + 0.1
STU 00712-0.155 0.075	20 ± 0.1
TU 00713+0.165 0.071	3 ± 0.1
2CR1 AEP 0.0305 ± 0.0273 0.0304 ± 0.0273 VPI 0.038 ± 0.0394 0.0395	7 ± 0.09
	0 ± 0.00
GWD 0.028 ± 0.050 0.030	0 ± 0.00 6 ± 0.00
MSI 0.0205 0.0207 0.020	0 ± 0.05
ECN 0.0202 0.0203	5 ± 0.00
ASW 0.027 0.0847 0.007	0 ± 0.05
	7 ± 0.08
ALD 0.0294±0.087/ 0.029	/ ± 0.08
Aivin 0.0209±0.071 0.0209±0.0781 MAL 0.0202±0.0783 0.0194	$+\pm0.07$
	9 ± 0.08
	2 ± 0.07
PEL 0.0199±0.0780 0.0202	5 ± 0.08
EAS 0.0186±0.0758 0.0184±0.0751 CHB 0.017/±0.0733 0.017	1 ± 0.07
	0 ± 0.07
CHS 0.0192 ± 0.0779 0.019	1 ± 0.07
CDX 0.0177±0.0747 0.0182	
KHV 0.0188±0.0769 0.0178	2 ± 0.07

Table 1. Average super-population and sub-population observed (H_o) and expected (H_e) heterozygosities across 418 CYP2D6, 613 UGT2B7, 5986

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Global opiate metabolism genetic variation FR Wendt *et al*

Gene Super-population Average He Average Ho Sub-population Average He Average Ho EUR 0.0189±0.0759 0.0192±0.0780 CEU 0.0185±0.0757 0.0193±0.080 GBR 0.0195±0.0771 0.0184±0.073 0.0184±0.073 0.0184±0.073 GBR 0.0182±0.0762 0.0191±0.000 BS 0.0185±0.0771 0.0185±0.0724 SAS 0.0174±0.0688 0.0173±0.0678 GH 0.0175±0.070 0.0185±0.0724 BEB 0.0170±0.0677 0.0155±0.070 0.0155±0.072 0.0155±0.0724 0.0155±0.0724 OPRM1 AFR 0.0405±0.101 0.0407±0.102 YR 0.0405±0.0744 0.0413±0.104 GWD 0.0322±0.0103 0.0292±0.0102 YR 0.0405±0.0144 0.0413±0.104 GWD 0.0322±0.010 0.0441±0.017 0.0143±0.0068 0.034±0.008 0.039±0.103 0.039±0.103 0.039±0.103 0.039±0.103 0.039±0.103 0.039±0.103 0.039±0.103 0.039±0.104 0.044±0.015 0.039±0.013 0.039±0.013 0.039±0.016 0.034±0.083	Table 1. (C	ontinued)					
EUR 0.0189 ± 0.0759 0.0192 ± 0.0780 CEU 0.0185 ± 0.0757 0.0134 ± 0.083 FIN 0.0185 ± 0.0771 0.0186 ± 0.075 0.0193 ± 0.0770 0.0186 ± 0.075 GBR 0.0122 ± 0.0762 0.01191 ± 0.080 0.0185 ± 0.0772 0.0191 ± 0.080 SAS 0.0174 ± 0.0688 0.0173 ± 0.0678 GIH 0.0175 ± 0.0677 0.0169 ± 0.066 PIL 0.0185 ± 0.072 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 OPRM1 AFR 0.0405 ± 0.101 0.0407 ± 0.102 VR 0.0408 ± 0.14 0.0173 ± 0.0771 CVPRM1 AFR 0.0405 ± 0.101 0.0407 ± 0.102 VR 0.0408 ± 0.14 0.0139 ± 0.103 CVPRM1 AFR 0.0405 ± 0.101 0.0407 ± 0.102 VR 0.0408 ± 0.104 0.0413 ± 0.106 CWK 0.0412 ± 0.14 0.0410 ± 0.10 CMG 0.039 ± 0.108 0.0422 ± 0.107 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0302 ± 0.0982 0.0237 ± 0.104 CLM 0.0394 ± 0.0985 0.0225 ± 0.0835 CHB 0.0232	Gene	Super-population	Average He	Average Ho	Sub-population	Average He	Average Ho
COMT 0.0195 ± 0.0771 0.0186 ± 0.073 FIN 0.0182 ± 0.0762 0.0191 ± 0.086 GBR 0.0182 ± 0.0762 0.0191 ± 0.086 SAS 0.0174 ± 0.0688 0.0173 ± 0.0678 GIH 0.0175 ± 0.0706 0.0191 ± 0.086 PIL 0.0182 ± 0.0772 0.0175 ± 0.0706 0.0192 ± 0.087 0.0159 ± 0.087 PIL 0.0185 ± 0.072 0.0175 ± 0.0707 0.0175 ± 0.0707 0.0174 ± 0.071 OPRM1 AFR 0.0405 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0413 ± 0.104 GWD 0.0392 ± 0.101 0.0407 ± 0.029 YRI 0.0408 ± 0.096 0.0399 ± 0.103 MAR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0309 ± 0.108 0.0442 ± 0.17 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0307 ± 0.094 0.0302 ± 0.0835 0.0302 ± 0.0835 0.0302 ± 0.0835 0.0302 ± 0.0825 0.0302 ± 0.0835 0.0225 ± 0.0822 0.0225 ± 0.0825 0.0211 ± 0.022 0.0225 ± 0.0825 0.0225 ± 0.0825 0.0225 ± 0.0825 0.0225 ± 0.0825 0.0211 ± 0.0242 ± 0.0235 ± 0.0845 <t< td=""><td></td><td>EUR</td><td>0.0189 ± 0.0759</td><td>0.0192 ± 0.0780</td><td>CEU</td><td>0.0185 ± 0.0757</td><td>0.0193 ± 0.0807</td></t<>		EUR	0.0189 ± 0.0759	0.0192 ± 0.0780	CEU	0.0185 ± 0.0757	0.0193 ± 0.0807
FIN 0.0184 ± 0.073 0.0188 ± 0.073 GR 0.0182 ± 0.073 0.0182 ± 0.073 GR 0.0173 ± 0.0678 GIH 0.0175 ± 0.076 BS 0.0175 ± 0.0778 0.0175 ± 0.0776 0.0175 ± 0.0776 PIL 0.0185 ± 0.0724 0.0185 ± 0.0724 0.0185 ± 0.0724 PIL 0.0165 ± 0.058 0.0175 ± 0.077 0.0174 ± 0.071 OPRM1 AFR 0.0405 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0413 ± 0.106 UW 0.0413 ± 0.106 0.0425 ± 0.101 0.0399 ± 0.102 MSL 0.0399 ± 0.103 GWD 0.0322 ± 0.101 0.0399 ± 0.102 MSL 0.0399 ± 0.103 0.0439 ± 0.103 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0302 ± 0.081 0.0225 ± 0.0727 ± 0.0727 ± 0.0727 ± 0.0727 ± 0.0727 ± 0.0727 ± 0.0727 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071 ± 0.071					TSI	0.0195 ± 0.0771	0.0186 ± 0.0738
GBR 0.0113 ± 0.073 0.0113 ± 0.073 0.0113 ± 0.073 SAS 0.0174 ± 0.0688 0.0173 ± 0.0678 GIH 0.0175 ± 0.076 0.01615 ± 0.0724 0.01615 ± 0.072 BEB 0.0174 ± 0.0677 0.0175 ± 0.097 0.0175 ± 0.097 0.0174 ± 0.071 OPRM1 AFR 0.0405 ± 0.010 0.0407 ± 0.102 TU 0.0175 ± 0.090 GWD 0.0392 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0410 ± 0.10 GWD 0.0392 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0410 ± 0.10 GWD 0.0392 ± 0.101 0.0407 ± 0.102 YRI 0.0403 ± 0.108 0.0432 ± 0.093 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0302 ± 0.0932 0.0302 ± 0.0932 AMR 0.0229 ± 0.0822 0.0228 ± 0.0835 CHB 0.0232 ± 0.081 0.0232 ± 0.081 PUR 0.0314 ± 0.0953 0.0304 ± 0.0949 0.0219 ± 0.0923 NKL 0.0225 ± 0.084 FEL 0.0224 ± 0.0810 0.0214 ± 0.0852 0.0225 ± 0.084 0.0210 ± 0.0825 0.0224 ± 0.081					FIN	0.0184 ± 0.0753	0.0188 ± 0.0785
BS 0.0173 ± 0.0688 0.0173 ± 0.0678 GH 0.0175 ± 0.073 0.0201 ± 0.081 PIL 0.0185 ± 0.0724 0.0185 ± 0.0724 0.0185 ± 0.0724 0.0185 ± 0.0724 OPRM1 AFR 0.0405 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0413 ± 0.106 UWK 0.0412 ± 0.104 0.0413 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0413 ± 0.106 GWD 0.0312 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0413 ± 0.106 GWD 0.0312 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0413 ± 0.106 GWK 0.0413 ± 0.106 0.0442 ± 0.101 0.0399 ± 0.100 0.0444 ± 0.010 0.010 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0302 ± 0.081 0.0313 ± 0.081 0.0313 ± 0.081 0.0313 ± 0.081 0.0313 ± 0.081 0.0313 ± 0.081 0.0313 ± 0.081 0.0215 ± 0.081 0.0210 ± 0.082 0.0235 ± 0.081 0.0210 ± 0.082 0.0235 ± 0.081 0.0210 ± 0.082 0.0235 ± 0.081 0.0210 ± 0.082 0.0225 ± 0.082 0.0210 ± 0.082 0.0224 ±					GBR	0.0182 ± 0.0762	0.0191 ± 0.0801
SAS 0.0174 ± 0.0688 0.0173 ± 0.0678 GH 0.0175 ± 0.0706 0.0165 ± 0.0724 0.0165 ± 0.00724 0.0165 ± 0.00724 0.0165 ± 0.0075 ± 0.0075 0.0175 ± 0.0707 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0175 ± 0.0079 0.0135 ± 0.0079 0.0079 0.0079 ± 0.0079 0.0079 ± 0.0079 0.0079 ± 0.0079 0.0079 ± 0.0079 0.00279 ± 0.0079 0.0279 ± 0.0079 <th< td=""><td></td><td></td><td></td><td></td><td>IBS</td><td>0.0193 ± 0.0778</td><td>0.0201 ± 0.0817</td></th<>					IBS	0.0193 ± 0.0778	0.0201 ± 0.0817
PIL 0.0185±0.0724 0.0185±0.072 OPRM1 AFR 0.0405±0.101 0.0407±0.102 YR 0.0175±0.0067 GWD 0.0175±0.0077 0.0175±0.0077 0.0175±0.0077 0.0175±0.0077 GWD 0.032±0.101 0.0407±0.102 YR 0.0408±0.104 0.0413±0.106 GWD 0.032±0.101 0.0339±0.105 0.0339±0.108 0.0339±0.108 0.04045±0.107 AMR 0.0299±0.0949 0.0291±0.0923 MXL 0.0330±0.0968 0.0337±0.094 AMR 0.0299±0.0949 0.0228±0.0835 CHB 0.0332±0.004 0.0337±0.004 FEAS 0.0225±0.0822 0.0228±0.0835 CHB 0.0332±0.003 0.021±0.0953 EAS 0.0229±0.0962 0.030±0.0980 FEL 0.024±0.0852 0.0225±0.077 CHK 0.0232±0.083 CHB 0.0232±0.083 0.021±0.0953 0.0232±0.083 FEL 0.0229±0.0962 0.030±0.0980 FEL 0.024±0.0852 0.0225±0.0828 GWR 0.0299±0.0962 0.030±0.0980 GBR 0.0299±0.0967 </td <td></td> <td>SAS</td> <td>0.0174 ± 0.0688</td> <td>0.0173 ± 0.0678</td> <td>GIH</td> <td>0.0175 <u>+</u> 0.0706</td> <td>0.0169 ± 0.0666</td>		SAS	0.0174 ± 0.0688	0.0173 ± 0.0678	GIH	0.0175 <u>+</u> 0.0706	0.0169 ± 0.0666
CPRM1 AFR 0.0405 ± 0.101 0.0407 ± 0.027 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0677 0.0175 ± 0.0670 0.0174 ± 0.017 0.0175 ± 0.0670 0.0174 ± 0.017 0.0175 ± 0.0670 0.0174 ± 0.017 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0175 ± 0.0690 0.0332 ± 0.083 0.0332 ± 0.083 0.0332 ± 0.083 0.0332 ± 0.083 0.0232 ± 0.017 0.0309 ± 0.090 0.0039 ± 0.090 0.0031 ± 0.0953 0.0037 ± 0.094 0.0337 ± 0.094 0.0337 ± 0.094 0.0332 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083 0.0232 ± 0.083					PJL	0.0185 ± 0.0724	0.0185 ± 0.0723
SID 0.0165 ± 0.0638 0.0159 ± 0.0637 OPRMI AFR 0.0405 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0413 ± 0.104 UWK 0.0408 ± 0.104 0.0413 ± 0.106 UWK 0.0408 ± 0.104 0.0413 ± 0.106 GWD 0.0392 ± 0.101 0.0399 ± 0.103 0.0399 ± 0.103 0.0389 ± 0.0086 0.0384 ± 0.098 MR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0302 ± 0.0982 0.0327 ± 0.106 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0302 ± 0.0982 0.0303 ± 0.0934 EAS 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0224 ± 0.0852 0.0225 ± 0.0307 ± 0.094 ELR 0.0299 ± 0.0962 0.0302 ± 0.0980 CHS 0.0232 ± 0.0835 0.0224 ± 0.0835 FEN 0.0229 ± 0.0962 0.0302 ± 0.0980 CHS 0.0232 ± 0.0834 0.0231 ± 0.0923 EUR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0232 ± 0.0837 0.0232 ± 0.0835 GBR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0981 0.0329 ± 0					BEB	0.0170 ± 0.0677	0.0175 ± 0.0695
OPRM1 AFR 0.0405 ± 0.101 0.0407 ± 0.102 YRI 0.0408 ± 0.104 0.0412 ± 0.104 0.0413 ± 0.106 GWD 0.0392 ± 0.010 0.0412 ± 0.104 0.0410 ± 0.10 0.039 ± 0.105 0.0392 ± 0.010 0.0394 ± 0.008 MSL 0.0300 ± 0.0106 0.0412 ± 0.108 0.0430 ± 0.108 0.0425 ± 0.107 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0306 ± 0.0982 0.0327 ± 0.018 AMR 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0322 ± 0.0822 0.0327 ± 0.018 EAS 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0232 ± 0.0831 0.0235 ± 0.084 EUR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0981 0.0226 ± 0.0835 CDX 0.0228 ± 0.0831 0.0258 ± 0.0888 GBR 0.0299 ± 0.0991 0.0291 ± 0.0939 SAS 0.0259 ± 0.0881 0.0258 ± 0.0888 GH 0.0264 ± 0.0861 0.0264 ± 0.0891 GBR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0981 0.0309 ± 0.097 FIN 0.0265 ± 0.08					SIU	0.0165 ± 0.0658	0.0159 ± 0.0631
CPRMI AFR 0.0405 ± 0.101 0.0407 ± 0.102 TH 0.0408 ± 0.104 0.0413 ± 0.104 GWD 0.0392 ± 0.101 0.0399 ± 0.102 UWK 0.0412 ± 0.104 0.0410 ± 0.10 GWD 0.0392 ± 0.108 0.0399 ± 0.108 0.0399 ± 0.108 0.0425 ± 0.107 ASW 0.0309 ± 0.100 0.0414 ± 0.108 0.0425 ± 0.107 ACB 0.0396 ± 0.100 0.0414 ± 0.103 ACB 0.0396 ± 0.100 0.0414 ± 0.103 ACB 0.0302 ± 0.0982 0.0327 ± 0.108 PUR 0.0313 ± 0.0953 0.0307 ± 0.094 CLM 0.0304 ± 0.0954 0.0309 ± 0.096 CLM 0.0304 ± 0.0954 0.0321 ± 0.087 PUR 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0223 ± 0.083 CDX 0.0225 ± 0.0823 0.0226 ± 0.0835 0.0224 ± 0.0835 0.0224 ± 0.0835 CDX 0.0229 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0984 0.0329 ± 0.097 EUR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0981 0.0329 ± 0.097	000441		0.0405 . 0.101	0.0407 . 0.102	IIU	$0.01/5 \pm 0.0/0/$	$0.01/4 \pm 0.0/13$
COMT AFR 0.0499 ± 0.104 0.04100 ± 0.104 0.04100 ± 0.101 GWD 0.0392 ± 0.104 0.0399 ± 0.108 0.0394 ± 0.108 0.0425 ± 0.107 ASW 0.0309 ± 0.100 0.0414 ± 0.105 ASW 0.0302 ± 0.0982 0.0327 ± 0.106 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0302 ± 0.0982 0.0302 ± 0.0982 CLM 0.0314 ± 0.0953 0.0307 ± 0.094 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0232 ± 0.083 FEAS 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0232 ± 0.083 0.0235 ± 0.084 CHS 0.0223 ± 0.083 0.0231 ± 0.083 0.0231 ± 0.083 0.0228 ± 0.087 EUR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0984 0.0302 ± 0.098 GBR 0.0291 ± 0.0921 0.0302 ± 0.0980 CEU 0.0304 ± 0.0984 0.0309 ± 0.097 SAS 0.0259 ± 0.0861 0.0258 ± 0.0888 GH 0.0299 ± 0.0967 0.0315 ± 0.103 GWD 0.0499 ± 0.118 0.0499 ± 0.118 0.0479 ± 0.118 0.0467 ± 0.144 <t< td=""><td>OPRIMI</td><td>AFK</td><td>0.0405 ± 0.101</td><td>0.0407 ± 0.102</td><td>Y RI</td><td>0.0408 ± 0.104</td><td>0.0413 ± 0.106</td></t<>	OPRIMI	AFK	0.0405 ± 0.101	0.0407 ± 0.102	Y RI	0.0408 ± 0.104	0.0413 ± 0.106
COMT AFR 0.0299±0.0962 0.0291±0.0980 CEU 0.0394±0.001 0.0299±0.0961 0.0394±0.001 0.0441±0.102 AMR 0.0299±0.0949 0.0291±0.0923 MXL 0.0302±0.0982 0.0327±0.100 ACB 0.0396±0.100 0.0441±0.103 ACB 0.0396±0.100 0.0404±0.103 CLM 0.0304±0.0953 0.0307±0.094 PUR 0.0313±0.0953 0.0307±0.094 PUR 0.0313±0.0953 0.0307±0.094 PUR 0.0324±0.0852 0.0225±0.084 DT 0.0204±0.0852 0.0225±0.084 DT 0.0204±0.0852 0.0225±0.084 CHB 0.0232±0.083 0.0225±0.084 DT 0.0204±0.0984 0.0210±0.082 CHS 0.0223±0.0835 0.0224±0.0835 0.0224±0.087 CHS 0.0223±0.0835 0.0224±0.087 CHS 0.0223±0.0835 0.0224±0.087 CDX 0.0223±0.0835 0.0224±0.087 CDX 0.0223±0.0835 0.0224±0.087 FIN 0.0229±0.0960 0.029±0.0939 0.0293±0.097 FIN 0.0299±0.0961 0.0300±0.0981 CDX 0.0229±0.0960 0.0229±0.0957 CEU 0.0304±0.0984 0.0302±0.0988 CEU 0.0304±0.0984 0.0302±0.0980 CEU 0.0304±0.0980 0.0224±0.0880 CEU 0.0304±0.0980 0.0224±0.0880 CEU 0.0304±0.0980 0.0224±0.0880 CEU 0.0304±0.0980 0.0224±0.0880 CEU 0.0304±0.0981 0.0302±0.0980 CEU 0.0304±0.0981 0.0302±0.0280 CEU 0.0304±0.0981 0.0302±0.0280 CEU 0.0254±0.0880 0.0264±0.080 CEU 0.0254±0.0880 0.0264±0.0180 CEU 0.0254±0.0880 0.0264±0.0180 CEU 0.0254±0.0880 0.0264±0.0180 CEU 0.0254±0.0880 0.0264±0.0180 CEU 0.0499±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0.118 0.0479±0					LWK	0.0412 ± 0.104	0.04100 ± 0.102
COMT AFR 0.0453 ± 0.098 0.0435 ± 0.108 0.0442 ± 0.107 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0306 ± 0.108 0.0402 ± 0.108 AMR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0306 ± 0.0982 0.0327 ± 0.106 AMR 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0302 ± 0.0982 0.0225 ± 0.074 EAS 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0223 ± 0.0833 0.0225 ± 0.074 CHS 0.0235 ± 0.0844 0.0210 ± 0.0822 0.0835 0.0744 ± 0.0853 0.0225 ± 0.074 CHS 0.0223 ± 0.0810 0.0210 ± 0.0825 0.0228 ± 0.0835 0.0228 ± 0.0835 0.0228 ± 0.0810 0.0210 ± 0.0825 CDX 0.02299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0984 0.0329 ± 0.0957 0.0226 ± 0.0829 0.0226 ± 0.0829 0.0226 ± 0.0829 0.0226 ± 0.0829 0.0226 ± 0.0829 0.0226 ± 0.0829 0.0226 ± 0.0829 0.0226 ± 0.0929 0.0265 ± 0.0990 0.0221 ± 0.0957 0.0254 ± 0.0924 0.0309 ± 0.0996 0.0256 ± 0.0991 0.0265 ± 0.0991 0.0265 ± 0.0991					GVVD	0.0392 ± 0.101	0.0399 ± 0.105
COMT AFR 0.0299 ± 0.0949 0.0291 ± 0.0923 MXL 0.0309 ± 0.100 0.0441 ± 0.105 ACB 0.0396 ± 0.100 0.0441 ± 0.105 0.0307 ± 0.0982 0.0327 ± 0.108 PUR 0.0313 ± 0.0953 0.0307 ± 0.094 0.0307 ± 0.094 0.0307 ± 0.094 CLM 0.0344 ± 0.0852 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0232 ± 0.083 0.0235 ± 0.082 FEL 0.0244 ± 0.0852 0.0225 ± 0.0822 0.0228 ± 0.0835 CHS 0.0224 ± 0.083 0.0235 ± 0.0834 0.0235 ± 0.0834 0.0235 ± 0.0834 0.0241 ± 0.0852 0.0225 ± 0.0824 0.0241 ± 0.0852 0.0225 ± 0.0823 0.0241 ± 0.0852 0.0225 ± 0.077 0.0215 ± 0.0834 0.0235 ± 0.0834 0.0241 ± 0.0852 0.0225 ± 0.073 0.0210 ± 0.0823 0.0235 ± 0.0834 0.0241 ± 0.0852 0.0225 ± 0.073 0.0210 ± 0.0823 0.0235 ± 0.0834 0.0241 ± 0.0852 0.0225 ± 0.073 0.0241 ± 0.0852 0.0224 ± 0.087 0.0241 ± 0.0852 0.0241 ± 0.0852 0.0241 ± 0.0852 0.0241 ± 0.0852 0.0241 ± 0.0852 0.0241 ± 0.0852 0.0241 ± 0.0852 0.0241 ± 0.0852 0.0245 ± 0.0852 0.0241 ± 0.0852					IVISL	0.0380 ± 0.0968	0.0384 ± 0.0983
$COMT AFR \\ COMT COMT AFR \\ COMT COMT COMT COMT AFR \\ COMT COMT $						0.0430 ± 0.108	0.0425 ± 0.107
$COMT AFR \\ COMT COMT COMT \\ AFR \\ COMT COMT \\ COMT \\ AFR \\ COMT COMT \\ COMT \\ AFR \\ COMT \\ COMT \\ COMT \\ AFR \\ COMT \\ COMT \\ AFR \\ COMT \\ COMT \\ COMT \\ AFR \\ COMT \\ COMT \\ COMT \\ AFR \\ COMT \\ COMT \\ COMT \\ COMT \\ AFR \\ COMT \\$					ASVV	0.0390 ± 0.100	0.0414 ± 0.109
AMR 0.0239 ± 0.0349 0.0221 ± 0.0323 MML 0.0301 ± 0.0353 0.0307 ± 0.034 PUR 0.0313 ± 0.0953 0.0307 ± 0.094 0.0309 ± 0.0309 0.0309 CLM 0.0304 ± 0.0852 0.0325 ± 0.0822 0.0228 ± 0.0835 CHB 0.0232 ± 0.083 0.0225 ± 0.0822 EAS 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0235 ± 0.0834 0.0210 ± 0.0822 CDX 0.0223 ± 0.0835 0.0228 ± 0.0835 0.0228 ± 0.0835 0.0228 ± 0.0835 EUR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0984 0.0302 ± 0.0986 FIN 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0984 0.0302 ± 0.0986 SAS 0.0259 ± 0.0881 0.0258 ± 0.0888 GIH 0.0266 ± 0.0897 0.0265 ± 0.090 PJL 0.0256 ± 0.0880 0.0264 ± 0.0924 BEB 0.0256 ± 0.0880 0.0264 ± 0.0924 BEB 0.0259 ± 0.0881 0.0499 ± 0.118 YRI 0.0479 ± 0.118 0.0474 ± 0.117 0.0264 ± 0.0828 COMT AFR 0.0489 ± 0.118 0.049 ± 0.			0.0200 + 0.0040	0.0201 + 0.0022	ACD MVI	0.0390 ± 0.100	0.0404 ± 0.103
COMT AFR 0.0489 ± 0.118 0.049 ± 0.118 V0.025 ± 0.081 0.030 ± 0.039 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0.030 ± 0		AIVIN	0.0299 ± 0.0949	0.0291 ± 0.0923		0.0302 ± 0.0962 0.0313 ± 0.0953	0.0327 ± 0.108
COM C00244 ± 0.0852 0.0224 ± 0.0852 0.0224 ± 0.077 EAS 0.0225 ± 0.0822 0.0228 ± 0.0835 CHB 0.0235 ± 0.083 0.0235 ± 0.071 JPT 0.0206 ± 0.0810 0.0214 ± 0.0852 0.0228 ± 0.0835 0.0228 ± 0.0835 0.0228 ± 0.0835 CHS 0.0223 ± 0.0835 0.0228 ± 0.0835 0.0228 ± 0.0835 0.0228 ± 0.0829 EUR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0984 0.0302 ± 0.0980 SAS 0.0259 ± 0.0881 0.0258 ± 0.0888 GIH 0.0299 ± 0.0967 0.0315 ± 0.103 GBR 0.0297 ± 0.0960 0.0292 ± 0.0951 BS 0.0304 ± 0.0981 0.0309 ± 0.099 SAS 0.0259 ± 0.0881 0.0258 ± 0.0888 GIH 0.0266 ± 0.0897 0.0265 ± 0.090 BEB 0.0250 ± 0.0860 0.0264 ± 0.092 0.0267 ± 0.0914 ITU 0.0254 ± 0.0887 0.0248 ± 0.0887 COMT AFR 0.0489 ± 0.118 0.049 ± 0.118 YRI 0.0479 ± 0.114 GWD 0.0254 ± 0.0887 0.0264 ± 0.092 COMT AFR 0.0489 ± 0.120 <td></td> <td></td> <td></td> <td></td> <td></td> <td>0.0313 ± 0.0933</td> <td>0.0307 ± 0.0943</td>						0.0313 ± 0.0933	0.0307 ± 0.0943
$COMT AFR \\ COMT AFR \\ COMT AFR \\ COMT AFR \\ 0.0453 \pm 0.123 \\ COMT \\ AFR \\ 0.0453 \pm 0.123 \\ 0.0453 \pm 0.123 \\ 0.0453 \pm 0.123 \\ 0.0453 \pm 0.123 \\ 0.0442 \pm 0.123 \\ 0.0442 \pm 0.121 \\ 0.0444 \pm 0.121 \\ 0.0445 \pm 0.0445 \pm 0.123 \\ 0.0445 \pm 0.123 \\ 0.0445 \pm 0.123 \\ 0.0442 \pm 0.121 \\ 0.0445 \pm 0.125 \\ 0.0445 \pm 0.121 \\ 0.0445 \pm 0.120 \\ 0.0445 \pm 0.121 \\ 0.0445 \pm 0.120 \\ 0.0445 \pm 0.121 \\ 0.0445 \pm 0.120 $					DEI	0.0304 ± 0.0954	0.0309 ± 0.0903
COMT AFR 0.0429 ± 0.0962 0.0429 ± 0.0980 CEU 0.0235 ± 0.0834 0.0241 ± 0.0852 COMT AFR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0984 0.0302 ± 0.0980 COMT AFR 0.0259 ± 0.0881 0.0258 ± 0.0888 GIH 0.0269 ± 0.0997 0.0302 ± 0.0980 COMT AFR 0.0259 ± 0.0881 0.0258 ± 0.0888 GIH 0.0266 ± 0.0897 0.0292 ± 0.0992 COMT AFR 0.0489 ± 0.118 0.049 ± 0.118 YRI 0.0479 ± 0.0118 0.0467 ± 0.014 AMR 0.0453 ± 0.123 0.0442 ± 0.121 MXL 0.0442 ± 0.121 0.0462 ± 0.128 AMR 0.0453 ± 0.123 0.0442 ± 0.121 MXL 0.0462 ± 0.128 0.0445 ± 0.128		FΔS	0.0225 ± 0.0822	0.0228 ± 0.0835	CHR	0.0244 ± 0.0002	0.0225 ± 0.0778 0.0235 ± 0.0844
$COMT = AFR = 0.049 \pm 0.0962 = 0.0302 \pm 0.0980 = 0.0235 \pm 0.0834 = 0.0241 \pm 0.0853 = 0.0235 \pm 0.0834 = 0.0241 \pm 0.0853 = 0.0228 \pm 0.087 = 0.0226 \pm 0.0833 = 0.0228 \pm 0.087 = 0.0226 \pm 0.0833 = 0.0228 \pm 0.087 = 0.0226 \pm 0.0833 = 0.0228 \pm 0.087 = 0.0226 \pm 0.0839 = 0.0229 \pm 0.0980 = TSI = 0.0290 \pm 0.0967 = 0.0315 \pm 0.103 = 0.0309 \pm 0.0997 = 0.0304 \pm 0.0984 = 0.0309 \pm 0.0997 = 0.0304 \pm 0.0981 = 0.0399 \pm 0.0997 = 0.0304 \pm 0.0981 = 0.0258 \pm 0.0888 = GIH = 0.0256 \pm 0.0880 = 0.0265 \pm 0.0900 = PJL = 0.0256 \pm 0.0880 = 0.0265 \pm 0.0900 = PJL = 0.0256 \pm 0.0887 = 0.0265 \pm 0.0901 = 0.0256 \pm 0.0987 = 0.0265 \pm 0.0981 = 0.0258 \pm 0.0888 = 0.0256 \pm 0.0887 = 0.0265 \pm 0.0900 = PJL = 0.0256 \pm 0.0887 = 0.0267 \pm 0.0911 = TU = 0.0253 \pm 0.0887 = 0.0267 \pm 0.0911 = TU = 0.0253 \pm 0.0887 = 0.0248 \pm 0.0881 = TU = 0.0256 \pm 0.0887 = 0.0248 \pm 0.0881 = 0.049 \pm 0.118 = 0.0479 \pm 0.118 = 0.0473 \pm 0.112 = 0.0520 \pm 0.128 = 0.0520 \pm 0.0260 = 0.028 = 0.0481 \pm 0.017 = 0.0445 \pm 0.0120 = 0.0485 \pm 0.0120 = 0.0445 \pm 0.0120 = 0.044$		LAJ	0.0225 1 0.0022	0.0220 - 0.0055	IPT	0.0232 ± 0.003	0.0233 ± 0.0044 0.0210 ± 0.0824
$COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 CDX \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 CEU \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 YRI \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 YRI \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 YRI \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 YRI \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 YRI \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 YRI \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 YRI \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.018 YRI \\ COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT COMT AFR 0.0489 \pm 0.118 0.049 \pm 0.118 YRI \\ COMT 0.0484 \pm 0.117 YRI YRI \\ COMT 0.0484 \pm 0.117 YRI YRI \\ COMT 0.0484 \pm 0.117 YRI YR$					CHS	0.0235 ± 0.0834	0.0210 ± 0.0024
KHV 0.0226 ± 0.0829 0.0226 ± 0.0830 EUR 0.0299 ± 0.0962 0.0302 ± 0.0980 CEU 0.0304 ± 0.0984 0.0302 ± 0.098 TSI 0.0299 ± 0.0967 0.0315 ± 0.103 GBR 0.0297 ± 0.0960 0.0292 ± 0.095 IBS 0.0304 ± 0.0981 0.0309 ± 0.0994 SAS 0.0259 ± 0.0881 0.0258 ± 0.0888 GIH 0.0266 ± 0.0897 0.0265 ± 0.0900 PJL 0.0256 ± 0.0880 0.0264 ± 0.0927 BEB 0.0256 ± 0.0880 0.0264 ± 0.0927 SAS 0.0259 ± 0.0881 0.0258 ± 0.0888 GIH 0.0266 ± 0.0897 0.0267 ± 0.0910 PJL 0.0256 ± 0.0880 0.0264 ± 0.0827 0.0267 ± 0.0910 ITU 0.0254 ± 0.0887 0.0248 ± 0.0888 COMT AFR 0.0489 ± 0.118 0.049 ± 0.118 YRI 0.0493 ± 0.118 0.0479 ± 0.114 GWD 0.0493 ± 0.120 0.0488 ± 0.117 0.0473 ± 0.120 0.0488 ± 0.117 0.0473 ± 0.120 AMR 0.0453 ± 0.123 0.0442 ± 0.121 MXL 0.0442 ± 0.121 0.0462 ± 0.128 PUR </td <td></td> <td></td> <td></td> <td></td> <td>CDX</td> <td>0.0223 ± 0.0835</td> <td>0.0228 ± 0.0873</td>					CDX	0.0223 ± 0.0835	0.0228 ± 0.0873
$\begin{array}{c c c c c c c c c c c c c c c c c c c $					KHV	0.0226 ± 0.0829	0.0226 ± 0.0830
COMT AFR 0.0489 ± 0.118 0.049 ± 0.118 VRI 0.0493 ± 0.097 0.0293 ± 0.097 COMT AFR 0.0259 ± 0.0881 0.0258 ± 0.0888 GIH 0.0266 ± 0.0897 0.0265 ± 0.090 PJL 0.0266 ± 0.0897 0.0265 ± 0.090 PJL 0.0266 ± 0.0897 0.0265 ± 0.090 BEB 0.0259 ± 0.0881 0.0258 ± 0.0888 GIH 0.0266 ± 0.0897 0.0267 ± 0.090 BEB 0.0250 ± 0.0860 0.0245 ± 0.0857 0.0267 ± 0.090 BEB 0.0267 ± 0.091 COMT AFR 0.0489 ± 0.118 0.049 ± 0.118 YRI 0.0479 ± 0.118 0.0479 ± 0.114 GWD 0.0493 ± 0.121 0.0520 ± 0.128 MSL 0.0479 ± 0.112 0.0514 ± 0.131 ACB 0.0493 ± 0.120 0.0481 ± 0.117 0.0473 ± 0.120 0.0481 ± 0.117 ACB 0.0493 ± 0.120 0.0481 ± 0.112 0.0462 ± 0.128 ACB 0.0462 ± 0.128 ACB 0.0461 ± 0.121 0.0462 ± 0.128 0.0445 ± 0.120 0.0445 ± 0.120 0.0445 ± 0.120		EUR	0.0299 + 0.0962	0.0302 + 0.0980	CEU	0.0304 + 0.0984	0.0302 + 0.0987
$COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.118 0.049 \pm 0.018 0.0254 \pm 0.0887 0.0256 \pm 0.0987 \\ ITU \qquad 0.0256 \pm 0.0887 0.0256 \pm 0.0987 \\ ITU \qquad 0.0256 \pm 0.0887 0.0257 \pm 0.0916 \\ ITU \qquad 0.0256 \pm 0.0887 0.0267 \pm 0.0916 \\ ITU \qquad 0.0254 \pm 0.0887 0.0248 \pm 0.0887 \\ ITU \qquad 0.0254 \pm 0.0887 0.0248 \pm 0.0887 \\ ITU \qquad 0.0254 \pm 0.0887 0.0248 \pm 0.0887 \\ ITU \qquad 0.0254 \pm 0.0887 0.0248 \pm 0.0887 \\ ITU \qquad 0.0254 \pm 0.0887 0.0248 \pm 0.0887 \\ ITU \qquad 0.0254 \pm 0.0887 0.0248 \pm 0.0887 \\ ITU \qquad 0.0254 \pm 0.0887 0.0248 \pm 0.0887 \\ ITU \qquad 0.0254 \pm 0.0887 0.0248 \pm 0.0887 \\ ITU \qquad 0.0479 \pm 0.118 0.0479 \pm 0.118 \\ IWK \qquad 0.0493 \pm 0.118 0.0479 \pm 0.118 \\ IWK \qquad 0.0493 \pm 0.118 0.0479 \pm 0.114 \\ IWK \qquad 0.0493 \pm 0.112 0.0520 \pm 0.128 \\ MSL \qquad 0.0484 \pm 0.117 0.0514 \pm 0.131 \\ ASW \qquad 0.0503 \pm 0.120 0.0488 \pm 0.120 \\ ACB \qquad 0.0493 \pm 0.120 0.0481 \pm 0.117 \\ AKB \qquad 0.0453 \pm 0.123 0.0442 \pm 0.121 MXL 0.0442 \pm 0.121 0.0462 \pm 0.128 \\ PUR \qquad 0.0466 \pm 0.125 0.0453 \pm 0.125 \\ IWK = 0.0453 \pm 0.124 0.0442 \pm 0.121 0.0445 \pm 0.0124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.0124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.0124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.0124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.124 0.0445 \pm 0.124 0.0445 \pm 0.124 \\ IWK = 0.0445 \pm 0.0145 0.0445 \pm 0.0145 0.0445 \pm 0.0145 \\ IWK = 0.0445 \pm 0.0145 0.0445 \pm 0.0145 0.0445 \pm 0.0145 0.0445 \pm 0.0145 \\ IWK = 0.0445 \pm 0.0145 0.0445 0.0445 0.0455 0.0445 0.0145 0.0445 0.0145 0.045$			010233 - 010302	0.0002 - 0.0000	TSI	0.0290 + 0.0939	0.0293 ± 0.0977
$COMT AFR \qquad 0.0489 \pm 0.118 0.049 \pm 0.118 0.049 \pm 0.118 COMP \pm 0.0493 \pm 0.029 \pm 0.0483 \pm 0.0499 \pm 0.0118 COMP \pm 0.0118 COMP \pm 0.0499 \pm 0.0118 COMP \pm 0.0120 COMP \pm 0.0$					FIN	0.0299 ± 0.0967	0.0315 ± 0.103
$COMT \text{AFR} \qquad 0.0489 \pm 0.118 0.0258 \pm 0.0888 GIH \\ 0.0258 \pm 0.0888 GIH \\ 0.0256 \pm 0.0880 0.0266 \pm 0.0897 \\ 0.0266 \pm 0.0880 0.0264 \pm 0.0926 \\ 0.0256 \pm 0.0880 0.0264 \pm 0.0926 \\ 0.0256 \pm 0.0880 0.0264 \pm 0.0926 \\ 0.0263 \pm 0.0897 0.0267 \pm 0.0916 \\ ITU \\ 0.0254 \pm 0.0887 0.0267 \pm 0.0916 \\ ITU \\ 0.0254 \pm 0.0887 0.0248 \pm 0.0887 \\ ITU \\ 0.0479 \pm 0.118 0.0479 \pm 0.118 \\ 0.0479 \pm 0.118 0.0479 \pm 0.118 \\ UWK \\ 0.0493 \pm 0.121 0.0520 \pm 0.128 \\ MSL \\ 0.0484 \pm 0.117 0.0514 \pm 0.121 \\ O.0503 \pm 0.120 0.0498 \pm 0.120 \\ ACB \\ 0.0493 \pm 0.120 0.0498 \pm 0.120 \\ ACB \\ 0.0461 \pm 0.121 0.0462 \pm 0.128 \\ PUR \\ 0.0461 \pm 0.124 0.0473 \pm 0.124 \\ O.0461 \pm 0.124 \\ O.0473 \pm 0.124 \\ O.0474 \pm 0.124$					GBR	0.0297 + 0.0960	0.0292 + 0.0957
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$					IBS	0.0304 ± 0.0981	0.0309 ± 0.0994
$COMT AFR \\ 0.0489 \pm 0.118 \\ 0.049 \pm 0.118 \\ 0.0479 \pm 0.118 \\ 0.0479 \pm 0.118 \\ 0.0479 \pm 0.118 \\ 0.0479 \pm 0.118 \\ 0.0499 \pm 0.121 \\ 0.0520 \pm 0.128 \\ 0.0484 \pm 0.117 \\ 0.0514 \pm 0.131 \\ ASW \\ 0.0503 \pm 0.120 \\ 0.0498 \pm 0.120 \\ 0.0442 \pm 0.121 \\ 0.0461 \pm 0.121 \\ 0.0461 \pm 0.124 \\ 0.0472 \pm 0.123 \\ 0.0472 \pm 0.121 \\ 0.0461 \pm 0.124 \\ 0.0472 \pm 0.127 \\ 0.0472 \pm $		SAS	0.0259 ± 0.0881	0.0258 ± 0.0888	GIH	0.0266 ± 0.0897	0.0265 ± 0.0901
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$			_	_	PJL	0.0256 ± 0.0880	0.0264 ± 0.0924
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					BEB	0.0250 ± 0.0860	0.0245 ± 0.0851
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$					STU	0.0263 ± 0.0897	0.0267 ± 0.0916
$\begin{array}{ccccc} COMT & AFR & 0.0489 \pm 0.118 & 0.049 \pm 0.118 & YRI & 0.0479 \pm 0.118 & 0.0467 \pm 0.114 \\ LWK & 0.0493 \pm 0.118 & 0.0479 \pm 0.114 \\ GWD & 0.0498 \pm 0.121 & 0.0520 \pm 0.128 \\ MSL & 0.0484 \pm 0.117 & 0.0473 \pm 0.114 \\ ESN & 0.0474 \pm 0.117 & 0.0514 \pm 0.131 \\ ASW & 0.0503 \pm 0.120 & 0.0498 \pm 0.120 \\ ACB & 0.0493 \pm 0.120 & 0.0481 \pm 0.117 \\ AMR & 0.0453 \pm 0.123 & 0.0442 \pm 0.121 & MXL & 0.0442 \pm 0.121 & 0.0462 \pm 0.128 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0461 \pm 0.124 & 0.0472 \pm 0.127 \\ PUR & 0.0472 \pm 0.$					ITU	0.0254 ± 0.0887	0.0248 ± 0.0883
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	COMT	AFR	0.0489 ± 0.118	0.049 ± 0.118	YRI	0.0479 <u>+</u> 0.118	0.0467 ± 0.114
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					LWK	0.0493 ± 0.118	0.0479 ± 0.114
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					GWD	0.0498 ± 0.121	0.0520 ± 0.128
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					MSL	0.0484 ± 0.117	0.0473 ± 0.114
$\begin{array}{c c c c c c c c c c c c c c c c c c c $					ESN	0.0474 ± 0.117	0.0514 ± 0.131
$\begin{array}{cccccccccccccccccccccccccccccccccccc$					ASW	0.0503 ± 0.120	0.0498 ± 0.120
AMR 0.0453 ± 0.123 0.0442 ± 0.121 MXL 0.0442 ± 0.121 0.0462 ± 0.123 PUR 0.0466 ± 0.125 0.0445 ± 0.120 0.0472 ± 0.123 0.0472 ± 0.123					ACB	0.0493 ± 0.120	0.0481 ± 0.117
PUR 0.0466 ± 0.125 0.0445 ± 0.126		AMR	0.0453 ± 0.123	0.0442 ± 0.121	MXL	0.0442 ± 0.121	0.0462 ± 0.128
$(1M)$ $(10261 \pm 0.1)/(1.0017) \pm 0.1/(1.0017)$					PUR	0.0466 ± 0.125	0.0445 ± 0.120
					CLM	0.0461 ± 0.124	$0.04/2 \pm 0.12/$
$\begin{array}{c} \text{PEL} & 0.0372 \pm 0.111 & 0.0392 \pm 0.123 \\ \text{C} & 0.0372 \pm 0.123 & 0.0125 \\ \text{PEL} & 0.0372 \pm 0.0123 & 0.0125 \\ \text{PEL} & 0.0125 & 0.0125 \\ \text{PEL} & 0.0372 \pm 0.0123 & 0.0125 \\ \text{PEL} & 0.0372 \pm 0.0123 & 0.0125 \\ \text{PEL} & 0.0372 & 0.0125 \\ \text{PEL} & 0.0372 & 0.0125 \\ \text{PEL} & 0.0125 & 0.0125 & 0.0125 \\ P$		EAC.	0.0420 - 0.124	0.0425 . 0.122	PEL	$0.03/2 \pm 0.111$	0.0392 ± 0.123
EAS 0.0429 ± 0.124 0.0425 ± 0.122 CHB 0.0442 ± 0.125 0.0442 ± 0.125		EAS	0.0429 ± 0.124	0.0425 ± 0.122	CHB	0.0442 ± 0.125	0.0423 ± 0.120
$JPI = 0.0442 \pm 0.124 = 0.0400 \pm 0.131$					JPI	0.0442 ± 0.124	0.0466 ± 0.131
						0.0411 ± 0.123	0.0420 ± 0.120
						0.0423 ± 0.123	0.0392 ± 0.113
		ELID	0.0425 + 0.122	0.0442 + 0.125		0.0424 ± 0.124	0.0410 ± 0.123
Lon 0.0455 ± 0.122 0.0445 ± 0.125 CEO 0.0455 ± 0.125 0.0455 ± 0.135 0.0457 + 0.125 CEO		EUN	0.0435 ± 0.122	0.0445 ± 0.125	TSI	0.0435 ± 0.125 0.0441 \pm 0.125	0.0450 ± 0.150 0.0467 ± 0.132
					EIN	0.0441 ± 0.123	0.0407 ± 0.133
FIN 0.0414±0.112 0.0401±0.112 GRP 0.0437±0.124 0.0426±0.124					GRR	0.0414 ± 0.115 0.0437 \pm 0.115	0.0401 ± 0.112 0.0436 \pm 0.12
IRS 0.0421 - 0.0451 - 0.0451 - 0.0451 - 0.0451 - 0.0451 - 0.125					IRS	$0.0+37 \pm 0.124$ 0.0428 \pm 0.124	$0.0+30 \pm 0.124$ 0.0451 \pm 0.120
545 0.0456+0.123 0.0437+0.118 GIH 0.0463+0.125 0.0460+0.124		SAS	0 0456 + 0 122	0.0437 ± 0.118	GIH	$0.0+20 \pm 0.122$ 0.0463 \pm 0.125	$0.0+51 \pm 0.129$ 0.0460 \pm 0.124
		545	$0.0+50 \pm 0.125$	$0.0+37 \pm 0.110$	PII	$0.0+0.5 \pm 0.125$ 0.0455 \pm 0.124	$0.0+0.0 \pm 0.124$ 0.0446 ± 0.123
RFR 0.0448 ± 0.123 ± 0.0449 ± 0.121					RER	$0.0+35 \pm 0.124$ 0.0448 ± 0.123	0.0404 ± 0.123
STIL 0.047 + 0.124 0.047 + 0.12					STU	0.0459 ± 0.123	0.0417 ± 0.117
ITU 0.0444 + 0.121 0.0452 + 0.126					ITU	0.0444 + 0.121	0.0452 + 0.126

Abbreviations: AFR, African; AMR, Ad Mixed American; ACB, African Caribbean in Barbados; ASW, American of African Ancestry in Southwest USA; BEB, Bengali from Bangladesh; CDX, Chinese Dai in Xishuangbanna, China; CEU, Utah Residence with Northern and Western Ancestry; CHB, Han Chinese in Beijing; CHS, Southern Han Chinese; CLM, Colombians from Medellin, Colombia; EAS, East Asian; ESN, Esan in Nigeria; EUR, European; FIN, Finnish in Finland; GBR, British in England and Scotland; GIH, Gujarati Indian from Houston, Texas; GWD, Gambian in Western Divisions in Gambia; IBS, Iberian Population in Spain; ITU, Indian Telugu from the United Kingdom; JPT, Japanese in Tokyo, Japan; KHV, Kinh in Ho Chi Minh City, Vietnam; LWK, Luhya in Webuye, Kenya; MSL, Mende in Sierra Leone; MXL, Mexican Ancestry from Los Angeles, USA; PEL, Peruvians from Lima, Peru; PJL, Punjabi from Lahore, Pakistan; PUR, Puerto Ricans from Puerto Rico; SAS, South Asian; STU, Sri Lankan Tamil from the United Kingdom; TSI, Toscani in Italia; YRI, Yoruba in Ibadan, Nigeria.

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Table 2. Number of loci that deviated from HWE expectations and the number of pairwise loci comparisons that exhibited LD for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1* and *COMT* polymorphisms in five super-populations and 26 sub-populations. Bonferroni corrected HWE *P*-values were 0.000120, 8.16×10^{-5} , 8.35×10^{-6} , 7.32×10^{-6} and 4.96×10^{-5} for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1* and *COMT*, respectively; Bonferroni corrected pairwise LD *P*-values were 5.34×10^{-7} , 2.67×10^{-8} , 2.24×10^{-8} and 9.87×10^{-8} for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1* and *COMT*, respectively.

Gene	Super-population	Significant HWE deviations	Significant LDs	Sub-population	Significant HWE deviations	Significant LDs
CYP2D6	AFR	4	3693	YRI	0	516
				LWK	0	500
				GWD	0	449
				MSL	0	452
				ESN	0	422
				ASW	0	331
	AMR	0	700	ACD MYI	0	034 383
		0	199	PUR	Û	560
				CLM	ů	504
				PEL	õ	380
	EAS	1	1048	CHB	0	438
				JPT	0	385
				CHS	0	455
				CDX	0	425
	5110			KHV	0	721
	EUR	0	1031	CEU	0	595
					0	494
					0	575
				IRS	0	402
	SAS	0	933	GIH	Û	402
	5/15	5	255	PJL	ő	443
				BEB	0	472
				STU	0	512
				ITU	0	393
UGT2B7	AFR	4	7728	YRI	2	4403
				LWK	0	3643
				GWD	2	4271
				MSL	1	4053
				ESN	2	4/11
				ASW	0	20/1
	AMD	2	7202	ACD MVI	0	2017
	AMIN	5	7202	PLIR	0	3526
				CLM	0	3731
				PEL	1	3160
	EAS	2	5308	CHB	36	24 147
				JPT	1	3965
				CHS	2	4500
				CDX	1	4174
	5110		<005	KHV	1	4313
	EUR	3	6295	CEU	1	4153
					0	3/93
				GRR	0	37/3
				IBS	1	4159
	SAS	3	6574	GIH	0	3405
				PJL	2	3968
				BEB	1	3542
				STU	1	3962
				ITU	3	4959
ABCB1	AFR	9	72 978	YRI	0	11 405
				LWK	0	4972
				GWD	1	12 227
				IVISL	2	14 988
					0	20/1
				ACB	1	13 847
	AMR	2	31 011	MXL	0	7170
				PUR	1	9362
				CLM	1	11 249
				PEL	0	5597
	EAS	5	37 802	CHB	2	15 053
				JPT	0	5892
				CHS	2	15 271
				CDX	0	6908
	ELID	2	76 677		1	9580
	EUK	2	20 037		2	10 442
				FIN	0	2122 2122
				GBR	1	8771
				IBS	1	9135
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Gene	Super-population	Significant HWE deviations	Significant LDs	Sub-population	Significant HWE deviations	Significant LDs
	SAS	3	25 566	GIH	1	8190
				PJL	1	9611
				BEB	1	8979
				STU	1	10 653
				ITU	1	9323
OPRM1	AFR	12	172 560	YRI	2	36 581
				LWK	1	27 603
				GWD	4	47 005
					2	33 978
					0	24 990
				AGW	1	18 034
	AMR	5	92 744	MXI	2	30 805
		5	JZ / ++	PUR	1	31 564
				CLM	2	36 436
				PEL	0	60 103
	EAS	5	62 824	CHB	2	33 915
				JPT	4	38 296
				CHS	2	32 577
				CDX	2	23 930
				KHV	5	42 291
	EUR	6	76 181	CEU	3	36 491
				TSI	2	32 190
				FIN	1	33 169
				GBR	4	37 849
	CAC	F	77 000	IBS	1	22 631
	SAS	5	// 803	GIH	1	30 /07
					4	41 4/2
					2	25 012
				ITU	7	33 269
COMT	AFR	1	7362	YRI	0	1421
com	7.1.1.	·	7562	LWK	õ	1428
				GWD	0	1252
				MSL	0	1003
				ESN	2	2492
				ASW	0	772
				ACB	0	1132
	AMR	2	7004	MXL	0	1196
				PUR	0	2068
				CLM	2	1669
	FAC	2	(71)	PEL	0	4661
	EAS	2	6/12	CHB	0	2396
					0	1940
				CDY	0	1777
				KHV	1	3079
	FUR	з	7835	CFU	1	2229
	LON	5	, 555	TSI	ò	1685
				FIN	2	2123
				GBR	0	2162
				IBS	0	2391
	SAS	2	7502	GIH	0	2202
				PJL	0	1870
				BEB	0	3969
				STU	3	5326
				ITU	0	1874

Abbreviations: ACB, African Caribbean in Barbados; AFR, African; AMR, Ad Mixed American; ASW, American of African Ancestry in Southwest USA; BEB, Bengali from Bangladesh; CDX, Chinese Dai in Xishuangbanna, China; CEU, Utah Residence with Northern and Western Ancestry; CHB, Han Chinese in Beijing; CHS, Southern Han Chinese; CLM, Colombians from Medellin, Colombia; EAS, East Asian; ESN, Esan in Nigeria; EUR, European; FIN, Finnish in Finland; GBR, British in England and Scotland; GIH, Gujarati Indian from Houston, Texas; GWD, Gambian in Western Divisions in Gambia; HWE, Hardy-Weinberg Equilibrium; IBS, Iberian Population in Spain; ITU, Indian Telugu from the United Kingdom; JPT, Japanese in Tokyo, Japan; KHV, Kinh in Ho Chi Minh City, Vietnam; LD, linkage disequilibrium; LWK, Luhya in Webuye, Kenya; MSL, Mende in Sierra Leone; MXL, Mexican Ancestry from Los Angeles, USA; PEL, Peruvians from Lima, Peru; PJL, Punjabi from Lahore, Pakistan; PUR, Puerto Ricans from Puerto Rico; SAS, South Asian; STU, Sri Lankan Tamil from the United Kingdom; TSI, Toscani in Italia; YRI, Yoruba in Ibadan, Nigeria.

54 damaging, or most likely damaging, polymorphisms (locus rs1135830, for example, can produce a non-synonymous amino acid change or a premature stop codon), 47 single-amino acid changes, 4 premature stop codons, 2 frame-shift mutations, 1 CNV, 1 in-frame insertion and 1 in-frame deletion mutations would arise. Fifty percent (80/160) of the intronic and/or splice-associated polymorphisms were scored by HSF (Figure 2a and Supplementary

Table 5). Seven of these loci (rs5030656, rs192358451, rs377504871, rs78854695, rs267608282, rs28371702 and rs267608275) were predicted to alter, or most likely alter, splicing of the gene. The locus rs28371702 is considered part of the haplotype for 35 * alleles although it has not been reported as functionally relevant.⁹ The remaining six polymorphisms have not been reported as part of a recognized * allele. Interestingly, the four intronic polymorphisms



Figure 1. Multidimensional scaling plots of *CYP2D6* polymorphism pairwise genetic distances of five super-populations and 26 sub-populations based on 1000 Genome Project Phase 3 genotype data. African (AFR) populations are marked with a blue diamond, Ad Mixed American (AMR) populations are marked with a green plus sign, East Asian (EAS) populations are marked with a red 'X', European (EUR) populations are marked with a purple minus sign and South Asian (SAS) populations are marked with a solid black circle.

that are recognized by The Human Cytochrome p450 Allele Nomenclature Database⁹ for causing splice-defects (883G>C [rs201377835], 1846G>A [rs3892097], 2950G>C (no rs number; invariable according to 1000 Genomes Project) and 2988G>A [rs28371725]) were either not scored by HSF or not considered variable sites in the 1000 Genomes Project and so genotypes were not exported from the UCSC Table Browser.

The Human CYP Allele Nomenclature Database⁹ was used to assign * alleles to each sample. 210 unique haplotypes were observed in the 1000 Genomes Project Phase 3 data set, representing 37 * alleles (Supplementary Table 6). The average super-population observed and expected heterozygosities were 0.72 ± 0.080 and 0.78 ± 0.091 , respectively. Using * allele assignments, *CYP2D6* significantly deviated from HWE expectations after Bonferroni correction in the AFR, AMR, EAS and SAS

super-populations (P < 0.0348 for AFR and P = 0.0420, 0.0442 and 0.0348 in AMR, EAS and SAS, respectively) and seven subpopulations (P = 0.000200, 0.0277, 0.00290, 0.00510, 0.0202, 0.157 and 0.423 in ASW, LWK, MSL, YRI, CLM, British in England and Scotland and STU, respectively). After Bonferroni correction (P = 0.01 and P = 0.0019 for super- and sub-populations, respectively), the AFR super-population (P < 0.01) and ASW sub-population (P = 0.000200) significantly deviated from HWE expectations. Of the 210 observed haplotypes, only 14 (6.67%) are identical to those reported in the Human CYP Allele Nomenclature Table. Though not reported in the reference table, 84.8% of the remaining haplotypes could be associated with a * allele based on the presence of causal polymorphisms, however, 18 of them could not. These haplotypes represent 0.499% (25/5008) of the total 1000 Genomes Project haplotypes and contain

Table 3. Polymorphism effect categor algorithm so the total counts for each	ories for <i>CYP2D6, UGT2B</i> ; ch algorithm may not ec	7, ABCB1, qual the	<i>OPRM1</i> and <i>COMT</i> total of the other a	and pro Igorithm	moter regions. No is and may be dif	ote that r ferent th	iot all polymorp an the total nun	hisms we nber of p	re assigned a score olymorphisms for e	by each ach gene	variant effect (N).
Algorithm	Effect category	CYF	2D6 (N = 119)	NGT	2B7 (N=55)	ABCE	11 (N = 94)	Ю	(N = 75)	CO	<i>MT</i> (N = 45)
		Count	Average score	Count	Average score	Count	Average score	Count	Average score	Count	Average score
SIFT PolyPhen-2	Damaging Deleterious Tolerated Probably damaging Possibly damaging Benign	3 63 116 43 43	$\begin{array}{c} 0.00900 \pm 0.00870\\ 0.0157 \pm 0.0147\\ 0.634 \pm 0.3707\\ 0.978 \pm 0.0241\\ 0.743 \pm 0.147\\ 0.743 \pm 0.147\\ 0.116 \pm 0.129\\ \end{array}$	0 17 5 22 22	$\begin{array}{c} - \\ 0.0124 \pm 0.0182 \\ 0.666 \pm 0.397 \\ 0.663 \pm 0.322 \\ 0.963 \pm 0.0322 \\ 0.726 \pm 0.0986 \\ 0.0493 \pm 0.0933 \end{array}$	0 30 0 5 0 47 0	$\begin{array}{c} - \\ 0.0160 \pm 0.0167 \\ 0.286 \pm 0.239 \\ 9688 \pm 0.0377 \\ 0.692 \pm 0.117 \\ 0.505 \pm 0.0714 \end{array}$	10 0 6 6 16 5 21	$\begin{array}{c} 000400 \pm 0.00130\\ 0.00670 \pm 0.103\\ 0.324 \pm 0.384\\ 0.991 \pm 0.0209\\ 0.682 \pm 0.196\\ 0.0636 \pm 0.0917\\ \end{array}$	4 % % 0 4 [-	$\begin{array}{c} 0.0165 \pm 0.0158 \\ 0.00330 \pm 0.00580 \\ 0.616 \pm 0.364 \\ - \\ 0.718 \pm 0.194 \\ 0.0939 \pm 0.133 \\ 0.0939 \pm 0.133 \end{array}$
PKOVEAN Polymornhism <i>effect</i>	Deleterious Neutral	52 61 Count	- 4.89 ± 2.16 - 0.422 ± 0.978 Frequency (%)	37 37 Count	- 5.05 ± 2.41 - 0.204 ± 0.839 Frequency (%)	64 -	- 4.90 ± 2.23 - 0.708 ± 0.851 Frequency (%)	56 56 Count	- 4.54 ± 1.56 - 0.0130 ± 0.518 Frequency (%)	40 40	- 5.20 ± 1.94 - 0.186 ± 0.531 Franiency (%)
		COULL	irequercy (70)	COMIN	Lieducity (20)		requericy (20)	COMIN	inequericy (20)	COMIN	inequericy (20)
Damaging, no discrepancies Discrepancies, most likely damaging Discrepancies, most likely tolerated Tolerated, no discrepancies		36 118 53	30.3 15.1 8.40 1.65	35 5 3 35 5 3	21.8 5.45 9.09 63.6	12 50 50 50	12.8 13.8 20.2 53.2	0 36 36	0 22.7 17.3 48.0	4 8 «	8.89 2.22 2.22 80.0
					,						
Algorithm El	ffect category -	CVP2	:D6 (N = 80)	NGT2	<i>B7</i> (N = 104)	ABC	B1 (N = 564)	ō	PRM1 (N = 126)		DMT (N = 84)
		Count	Average score	Count	Average score	Count	Average score	Count	Average score	Count	Average score
HSF AI	lters	43	74.8 ± 6.15 74.8 ± 6.16 -0.165 ± 6.13 44.3 ± 10.4	62	74.2 ± 7.39 74.4 ± 8.56 1.50 ± 14.3 47.7 ± 7.14	293	72.6 ± 9.14 70.9 ± 9.08 3.92 ± 26.6 50.1 ± 15.5	64	70.7 ± 12.9 70.3 ± 11.6 6.16 ± 51.8 52.3 ± 15.5	49	70.6 ± 14.0 74.4 ± 9.51 11.7 ± 36.3 50.6 ± 12.1
ŪĀ	.reates ireaks	27	74.2 ± 6.88 71.7 ± 79.8 73.5 ± 7.38	22	73.3±6.69 55.6 ± 16.8 72.6±9.44	85	72.3 ± 7.80 73.0 ± 118 72.3 ± 9.28	40	70.8 ± 9.02 49.9 \pm 68.1 72.1 ± 10.1	23	75.7 ± 7.89 57.1 ± 42.3 74.9 ± 4.93
1	ctivates crvotic site	29	$43.8 \pm 13.2 \\ 26.8 \pm 15.7 \\ 35.2 + 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ 18.5 \\ $	24	53.4±13.1 24.4±27.1 46.7+0.445	151	51.8 ± 16.0 25.7 ± 30.7 51.6 ± 18.4	34	53.7 ± 16.8 23.2 ± 32.4 45.7 ± 6.29	16	48.6 ± 11.8 34.8 \pm 16.2 44.2 + 2.53
:		m	75.2 ± 7.88 182 ± 164	2	74.6±1.05 59.8±3.77	126	72.8 ± 8.14 79.58 ± 145.7	ω	69.4 ± 3.15 54.2 ± 22.2	Μ	71.0 ± 2.53 60.85 ± 3.46
Polymorphism effect		Count	Frequency (%)	Count	Frequency (%)	Count	Frequency (%)	Count	Frequency (%)	Count	Frequency (%)
Most likely effects splicing Potentially effects splicing Probably no effect on splicing		4 8 73	5.00 3.75 91.25	93 9 2	1.92 8.65 89.4	127 171 266	22.5 30.3 47.2	3 13 110	2.38 10.3 87.3	х 8 73	3.57 9.52 86.9
Abbreviations: HSF, Human Splicing Fii 'damaging' and 'deleterious' predictions in the predicted damage caused by a p	inder. SIFT, PolyPhen-2 ar s, and PolyPhen-2 'probabl polymorphism. ^{26–32} Avera	nd PROVI ly damag ge HSF s	EAN score cutoffs ar ing' and 'possibly dai cores are reference (e 0.05, 0 maging' p hg19) co	.5 and –2.5, respe oredictions, are qua nsensus score, mu	ectively, fo alitative cla tant consi	r distinguishing assifications indic ensus score and	between ating grea variation s	harmful and tolerate ter and lesser degree core. ⁴²	ed polym s of confi	orphisms. ²⁶⁻³⁵ SIFT dence, respectively,

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Figure 2. Qualitative summary of variant effect predictions. Each grey box represents a single gene: *CYP2D6* (**a**), *UGT2B7* (**b**), *ABCB1* (**c**), *OPRM1* (**d**) and *COMT* (**e**); the top vertical bars of each gene represent exonic polymorphisms scored by Sort Intolerant From Tolerant (SIFT), PolyPhen-2 and/or PROVEAN, the bottom bars represent intronic and splice-associated polymorphisms within 1000 bases of an exon that were scored by Human Splicing Finder (HSF), and black lines spanning both sections represent large unscored intronic regions that were removed; *CYP2D6* (**a**) and *UGT2B7* (**b**) are to scale while *ABCB1* (**c**), *OPRM1* (**d**) and *COMT* (**e**) have large intronic sequences (vertical black lines) removed; hg19 reference genome coordinates are provided.

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Table 4. CYP2D6 metabolizer status counts and frequencies in 5 super-populations (bold) and 26 sub-populations based on available 1000 Genomes Phase 3 causative SNP genotype data. The number of individuals in each population is indicated in parentheses; 'Undetermined' metabolizer phenotype individuals contain at least one *CYP2D6** allele with unknown effect on enzyme activity.

Population		Poor	Inte	rmediate	Ex	tensive	Ult	rarapid	Unde	etermined
	Count	Frequency								
AFR (661)	9	0.0136	35	0.0530	564	0.853	0	0	53	0.0802
ACB (96)	2	0.0208	6	0.0625	82	0.8542	0	0	6	0.0625
GWD (113)	1	0.00885	2	0.0177	103	0.912	0	0	7	0.0619
ESN (99)	1	0.0101	11	0.111	79	0.798	0	0	8	0.0808
MSL (85)	3	0.0353	2	0.0235	70	0.824	0	0	10	0.118
YRI (108)	0	0	5	0.0463	97	0.898	0	0	6	0.0556
LWK (99)	0	0	4	0.0404	84	0.848	0	0	11	0.111
ASW (61)	2	0.0328	5	0.0820	49	0.803	0	0	5	0.0820
AMR (347)	10	0.0288	10	0.0288	291	0.839	0	0	36	0.104
PUR (104)	6	0.0577	5	0.0481	81	0.779	0	0	12	0.115
CLM (94)	4	0.0426	4	0.0426	74	0.787	0	0	12	0.128
PEL (85)	0	0	0	0	78	0.918	0	0	7	0.0824
MXL (64)	0	0	1	0.0156	58	0.906	0	0	5	0.0781
EAS (504)	0	0	13	0.0258	488	0.968	0	0	3	0.00595
CHS (105)	0	0	3	0.0286	100	0.952	0	0	2	0.0190
CDX (93)	0	0	3	0.0323	89	0.957	0	0	1	0.0108
KHV (99)	0	0	5	0.0505	94	0.949	0	0	0	0
CHB (103)	0	0	2	0.0194	101	0.981	0	0	0	0
JPT (104)	0	0	0	0	104	1	0	0	0	0
EUR (503)	29	0.0577	32	0.0636	433	0.861	0	0	9	0.0179
CEU (99)	5	0.0505	9	0.0909	81	0.818	0	0	1	0.0101
GBR (91)	11	0.121	11	0.121	68	0.747	0	0	1	0.0110
IBS (107)	3	0.0280	2	0.0187	98	0.916	0	0	4	0.0374
TSI (107)	5	0.0467	7	0.0654	93	0.869	0	0	2	0.0187
FIN (99)	5	0.0505	3	0.0303	90	0.909	0	0	1	0.0101
SAS (489)	10	0.0204	24	0.0491	441	0.902	2	0.00409	12	0.0245
PJL (96)	1	0.0104	7	0.0729	87	0.906	0	0	1	0.0104
BEB (86)	2	0.0233	5	0.0581	76	0.884	0	0	3	0.0349
STU (102)	3	0.0294	4	0.0392	90	0.882	1	0.00980	4	0.0392
ITU (102)	3	0.0294	5	0.0490	90	0.882	1	0.00980	3	0.0294
GIH (103)	1	0.00971	3	0.0291	98	0.951	0	0	1	0.00971

Abbreviations: AFR, African; AMR, Ad Mixed American; ACB, African Caribbean in Barbados; ASW, American of African Ancestry in Southwest USA; BEB, Bengali from Bangladesh; CDX, Chinese Dai in Xishuangbanna, China; CEU, Utah Residence with Northern and Western Ancestry; CHB, Han Chinese in Beijing; CHS, Southern Han Chinese; CLM, Colombians from Medellin, Colombia; EAS, East Asian; EUR, European; ESN, Esan in Nigeria; FIN, Finnish in Finland; GBR, British in England and Scotland; GIH, Gujarati Indian from Houston, Texas; GWD, Gambian in Western Divisions in Gambia; IBS, Iberian Population in Spain; ITU, Indian Telugu from the United Kingdom; JPT, Japanese in Tokyo, Japan; KHV, Kinh in Ho Chi Minh City, Vietnam; LWK, Luhya in Webuye, Kenya; MSL, Mende in Sierra Leone; MXL, Mexican Ancestry from Los Angeles, USA; PEL, Peruvians from Lima, Peru; PJL, Punjabi from Lahore, Pakistan; PUR, Puerto Ricans from Puerto Rico; SAS, South Asian; STU, Sri Lankan Tamil from the United Kingdom; TSI, Toscani in Italia; YRI, Yoruba in Ibadan, Nigeria.

combinations of functionally relevant amino acid changes (Supplementary Table 6).

MP was assigned according to Gaedigk *et al.*⁴⁴ (Table 4). A χ^2 goodness-of-fit test indicated no significant differences between observed MP frequencies of 1000 Genomes Project superpopulation data and theoretical predictions (*P*=0.99), previously reported values for general United States major population groups (*P*=0.54),⁴⁵ and world populations (African, American, East Asian, European and South Central Asian; *P*=0.99).²⁴

EM individuals were used to create principal component analysis plots by population (Figure 3). By super-population, the EM individuals display six prominent clusters with minimal overlap between AFR and EAS super-populations and considerable spread of the AMR, EUR and SAS populations across the entire plot. PC1 and PC2 explain greater than 5% of the variance for 10 and 8 polymorphisms, respectively. The same clustering pattern is observed for sub-populations with little clustering observed within populations (data not shown).

UGT2B7, ABCB1, OPRM1 and COMT

Allele frequencies for 613 UGT2B7 polymorphisms (585 SNPs and 28 INDELs), 5986 ABCB1 polymorphisms (5775 SNPs, 210 INDELs

and one CNV), 6831 *OPRM1* polymorphisms (6561 SNPs, 267 INDELs, 2 ALU element insertions and 1 CNV) and 1007 *COMT* polymorphisms (973 SNPs, 33 INDELs and one CNV) in 5 super-populations and 26 sub-populations are listed in Supplementary Tables 7–10.

The average super-population and sub-population observed and expected heterozygosities are listed in Table 1. A full list of each polymorphism and respective population-specific observed and expected heterozygosities are shown in Supplementary Tables 11–14.

A summary of the total number of polymorphisms in each gene and population that deviated from HWE expectations is listed in Table 2. A comprehensive list of HWE p-values for each polymorphism in each population is provided in Supplementary Tables 15–18. After Bonferroni correction, *UGT2B7* loci rs541550034 and rs57075995 ($P < 8.16 \times 10^{-5}$), *ABCB1* loci rs546527793 and rs570 071012 ($P < 8.35 \times 10^{-6}$), and *OPRM1* loci rs147765820, rs376391508, rs77321666 and rs111829729 ($P < 7.32 \times 10^{-6}$) deviated from HWE expectations in all five super-populations. While no *COMT* loci deviated from HWE expectations in the five super-populations ($P = 4.97 \times 10^{-5}$), it should be noted that the loci rs138433986 and rs11912354 did deviate from HWE expectations



Figure 3. Principal component (PC) analysis of *CYP2D6* extensive metabolizers using genotypes of 418 polymorphisms from 1000 Genomes Project Phase 3. Samples are clustered according to super-population; rs numbers are provided for those loci best explained by PC1 and PC2; functional relevance of the polymorphism is indicated in reference to The Human Cytochrome p450 Allele Nomenclature Table⁹ and concordance with variant effect prediction generated by SIFT, PolyPhen-2, PROVEAN and HSF with green and red cells indicating tolerance and damage, respectively.

in the AMR, EAS, EUR and SAS populations (P = 0.0009 and 0.0009). One sub-population, CHB, exhibited more deviations from HWE expectations than that due to chance alone (that is, ~20).

A summary of the total number of pairwise loci comparisons that demonstrated significant LDs are listed in Table 2 and the distribution of LD *P*-values is shown in Supplementary Figures 3–6. After Bonferroni correction, sub-populations exhibited an average of 4683 ± 4004 , 9489 ± 3368 , 33303 ± 9716 and 2154 ± 1071 significant LDs for *UGT2B7*, *ABCB1*, *OPRM1* and *COMT*, respectively. Pairwise LD heat-maps of *UGT2B7*, *ABCB1*, *OPRM1* and *COMT* polymorphisms in five major super-populations (Supplementary Figures 7–10) show no substantial linkage blocks.

In contrast to *CYP2D6*, the individual MDS plots for *UGT2B7*, *ABCB1*, *OPRM1* and *COMT* show substantial separation for all super-populations (Figure 4). Within super-populations, sub-populations cluster relatively well with minimal overlap between super-populations. Considering the entire data set of ~ 15 000 polymorphisms, MDS plots of super-populations follow the pattern observed with single-gene plots. However, sub-populations do not show any clustering within their respective super-populations.

Variant effect prediction was performed on 613 UGT2B7, 5986 ABCB1, 6831 OPRM1 and 1007 COMT polymorphisms to generate SIFT, PolyPhen-2 and PROVEAN scores (Supplementary Tables 19-22).³²⁻⁴¹ A summary of the average score and frequency of each variant effect is displayed in Table 3. Of the damaging, or most likely, damaging, exonic polymorphisms in UGT2B7, ABCB1, OPRM1 and COMT, 100% (15/15, 25/25, 17/17 and 5/5 polymorphisms in UGT2B7, ABCB1, OPRM1 and COMT, respectively) are the result of single-amino acid changes. Intronic polymorphisms were analyzed further using HSF (Table 3). Those most likely to alter splicing of UGT2B7, OPRM1 and COMT account for < 5% of the total number of polymorphisms scored by HSF. The intronic polymorphisms of ABCB1 predicted to most likely, or potentially, alter splicing account for over 50% of the total (Table 3). These polymorphisms are distributed across introns 1 through 16, with very few splice-altering polymorphisms occurring after intron 16 (Figure 2c). In addition, one COMT polymorphism was recognized by the variant effect predictors as a frame-shift mutation (rs563298832) but was not assigned a score by the three algorithms used. Manual inspection of the locus in IGV shows the CATT deletion within intron 5 so assignment as a frame-shift mutation is incorrect. The HSF algorithm did not score this locus either. It is possible that this intronic polymorphism is damaging to the resulting protein, however, this assumption is not supported or refuted by the data presented.

Intergenic linkage disequilibria

A total of 1349 polymorphisms across all five target genes were assigned SIFT, PolyPhen-2, PROVEAN and/or HSF scores. Tests for pairwise LD were performed on this subset of loci to address potential linkage disequilibria between polymorphisms that may alter the activity of multiple proteins. After Bonferroni correction (5.50×10^{-8}) , 9573 AFR, 1328 AMR, 2517 EAS, 3134 EUR and 2583 SAS significant pairwise LDs were observed between polymorphic loci of different genes (P < 0.0004, Supplementary Table 23). The number of significant pairwise LDs is less than that due to chance alone (that is, ~45 461), however, those that contain two causal polymorphisms may be clinically significant. After removal of significant pairwise LDs containing loci which deviate from HWE expectations, there were 539, 12, 124, 282 and 128 significant pairwise LDs in the AFR, AMR, EAS, EUR and SAS populations, respectively, between polymorphic loci in different genes that are predicted to be damaging, or most likely damaging to the resulting protein (Figure 5). Two polymorphisms are part of 82.2, 98.4, 46.8 and 85.9% of these significant pairwise LDs within AFR, EAS, EUR and SAS, respectively (rs5885589 and rs677830). Rs5885589 is an ABCB1 intronic polymorphism which breaks an existing splice site and activates a cryptic splice site just upstream of exon 17. Rs677830 is found within exon 4 of OPRM1 and confers glutamine411stop in transcript variant 1B5. https://www.ncbi.nlm. nih.gov/nuccore/NM_001145286.2. The AMR population does not have a substantial percentage of pairwise LDs associated with a single polymorphism.

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Figure 4. Multidimensional scaling plots of *UGT2B7*, *ABCB1*, *OPRM1* and *COMT* polymorphism pairwise genetic distances of 5 super-populations and 26 sub-populations based on 1000 Genome Project Phase 3 genotype data. African (AFR) populations are marked with a blue diamond, Ad Mixed American (AMR) populations are marked with a green plus sign, East Asian (EAS) populations are marked with a red 'X', European (EUR) populations are marked with a purple minus sign and South Asian (SAS) populations are marked with a solid black circle.



Figure 5. Summary of significant pairwise linkage disequilibria between polymorphisms on different genes in five major super-populations: African (AFR), Ad Mixed American (AMR), East Asian (EAS), European (EUR) and South Asian (SAS).

DISCUSSION

Our study is limited by two factors. First, the coverage requirement for the 1000 Genomes Project is ~4×, producing an inherent level of missing variants or error in the sequence data. Second, due to limited size in each sub-population, some rare alleles may not be observed due to sample size. When data are generated in-house with greater sub-population samples sizes, greater coverage can be applied that will reduce the level of error and increase the chance of observing rare alleles. However, our analyses add to the population studies on pharmacogenetically interesting genes at global scale.^{46–48}

Potential contributors to the number of significant deviations from HWE expectations that were observed for *CYP2D6* and *UGT2B7* polymorphisms in the ACB and CHB populations, respectively, are allele drop-out, the effects of selection and/or population substructure. For both sub-populations, some degree of substructure has been reported.^{49–51} The Barbadian (ACB) population has demonstrated a higher degree of substructure relative to other ancestral African populations.^{49,50} The Han Chinese also show some degree of substructure attributed to northern and southern Han populations. It has been shown that the 1000 Genomes CHB population contains individuals from these Han sub-groups.⁵¹

The 1000 Genomes Project contains self-reported healthy individuals and as such, the prevalence of *CYP2D6* PM, IM and UM metabolizers may not reflect previously published data sets focusing on cohorts of affected individuals. The principal component analysis plots of EMs explain relatively little variation (5.0 and 3.2%, respectively, for principle components one and two). These data support previous work demonstrating some level of intra-metabolizer status variability as well as intra-sub-population variability, which is supported by MDS plot of each population.

The CYP2D6 MDS plots show separation of AFR and EAS from the cluster of AMR, EUR and SAS, supporting previously reported clinical differences between these populations.⁵² Lack of tight subpopulation (within super-population) clustering supports previous findings that CYP2D6 activity variation may be greater within than between super-populations.⁵³ For example, the sub-populations within the EAS super-population (CDX, CHB, Southern Han Chinese, KHV and JPT) do not cluster tightly. The MDS plot indicates that the Chinese and Vietnamese populations (CDX, CHB, Southern Han Chinese and KHV) may be different from the Japanese (JPT) population. While minimal, this Asian variability is not novel and may be clinically significant when treating patients of these ancestries.⁵⁴ MDS plots of UGT2B7, ABCB1, OPRM1 and COMT show considerably less between super-population clustering, specifically of the SAS, EUR and AMR populations, suggesting that differences in these genes may be somewhat associated to super-populations. MDS plots of ~15 000 polymorphisms do not show sub-population clustering with their respective superpopulations. This observation may be explained by the extreme allele frequency differences between sub-populations of the same super-population. For example, the OPRM1 SNP, rs66579098, has alternate allele frequencies of 0.27, 0.33, 0.52 and 0.78 in the PUR, CLM, MXL and PEL sub-populations, respectively (belonging to the AMR super-population).^{26,55}

Tests for pairwise LD of damaging, or likely damaging, polymorphisms in all five genes showed association between polymorphisms from all genes. The rs677830 (*OPRM1*) and rs5885589 (*ABCB1*) account for a substantial percentage of significant pairwise LDs in the AFR, EAS, EUR and SAS populations. These significant LDs may be clinically relevant due to the potential for multilocus interactions.⁴⁴ To our knowledge, rs677830 and rs5885589 have not been reported as causal polymorphisms. Interactions between these loci, or others, may be responsible for compensation when a damaging polymorphism dramatically alters normal protein activity, as suggested by Bartošová *et al.*⁵⁶ and Barratt *et al.*⁵⁷ with *ABCB1* and *OPRM1*

In conclusion, baseline population summary statistics are presented on five genes involved in opiate metabolism that have been implicated in phenotypic variability leading to idiosyncratic responses in patients. This study demonstrates some genetic association between *CYP2D6* and *UGT2B7*, *ABCB1*, *OPRM1* and *COMT* that will be important for future pharmacogenetic studies and combinatorial genetic approaches for patient care.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We would like to thank Emily Perry from the 1000 Genomes Helpdesk for assistance with extracting information from the Table Browser.

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Supplementary Information accompanies the paper on the The Pharmacogenomics Journal website (http://www.nature.com/tpj)