Supplemental Table 1. Population information

Populations	Population detail	Sample ID	Number of sample	Subtotal
EUR	CEU: Utah residents with northern and western European ancestry	NA06984 to NA12890	85	
	FIN: Finnish in Finland	HG00171 to HG00384	93	
	GBR: British in England and Scotland	HG00096 to HG01334	89	
	IBS: Iberian populations in Spain	HG01515 to HG01626	14	
	TSI: Toscani in Italy	NA20502 to NA20828	98	379
ASN	CHB: Han Chinese in Beijing	NA18525 to NA18757	97	
	CHS: Southern Han Chinese	HG00403 to HG00708	100	
	JPT: Japanese in Tokyo, Japan	NA18939 to NA19088	89	286
AFR	ASW: African Ancestry in southwest, USA	NA19625 to NA20414	61	
	LWK: Luhya in webuye, Kenya	NA19020 to NA19474	97	
	YRI: Yoruba in Ibadan, Nigeria	NA18486 to NA19257	88	246
AMR	CLM: Colombian in Medellin, Colombia	HG01112 to HG01551	60	
	MXL: Mexican Ancestry in Los Angeles, CA	NA19648 to NA19795	66	
	PUR: Puerto Rican in Puerto Rico	HG00553 to HG01204	55	181
		total	1092	

Supplemental Table 2. SNP information

SNP	Chr position*	rs#	allele name	nucleotide change#
SNP1	42412711	rs5758550	enhancer	A>G
SNP2	42523610	rs59421388	**29*	G>A
SNP3	42523805	rs28371725	**41*	G>A
SNP4	42523943	rs16947	**2*	C>T
SNP5	42524175	rs5030656	**9*	delete AGA
SNP6	42524244	rs35742686	**3*	delete A
SNP7	42524974	rs3892097	**4*	G>A
SNP8	42525086	rs5030655	**6*	delete T
SNP9	42525772	rs28371706	**17*	C>T
SNP10	42526694	rs1065852	**10*	C>T
SNP11	42528382	rs1080985	promoter	C>G

note: * Chromosome position in GRCh37 coordinate; # chromasome minus strain as reference

Supplemental Table 3. Demographics of human liver microsomes (HLMs).

Number of HLM	Mean age	Race	Gender
109	49±13 y	Caucasain	male=58; female=51
13	51±15 y	African American	male=8; female=5

Supplemental Table 4. Detail information of other functional SNPs in individuals carrying haplotypes containing rs5758550 and/or rs16947.
The table shows the number of other functional SNPs (alleles) located on the same or the opposite allele as H1, H2 or H3 in different populations.

Haplotypes	Other alleles (SNPs)	EUR		ASN		AFR		AMR	
		Allele count		Allele count		Allele count		Allele count	
		On same allele	On opposite allele	On same allele	On opposite allele	On same allele	On opposite allele	On same allele	On opposite allele
rs5758550, no rs16947 (H1)	*4 (rs3892097 & rs1065852)	5	1[a]			1	3	2	1
	*3 (rs35742686)	1							
	*10 (rs1065852)			4	1[a]				
	*6 (rs5030655)		1						
	*17 (rs28371706)						12		
rs5758550 + rs16947 (H2)	*4 (rs3892097 & rs1065852)		31				9		6
	*3 (rs35742686)		2						
	*6 (rs5030655)		3				2		1
	*10 (rs1065852)		6		22			2	1
	*9 (rs5030656)		1				2		1
	*17 (rs28371706)					92	41[a]	2	
rs16947, no rs5758550 (H3)	*4 (rs3892097 & rs1065852)		18		1		5		10
	*3 (rs35742686)		1				1		
	*6 (rs5030655)		2			4	2[a]		
	*10 (rs1065852)		1	3	20		2		
	*9 (rs5030656)		1			3	1[a]		1
	*17 (rs28371706)					13	27		

note: [a.] homozygous carrier

Suplemental Table 5. Genotyping panel and association between allelic variants and CYP2D6 enzyme activity

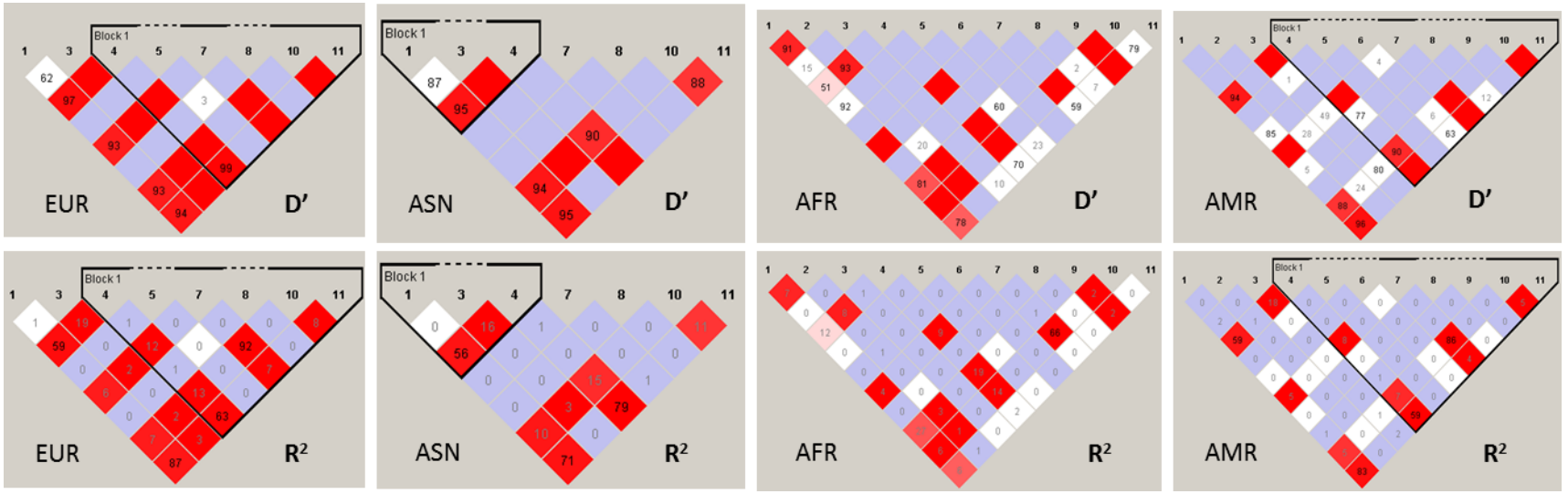
Functional status	Activity score	Alleles or SNPs
Normal activity	1	**1*
Reduced activity	0.5	**2, *9, *10, *17* and other rare alleles (**49, *50, *54, *55, *59, *69, *72*)
No activity	0	**3, *4, *5, *6* and other rare alleles (**7, *8, *11, *12, *13, *14, *15, *16, *18, *19, *20, *21, *31, *36, *38, *40, *42, *44, *47, *51, *56, *57, *62*)
Enhanced activity	>1	rs5758550, gene copy number variations

Supplemental Table 6. CYP2D6 Variants Detected in GeneSight Assay Platform

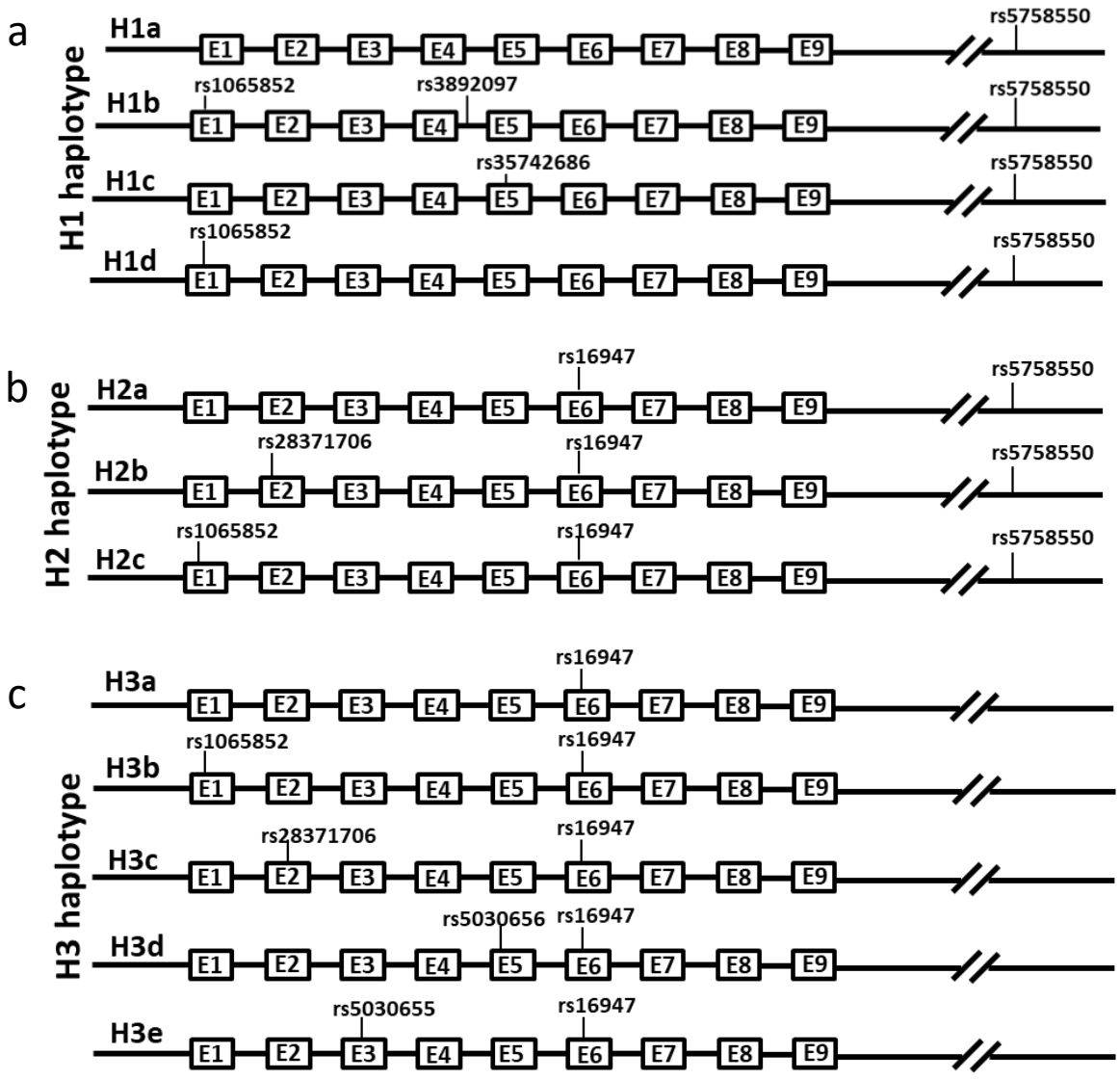
CYP2D6 *1, *2 (NM_000106.5:c.886C>T; c.1457G>C), *2A (NM_000106.5:c.-1584C>G; c.886C>T; c.1457G>C), *3 (NM_000106.5:c.775delA), *4 (NM_000106.5:c.506-1G>A; c.100C>T; c.1457G>C), *5 (CYP2D6 Deletion), *6 (NM_000106.5:c.454delT), *7 (NM_000106.5:c.971A>C), *8 (NM_000106.5:c.505G>T; c.886C>T; c.1457G>C), *9 (NM_000106.5:c.841_843delAAG), *10 (NM_000106.5:c.100C>T; c.1457G>C), *11, *12 (NM_000106.5:c.124G>A; c.886C>T; c.1457G>C), *14 (NM_000106.5:c.505G>A; c.886C>T; c.1457G>C), *15, *17 (NM_000106.5:c.320C>T; c.886C>T; c.1457G>C), *41 (NM_000106.5:c.985+39G>A; c.886C>T; c.1457G>C), gene duplication;

Supplemental Table 7. CYP2D6 alleles in HLMs

Allele	Allele count	Minor allele frequency
CYP2D6*1	85	0.348
CYP2D6 *2	3	0.012
CYP2D6 *2A	64	0.262
CYP2D6 *3	5	0.020
CYP2D6 *4	38	0.156
CYP2D6 *5	8	0.033
CYP2D6 *6	1	0.004
CYP2D6 *9	8	0.033
CYP2D6 *10	3	0.012
CYP2D6 *17	4	0.016
CYP2D6 *41	25	0.102
total	244	



Supplemental figure 1. Linkage disequilibrium (LD) values for 11 SNPs in different populations. The identity and location of SNPs 1-11 are provided in Table 1. The number in each square represents the R^2 or D' LD value. Note the high LD between SNP1 (enhancer rs5758550) and SNP4 (*2 allele), and other upstream SNPs, all >100kb distant from SNP1. SNP2, SNP6 and SNP9 are absent in EUR and ASN. EUR: European Ancestry, ASN: Asian Ancestry, AFR: African Ancestry, AMR: Americas Ancestry.



Supplemental Figure 2. Haplotype structural map of haplotypes H1 (a), H2 (b), and H3(c).