Supplement to: Comparison of Genome Sequencing and Clinical Genotyping for Pharmacogenes

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Supplemental Materials

CYP2D6 copy number and allele composition

One characteristic of WES is that for patients with *CYP2D6* duplications, one may deduce which *CYP2D6* allele was duplicated by examining the ratio of read counts between reference and alternative genotypes (Supplemental Table 3, Supplemental Figure 6). Among patients who had heterozygous genotypes at any *CYP2D6* SNV/indel, the read count ratios between reference allele and alternative allele observed in patients with gene duplications should differ from those observed in patients with two copies of the gene: i.e. 2 (Refx2/Alt) or 0.5 (Ref/Altx2) for those with a duplicated allele vs. 1 (Ref/Alt) for those with no duplication. For example, there were three patients with *CYP2D6* duplications (CN=3) who also had heterozygous genotypes at variant positions *CYP2D6*2* (R296C and S486T) (Supplemental Table 3). By examining the read count ratio, we could determine that one patient was **1x2/*2* while two patients were **1/*2x2*. Additionally, we examined the read count ratios in the two duplications that were called by WES but not by clinical qPCR. In both of these cases, the read count ratios could not be differentiated from those in patients with two copies of *CYP2D6*. Therefore, it is possible that by effectively analyzing read count ratios among heterozygous loci, one could further refine the copy number estimation by WES.

Table Legends

Supplemental Table 1: CPIC important variants interrogated (n=127)

Supplemental Table 2: Genotyping call rates, minor allele frequency (MAF), p value for Hardy-Weinberg Equilibrium (HWE) within patients of > 90% European ancestry, and average read depth for WES and WGS for CPIC important SNV/indel variants by DMET, WES and WGS (n=124 variants). *CYP2D6*5*, *CYP2D6/CYP2D7* and *HLA-B* are not included. For concordance, the number of patients evaluable by each of the two method comparisons is listed, and concordance is listed in the format of "a/b(c)", where "a" is the number of discrepant genotypes, "b" is the number of concordant genotypes and "c" is the number of concordant non-reference genotypes. NA = not applicable (variant not ascertained by one or both methods).

Supplemental Table 3. Inferred haplotype composition in patients with *CYP2D6* duplication. Shown are log2-transformed read depth ratios in patients with heterozygous genotypes and with polyploid *CYP2D6* copy number as determined by either WES or qPCR. The read depth ratios are defined as the ratio of number of reads with alternative allele over number of reads with reference allele. Among patients with diploid *CYP2D6* copy numbers, the log transformed read depth ratios are within -0.6 to 0.6 except for chr22:42526694 (P34S) (Supplemental Figure 6). In all five patients with consistent *CYP2D6* duplication by both WES and CNV (patient #1-#5), we can definitively infer their haplotype compositions. In two patients with conflicting WES and qPCR CNVs (#6 and 7), the WES read depth ratios do not support duplication as inferred by XHMM. In the other three patients (#8-10), the WES read ratios also yield ambiguity, which suggests the possible presence of a *CYP2D6/CYP2D7* hybrid. Hom_Ref and Hom_Alt indicate that the patient's DNA was homozyous for the reference or alternative allele, respectively at that variant. WES and qPCR CNV indicate the number of copies of *CYP2D6* estimated using WES vs using qPCR methods, respectively.

Supplemental Table 4. Coverage of coding regions of CPIC important genes by WES . *WES or WGS coverage of exonic region is calculated as % of exonic nucleotides that were interrogated at >=10X in 95% of patients. *UGT1A1* data is based on the first exon that is unique to *UGT1A1*.

Supplemental Table 5. Coverage of exonic regions of CPIC important genes by WES or WGS by exon.

Supplemental Table 6. Coding variants discovered by WES or WGS that were not included among CPIC important variants. 6A). Coding variants discovered by WES that were not included among CPIC important variants. ExonicFunc.refGene and AA.Change (amino acid substitution) are based on annotation from Refseq release 69 (genome assembly GRCh37/hg19) ; snp138 provides the rs ID number for each variant based on build 138 of dbSNP; ExAC.maf is the minor allele frequency among all samples (multiple races) based on http://exac.broadinstitute.org/ (version 0.3); CADD Score is the estimated Combined Annotation Dependent Depletion score based on http://cadd.gs.washington.edu/ (v1.3), higher CADD score indicate possible damaging variants. 6B). Coding variants discovered by WGS that were not included among CPIC important variants.

Supplemental Table 7. Number of coding variations observed in exomes of unrelated individuals (n=60,706) in CPIC important genes as reported by ExAC database (http://exac.broadinstitute.org/ version 0.3). Listed are 12 CPIC important genes (excluding *HLA*-B) and all coding variants reported by ExAC, including CPIC important variants. Loss of function variants include "stop gained" and "frameshift" variants.

Figure Legends:

Supplemental Figure 1. Workflow comparing WES and DMET genotyping for CPIC important variants

Supplemental Figure 2: Workflow comparing WGS and DMET genotyping for CPIC important variants

Supplemental Figure 3. Allele frequencies observed in our cohort interrogated by A) WES (n= 51 variants) or B) WGS (n=40 variants) compared with allele frequencies reported in ExAC database (http://exac.broadinstitute.org/ version 0.3). Allele frequencies shown are in subjects with European ancestry only.

Supplemental Figure 4. Minor allele fraction (based on sequencing reads) distribution among heterozygous genotypes in our cohort interrogated by A) WES and B) WGS. Histogram shows minor allele fraction (MAFrac) in heterozygous calls generated by WES and WGS that were in concordance with DMET genotypes. All discordant genotypes had lower MAFrac by sequencing (marked by unshaded bars).

Supplemental Figure 5. *HLA-B* haplotypes determined by WES compared with clinical molecular assays and WGS. Arcs of same color indicate concordant genotyping results. Arcs of different colors indicate discordant calls. The actionable *HLA-B* variants *5801 and *5701 are highlighted.5A. *HLA-B* haplotypes inferred using WES and clinical molecular assays (n=66). 5B. *HLA-B* haplotypes inferred using WGS and clinical molecular assays (n=16).

Supplemental Figure 6. Distribution of read depth ratios of heterozygous genotypes among patients with diploid *CYP2D6* copy numbers. Shown are distributions of read depth ratios defined as the ratio of number of reads with alternative allele over number of reads with reference allele. The read depth ratios were log2 transformed. Only patients who were heterozygous at the SNVs and also had diploid *CYP2D6* as determined by both WES and qPCR were included. Shown are 4 representative *CYP2D6* SNVs with highest minor allele frequencies among 83 patients with diploid *CYP2D6* copy numbers. All show narrow range between -0.6 and 0.6, except for chr22:42526694(P34S).

Supplemental Figure 7. Coverage of coding regions by gene by WES and WGS. Solid line indicates median coverage at each base (n=636 patients). Dotted line indicate the 5th percentile of coverage, i.e.

95% of samples have coverage above the dotted line. Red horizontal line indicates 10X coverage. For *G6PD*, green are males and blue are females.

Supplemental Figure 8. Coverage of coding regions by gene by WGS. Solid line indicates median coverage at each base (n=68 patients). Dotted line indicate the 5th percentile of coveage, i.e. 95% of samples have coverage above the dotted line. Red horizontal line indicates 10X coverage. For *G6PD*, green are males and blue are females.

Supplemental Figure 9. Aligned reads from a patients carrying *CYP2D6**20 T>TC variant using WGS. Display was centered at *CYP2D6**20 (chr22:42524819). "C" in red indicates reads with insertion T>TC at this position comparing with reference genome as indicated by ".". All reads with "TC" at this position also have multiple non-reference genotypes (nucleotides in red). This suggests the sequences with "TC" likely align to *CYP2D6* paralog.

Supplemental Table 1: CPIC important variants interrogated (n=127)

Gene	Alias	dbSNP ID	Variant Type	chr.pos (hg19)	SNV.func	Contributing to Starred Alleles
CFTR	G178R	rs80282562	SNV	chr7:117174372	missense	
CFTR	F508del(TCT)	rs199826652	indel	chr7:117199645	inframe_deletion	
CFTR	F508del(CTT)	rs113993960	indel	chr7:117199646	inframe_deletion	
CFTR	S549R(A>C)	rs121908757	SNV	chr7:117227853	missense	
CFTR	S549N	rs121908755	SNV	chr7:117227854	missense	
CFTR	S549R(T>G)	rs121909005	SNV	chr7:117227855	missense	
CFTR	G551S	rs121909013	SNV	chr7:117227859	missense	
CFTR	G551D	rs75527207	SNV	chr7:117227860	missense	
CFTR	G1244E	rs267606723	SNV	chr7:117282505	missense	
CFTR	S1251N	rs74503330	SNV	chr7:117282526	missense	
CFTR	S1255P	rs121909041	SNV	chr7:117282537	missense	
CFTR	G1349D	rs193922525	SNV	chr7:117304824	missense	
CYP2C19	-806C>T	rs12248560	SNV	chr10:96521657	upstream_gene	**17*
CYP2C19	M1V	rs28399504	SNV	chr10:96522463	start_lost	**4*
CYP2C19	W120R	rs41291556	SNV	chr10:96535173	missense	**8*
CYP2C19	R132Q	rs72552267	SNV	chr10:96535210	missense	**6*
CYP2C19	W212X	rs4986893	SNV	chr10:96540410	stop_gained	**3*
CYP2C19	P227P	rs4244285	SNV	chr10:96541616	synonymous	**2*
CYP2C19	19294T>A	rs72558186	SNV	chr10:96541756	splice_donor	**7*
CYP2C19	R433W	rs56337013	SNV	chr10:96612495	missense	**5*
CYP2C9	L90P	rs72558187	SNV	chr10:96701715	missense	**13*
CYP2C9	3531_3540del	rs72558188	indel	chr10:96701970	frameshift	**25*
CYP2C9	R144C	rs1799853	SNV	chr10:96702047	missense	**2, *24, *35*
CYP2C9	R150H	rs7900194	SNV	chr10:96702066	missense	**8, *27*
CYP2C9	S162X	rs72558190	SNV	chr10:96707539	stop_gained	**15*

CYP2C9	10601delA	rs9332131	indel	chr10:96709039	frameshift	**6*
CYP2C9	I327T	rs57505750	SNV	chr10:96740958	missense	**31*
CYP2C9	R335W	rs28371685	SNV	chr10:96740981	missense	**11*
CYP2C9	I359L	rs1057910	SNV	chr10:96741053	missense	**3,*18*
CYP2C9	I359T	rs56165452	SNV	chr10:96741054	missense	**4*
CYP2C9	D360E	rs28371686	SNV	chr10:96741058	missense	**5*
CYP2C9	P489S	rs9332239	SNV	chr10:96748777	missense	**12*
CYP2D6	*CYP2D6*/2D7 hybrid	Not applicable	structure	*CYP2D6* gene region	geneconversion	
CYP2D6	**5*	Not applicable	structure	*CYP2D6* gene region	copynumber	
CYP2D6	S486T	rs1135840	SNV	chr22:42522613	missense	*2, *4, *10
CYP2D6	468_470dupVPT	rs765776661	indel	chr22:42522660	inframe	**18*
CYP2D6	R441C	rs730882171	SNV	chr22:42522749	missense	**62*
CYP2D6	R440H	rs267608319	SNV	chr22:42522751	missense	**31*
CYP2D6	K404Q	rs267608285	SNV	chr22:42522958	missense	**55*
CYP2D6	E383K	rs75386357	SNV	chr22:42523475	missense	**72*
CYP2D6	3259insGT	rs72549346	indel	chr22:42523533	frameshift	**42*
CYP2D6	R344X	rs147960066	SNV	chr22:42523592	stop_gained	**56*
CYP2D6	V338M	rs59421388	SNV	chr22:42523610	missense	**29*
CYP2D6	E334A	rs72549348	SNV	chr22:42523621	missense	**51*
CYP2D6	2988G>A	rs28371725	SNV	chr22:42523805	intron	**41,*69*
CYP2D6	2950G>C	rs72549349	SNV	chr22:42523843	splice_donor	**44*
CYP2D6	2927_2945ins	rs730882170	indel	chr22:42523846	frameshift	**101*
CYP2D6	H324P	rs5030867	SNV	chr22:42523858	missense	**7*
CYP2D6	R296C	rs16947	SNV	chr22:42523943	missense	**2, *8, *11, *12, *14, *17, *19, *20, *21, *29, ,*31, *40, *41, *42, *45, *51, *55, *56, *59, *69*

CYP2D6	2828C>del	rs267608279	indel	chr22:42523965	frameshift	**100*
CYP2D6	2615delAAG	rs5030656	indel	chr22:42524178	splice_region	**9*
CYP2D6	2587delGACT	rs72549351	indel	chr22:42524203	frameshift	**38*
CYP2D6	2573_2574insC	rs267608296	indel	chr22:42524220	frameshift	**21*
CYP2D6	T261I	rs267608297	SNV	chr22:42524237	missense	**54*
CYP2D6	R259X	rs35742686	indel	chr22:42524244	frameshift	**3*
CYP2D6	2539delAACT	rs72549353	indel	chr22:42524251	frameshift	**19*
CYP2D6	2291G>A	rs267608300	SNV	chr22:42524502	intron	**59*
CYP2D6	L213P	rs199535154	SNV	chr22:42524814	missense	**20*
CYP2D6	1973insG	rs72549354	indel	chr22:42524819	frameshift	**20*
CYP2D6	1863_1864ins	rs72549356	indel	chr22:42524929	inframe	**40*
CYP2D6	1846G>A	rs3892097	SNV	chr22:42524947	splice_acceptor	**4*
CYP2D6	G169RorX	rs5030865	SNV	chr22:42525035	stop_gained	**8, *14*
CYP2D6	E156A	rs267608302	SNV	chr22:42525080	missense	**50*
CYP2D6	W152X	rs5030655	indel	chr22:42525086	frameshift	**6*
CYP2D6	V136I	rs61736512	SNV	chr22:42525134	missense	**29*
CYP2D6	F120I	rs1135822	SNV	chr22:42525182	missense	**49*
CYP2D6	T107I	rs28371706	SNV	chr22:42525772	missense	**17, *40*
CYP2D6	883G>C	rs201377835	SNV	chr22:42525912	splice_acceptor	**11*
CYP2D6	R62W	rs267608311	SNV	chr22:42525917	missense	**57*
CYP2D6	137insT	rs72549357	indel	chr22:42526657	frameshift	**15*
CYP2D6	G42R	rs5030862	SNV	chr22:42526670	missense	**12*
CYP2D6	P34S	rs1065852	SNV	chr22:42526694	missense	**4, *10, *14A, *36, *47, *49, *56, *57, *69, *100, *101*
CYP2D6	R25W	rs267608313	SNV	chr22:42526721	missense	**47*
CYP3A5	27131insT	rs41303343	indel	chr7:99250393	frameshift	**7*

CYP3A5	14690G>A	rs10264272	SNV	chr7:99262835	synonymous	**6*
CYP3A5	6986A>G	rs776746	SNV	chr7:99270539	intron	**3*
DPYD	V995F	rs1801268	SNV	chr1:97544627	missense	**10*
DPYD	rs67376798T	rs67376798	SNV	chr1:97547947	missense	
DPYD	R886H	rs1801267	SNV	chr1:97564154	missense	**9B*
DPYD	c.1905+1G>A	rs3918290	SNV	chr1:97915614	splice_donor	**2A*
DPYD	P633X	rs72549303	indel	chr1:97915622	frameshift	**3*
DPYD	I560S	rs55886062	SNV	chr1:97981343	missense	**13*
DPYD	E386X	rs78060119	SNV	chr1:98039499	stop_gained	**12*
DPYD	V335L	rs72549306	SNV	chr1:98058899	missense	**11*
DPYD	R235W	rs1801266	SNV	chr1:98157332	missense	**8*
DPYD	c.295delTCAT	rs72549309	indel	chr1:98205971	frameshift	**7*
DPYD	C29R	rs1801265	SNV	chr1:98348885	missense	**9B,*9A*
DPYD	R21Q	rs80081766	SNV	chr1:98348908	missense	**12*
G6PD	Canton	rs72554665	SNV	chrX:153760484	missense	
G6PD	Chatham	rs5030869	SNV	chrX:153761205	missense	
G6PD	Kalyan	rs137852339	SNV	chrX:153761259	missense	
G6PD	Mediterranean	rs5030868	SNV	chrX:153762634	missense	
G6PD	A-	rs1050829	SNV	chrX:153763492	missense	
G6PD	Asahi	rs1050828	SNV	chrX:153764217	missense	
G6PD	Orissa	rs78478128	SNV	chrX:153764383	missense	
HLA-B	Haplotype	Not applicable	haplotype	*HLA*-B gene region	haplotype	
IFNL3	rs12979860	rs12979860	SNV	chr19:39738787	upstream_gene	
IFNL3	rs8099917	rs8099917	SNV	chr19:39743165	upstream_gene	
SLCO1B1	c.-11187G>A	rs4149015	SNV	chr12:21283322	upstream_gene	**17*
SLCO1B1	G71R	rs373327528	SNV	chr12:21325710	missense	**23*
SLCO1B1	F73L	rs56101265	SNV	chr12:21325716	missense	**2*

SLCO1B1	V82A	rs56061388	SNV	chr12:21327529	missense	**3*
SLCO1B1	N130D	rs2306283	SNV	chr12:21329738	missense	**5, *14, *15, *17, *31, *35*
SLCO1B1	P155T	rs11045819	SNV	chr12:21329813	missense	**14*
SLCO1B1	E156G	rs72559745	SNV	chr12:21329817	missense	**3*
SLCO1B1	V174A	rs4149056	SNV	chr12:21331549	missense	**5,*15,*17*
SLCO1B1	I353T	rs55901008	SNV	chr12:21353529	missense	**6*
SLCO1B1	G488A	rs59502379	SNV	chr12:21358933	missense	**31*
SLCO1B1	L643F	rs34671512	SNV	chr12:21391976	missense	**35*
SLCO1B1	D655G	rs56199088	SNV	chr12:21392011	missense	**10*
TPMT	Y240C	rs1142345	SNV	chr6:18130918	missense	**3C,*3A*
TPMT	R215H	rs56161402	SNV	chr6:18130993	missense	**8*
TPMT	c.626-1G>A	rs1800584	SNV	chr6:18131012	splice_acceptor	**4*
TPMT	Y180F	rs75543815	SNV	chr6:18134076	missense	**6*
TPMT	R163H	rs144041067	SNV	chr6:18139200	missense	**16*
TPMT	A154T	rs1800460	SNV	chr6:18139228	missense	**3B, *3A*
TPMT	G144R	rs72552737	SNV	chr6:18139258	missense	**10*
TPMT	C132Y	rs72552738	SNV	chr6:18139920	missense	**11*
TPMT	S125L	rs200220210	SNV	chr6:18139941	missense	**12*
TPMT	K119T	rs151149760	SNV	chr6:18143837	missense	**9*
TPMT	A80P	rs1800462	SNV	chr6:18143955	missense	**2*
TPMT	G71R	*TPMT*_*18	SNV	chr6:18148076	missense	**18*
TPMT	L49S	rs72552740	SNV	chr6:18148141	missense	**5*
TPMT	Q42E	*TPMT*_*17	SNV	chr6:18149235	missense	**17*
TPMT	E28V	rs72552742	SNV	chr6:18149276	missense	**13*
UGT1A1	**28*	rs8175347	indel	chr2:234668881	upstream_gene	**28*
VKORC1	-1639G>A	rs9923231	SNV	chr16:31107689	upstream_gene	

Supplemental Table 2: Genotyping call rates, minor allele frequency (MAF), p value for Hardy-Weinberg Equilibrium (HWE) within patients of > 90% European ancestry, and average read depth for WES and WGS for CPIC important SNV/indel variants by DMET, WES and WGS (n=124 variants). *CYP2D6*5*, *CYP2D6/CYP2D7* and *HLA-B* are not included. For concordance, the number of patients evaluable by each of the two method comparisons is listed, and concordance is listed in the format of "a/b(c)", where "a" is the number of discrepant genotypes, "b" is the number of concordant genotypes and "c" is the number of concordant non-reference genotypes. NA = not applicable (variant not ascertained by one or both methods).

		DMET (n=2656)			WES (n=636)				WGS (n=68)				Concordance		
Gene	Alias	Call rate	MAF	HWE P-value	Call rate	MAF	HWE P-value	Average read depth	Call rate	MAF	HWE P-value	Average read depth	WES vs. DMET (n=176)	WGS vs. DMET (n=68)	WES vs. WGS (n=16)
CFTR	G178R	NA	NA	NA	1	0	1	23.2	1	0	1	36.8	NA	NA	0/16(0)
CFTR	F508del(TCT)	NA	NA	NA	0.998	0.01	1	19	1	0	1	37.4	NA	NA	0/16(0)
CFTR	F508del(CTT)	NA	NA	NA	0.998	0	1	18.7	1	0	1	37.5	NA	NA	0/16(0)
CFTR	S549R(A>C)	NA	NA	NA	1	0	1	25.6	1	0	1	36.1	NA	NA	0/16(0)
CFTR	S549N	NA	NA	NA	1	0	1	25.6	1	0	1	37.2	NA	NA	0/16(0)
CFTR	S549R(T>G)	NA	NA	NA	1	0	1	25.6	1	0	1	36.5	NA	NA	0/16(0)
CFTR	G551S	NA	NA	NA	1	0	1	25.6	1	0	1	36.5	NA	NA	0/16(0)
CFTR	G551D	NA	NA	NA	1	0.001	1	25.6	1	0	1	36.5	NA	NA	0/16(0)
CFTR	G1244E	NA	NA	NA	1	0	1	22.2	1	0	1	36.6	NA	NA	0/16(0)
CFTR	S1251N	NA	NA	NA	1	0	1	22.4	1	0	1	35	NA	NA	0/16(0)
CFTR	S1255P	NA	NA	NA	1	0	1	22.4	1	0	1	34.8	NA	NA	0/16(0)
CFTR	G1349D	NA	NA	NA	1	0	1	22.8	1	0	1	31.3	NA	NA	0/16(0)
CYP2C19	-806C>T	1	0.204	0.389	NA	NA	NA	NA	1	0.184	1	35	NA	0/68(22)	NA
CYP2C19	M1V	1	0.001	1	1	0.001	1	24.1	1	0	1	35.7	0/176(0)	0/68(0)	0/16(0)
CYP2C19	W120R	0.999	0.002	1	1	0.005	1	26.1	1	0.001	1	32.6	0/174(0)	0/68(0)	0/16(0)
CYP2C19	R132Q	1	0	1	1	0	1	25.3	1	0	1	32.9	0/176(0)	0/68(0)	0/16(0)
CYP2C19	W212X	1	0.002	1	0.995	0.005	1	17.6	1	0.008	1	38.5	0/176(2)	0/67(0)	0/16(0)
CYP2C19	P227P	1	0.158	0.443	1	0.165	0.364	25.3	1	0.147	0.564	41.8	0/176(49)	0/68(20)	0/16(2)
CYP2C19	19294T>A	1	0	1	0.991	0	1	18.4	1	0	1	35.8	0/176(0)	0/68(0)	0/16(0)
CYP2C19	R433W	0.996	0	1	1	0	1	27.4	1	0	1	37	0/173(0)	0/67(0)	0/16(0)

CYP2C9	L90P	1	0	1	1	0	1	31.3	1	0	1	36.5	0/176(0)	0/68(0)	0/16(0)
CYP2C9	3531_3540del	1	0	1	1	0	1	30.8	1	0	1	29.6	0/176(0)	0/68(0)	0/16(0)
CYP2C9	R144C	0.99	0.082	0.458	1	0.121	1	35.1	1	0.118	1	28.9	0/169(44)	0/63(14)	0/16(4)
CYP2C9	R150H	NA	NA	NA	1	0.01	1	25.7	1	0.022	1	29.2	NA	NA	0/16(1)
CYP2C9	S162X	1	0	1	0.998	0	1	19.6	1	0	1	38.4	0/176(0)	0/68(0)	0/16(0)
CYP2C9	10601delA	1	0.004	1	0.998	0.002	1	20.9	1	0	1	31.7	0/176(0)	0/68(0)	0/16(0)
CYP2C9	I327T	NA	NA	NA	0.986	0	1	14.9	1	0	1	33.1	NA	NA	0/16(0)
CYP2C9	R335W	1	0.01	1	0.992	0.007	1	17.4	1	0.002	1	30.6	0/176(3)	0/68(0)	0/16(0)
CYP2C9	I359L	0.999	0.04	0.013	1	0.043	0.613	23.3	1	0.052	1	30.1	0/176(14)	0/68(7)	0/16(2)
CYP2C9	I359T	1	0	1	1	0	1	22	1	0	1	29.8	0/176(0)	0/68(0)	0/16(0)
CYP2C9	D360E	0.999	0.005	1	1	0.002	1	22.2	1	0.008	1	30	0/176(1)	0/68(1)	0/16(1)
CYP2C9	P489S	1	0.001	1	1	0.006	1	26.7	1	0.001	1	33.2	0/176(3)	0/68(0)	0/16(0)
CYP2D6	S486T	0.994	0.409	1	0.998	0.436	0.105	146.5	1	0.418	0.192	28	0/175(104)	0/67(41)	0/16(7)
CYP2D6	468_470dupVPT	1	0	1	1	0	1	33.4	0.975	0.002	1	25	0/176(0)	0/68(0)	0/16(0)
CYP2D6	R441C	NA	NA	NA	0.998	0.001	1	47	1	0	1	25.5	NA	NA	0/16(0)
CYP2D6	R440H	NA	NA	NA	0.998	0	1	46.9	1	0	1	25.7	NA	NA	0/16(0)
CYP2D6	K404Q	NA	NA	NA	0.998	0	1	47	1	0	1	26.3	NA	NA	0/16(0)
CYP2D6	E383K	NA	NA	NA	1	0.001	1	118.2	1	0	1	26.9	NA	NA	0/16(0)
CYP2D6	3259insGT	1	0.002	1	1	0.001	1	110.5	1	0	1	27.1	0/176(1)	0/68(0)	0/16(0)
CYP2D6	R344X	1	0.001	1	1	0	1	90.7	0.985	0	1	28.8	0/176(0)	0/68(0)	0/16(0)
CYP2D6	V338M	0.996	0.041	1	1	0.021	1	90.8	1	0.022	1	29.7	0/176(9)	0/67(3)	0/16(1)
CYP2D6	E334A	NA	NA	NA	1	0	1	89.2	1	0	1	27.3	NA	NA	0/16(0)
CYP2D6	2988G>A	1	0.065	0.324	0.995	0.096	0.817	42.1	1	0.09	1	26.5	0/176(33)	0/67(10)	0/16(2)
CYP2D6	2950G>C	1	0	1	0.994	0	1	41.9	0.985	0	1	26.3	0/176(0)	0/68(0)	0/16(0)
CYP2D6	2927_2945ins	NA	NA	NA	0.994	0	1	42	1	0	1	24.7	NA	NA	0/16(0)
CYP2D6	H324P	0.999	0.001	1	0.997	0.001	1	42.4	0.985	0.001	1	26.6	0/176(0)	0/68(0)	0/16(0)
CYP2D6	R296C	1	0.417	0.605	0.998	0.467	0.095	99.9	1	0.465	0.167	28.3	1/175(97)	0/67(37)	0/16(10)
CYP2D6	2828C>del	NA	NA	NA	0.998	0	1	42.3	1	0	1	26.2	NA	NA	0/16(0)
CYP2D6	2615delAAG	0.998	0.019	0.237	0.998	0.019	0.021	39.7	1	0.03	1	24.1	0/175(7)	0/66(4)	0/16(1)
CYP2D6	2587delGACT	0.998	0	1	0.998	0	1	40.1	1	0	1	27.7	0/176(0)	0/68(0)	0/16(0)
CYP2D6	2573_2574insC	NA	NA	NA	0.998	0	1	40.5	1	0	1	25.4	NA	NA	0/16(0)

CYP2D6	T261I	NA	NA	NA	0.998	0	1	40.7	1	0	1	27.9	NA	NA	0/16(0)
CYP2D6	R259X	1	0.011	1	0.998	0.008	1	41.4	1	0.023	1	28.3	0/176(4)	0/67(3)	0/16(0)
CYP2D6	2539delAACT	0.999	0	1	0.998	0	1	40.7	1	0	1	27	0/176(0)	0/68(0)	0/16(0)
CYP2D6	2291G>A	NA	NA	NA	NA	NA	NA	NA	1	0	1	25.2	NA	NA	NA
CYP2D6	L213P	NA	NA	NA	1	0.003	1	158.8	1	0.008	1	28.4	NA	NA	0/16(0)
CYP2D6	1973insG	1	0	1	1	0.003	1	158.3	1	0.008	1	28.1	2/174(0)	1/66(0)	0/16(0)
CYP2D6	1863_1864ins	0.999	0.004	1	1	0.003	1	163.7	1	0	1	27.7	2/174(1)	2/68(0)	0/16(0)
CYP2D6	1846G>A	0.999	0.142	0.017	1	0.166	0.745	179.2	1	0.169	1	22.1	2/174(48)	0/67(20)	0/16(4)
CYP2D6	G169RorX	0.999	0	1	0.998	0	1	153.9	0.845	0	1	19.7	0/176(0)	0/67(0)	0/15(0)
CYP2D6	E156A	NA	NA	NA	1	0	1	153.6	1	0	1	26.3	NA	NA	0/16(0)
CYP2D6	W152X	0.999	0.007	0.166	1	0.011	1	154.3	1	0.008	1	19.4	0/176(5)	0/67(1)	0/16(0)
CYP2D6	V136I	0.941	0.034	0	1	0.021	1	69.8	1	0.023	1	19.4	2/157(7)	1/55(0)	0/16(1)
CYP2D6	F120I	NA	NA	NA	0.998	0	1	63.5	1	0	1	27.4	NA	NA	0/16(0)
CYP2D6	T107I	0.994	0.083	1	0.981	0.041	1	26	1	0.03	1	13.9	0/175(7)	0/67(3)	0/16(1)
CYP2D6	883G>C	1	0	1	0.799	0	1	18.6	0.826	0	1	16.6	0/174(0)	0/68(0)	0/14(0)
CYP2D6	R62W	NA	NA	NA	0.821	0	1	18.5	1	0	1	27.4	NA	NA	0/15(0)
CYP2D6	137insT	1	0	1	0.983	0	1	22.8	1	0	1	26.5	0/176(0)	0/68(0)	0/16(0)
CYP2D6	G42R	1	0	1	0.992	0	1	23.8	0.959	0	1	26.3	0/176(0)	0/68(0)	0/16(0)
CYP2D6	P34S	0.999	0.173	0.012	0.998	0.196	0.207	33.1	1	0.217	0.409	24.4	0/176(58)	0/67(24)	0/16(5)
CYP2D6	R25W	NA	NA	NA	0.998	0	1	27.8	1	0	1	24.5	NA	NA	0/16(0)
CYP3A5	27131insT	1	0.046	1	0.984	0.022	1	13.9	1	0.008	1	37.7	0/176(5)	0/68(1)	0/16(0)
CYP3A5	14690G>A	1	0.048	1	1	0.02	1	27.7	1	0.015	1	35.7	0/176(4)	0/68(2)	0/16(0)
CYP3A5	6986A>G	0.999	0.34	0.824	NA	NA	NA	NA	1	0.199	1	35	NA	0/68(19)	NA
DPYD	V995F	1	0	1	1	0	1	33.7	1	0	1	34.3	0/176(0)	0/68(0)	0/16(0)
DPYD	rs67376798T	NA	NA	NA	1	0.004	1	22.9	0.998	0.002	1	36.4	NA	NA	0/16(0)
DPYD	R886H	0.996	0.002	1	1	0	1	22.8	1	0	1	40.8	0/167(0)	0/66(0)	0/16(0)
DPYD	c.1905+1G>A	1	0.002	1	0.998	0.001	1	17.4	1	0.001	1	40.3	0/176(0)	0/68(0)	0/16(0)
DPYD	P633X	1	0	1	1	0	1	18.6	1	0	1	34.6	0/176(0)	0/68(0)	0/16(0)
DPYD	I560S	1	0.001	1	1	0	1	26.2	1	0	1	34	0/176(0)	0/68(0)	0/16(0)
DPYD	E386X	NA	NA	NA	1	0	1	22.8	1	0	1	35.6	NA	NA	0/16(0)
DPYD	V335L	1	0	1	1	0	1	24.1	1	0	1	32.1	0/176(0)	0/68(0)	0/16(0)

DPYD	R235W	1	0	1	1	0.001	1	22.4	1	0	1	36.4	0/176(0)	0/68(0)	0/16(0)
DPYD	c.295delTCAT	1	0	1	1	0	1	19.3	1	0	1	35.4	0/176(0)	0/68(0)	0/16(0)
DPYD	C29R	0.998	0.301	0.615	1	0.247	0.092	40.9	1	0.242	0.323	34.6	0/175(71)	0/67(26)	0/16(6)
DPYD	R21Q	NA	NA	NA	1	0	1	25.5	1	0	1	36.2	NA	NA	0/16(0)
G6PD	Canton	0.999	0	1	1	0	1	29.7	0.758	0	1	14.5	0/174(0)	0/68(0)	0/11(0)
G6PD	Chatham	0.999	0.001	1	0.995	0	1	24.7	0.822	0	1	17	0/176(0)	0/68(0)	0/15(0)
G6PD	Kalyan	NA	NA	NA	1	0.001	1	26.5	0.828	0	1	17.5	NA	NA	0/15(0)
G6PD	Mediterranean	1	0.001	1	0.998	0	1	22.2	0.888	0	1	19.2	0/176(0)	0/68(0)	0/15(0)
G6PD	A-	0.989	0.13	1	1	0.06	0.004	28	1	0.066	1	18.8	0/173(9)	0/66(5)	0/16(2)
G6PD	Asahi	NA	NA	NA	1	0.021	1	39.9	1	0.03	1	18.7	NA	NA	0/16(2)
G6PD	Orissa	NA	NA	NA	1	0	1	36.5	0.919	0	1	19.4	NA	NA	0/13(0)
IFNL3	rs12979860	NA	NA	NA	NA	NA	NA	NA	1	0.375	0.272	19.8	NA	NA	NA
IFNL3	rs8099917	NA	NA	NA	NA	NA	NA	NA	1	0.147	1	41	NA	NA	NA
SLCO1B1	c.-11187G>A	0.999	0.036	1	NA	NA	NA	NA	1	0.052	1	41.3	NA	0/68(7)	NA
SLCO1B1	G71R	NA	NA	NA	1	0	1	23.2	1	0	1	40	NA	NA	0/16(0)
SLCO1B1	F73L	1	0	1	1	0	1	23	1	0	1	39.2	0/176(0)	0/68(0)	0/16(0)
SLCO1B1	V82A	1	0	1	0.995	0	1	18.2	1	0	1	36	0/176(0)	0/68(0)	0/16(0)
SLCO1B1	N130D	1	0.436	0.377	1	0.463	0.747	34.8	1	0.5	0.021	39.6	0/176(89)	0/68(30)	0/16(5)
SLCO1B1	P155T	0.997	0.112	0.915	1	0.121	1	26.8	1	0.125	1	40.7	0/174(38)	0/68(15)	0/16(2)
SLCO1B1	E156G	0.997	0	1	1	0	1	23.6	1	0	1	39.4	0/171(0)	0/68(0)	0/16(0)
SLCO1B1	V174A	1	0.099	0.183	1	0.127	1	48.5	1	0.184	1	38.3	0/176(39)	0/68(23)	0/16(5)
SLCO1B1	I353T	1	0	1	1	0	1	22.4	1	0	1	39	0/176(0)	0/68(0)	0/16(0)
SLCO1B1	G488A	0.998	0.017	1	0.998	0.007	1	21.6	1	0.008	1	39.2	0/174(3)	0/68(1)	0/16(1)
SLCO1B1	L643F	NA	NA	NA	1	0.047	0.565	24.5	1	0.052	1	40.9	NA	NA	0/16(3)
SLCO1B1	D655G	1	0	1	1	0	1	24	1	0	1	39.2	0/176(0)	0/68(0)	0/16(0)
TPMT	Y240C	0.999	0.045	1	1	0.047	1	27.4	1	0.052	1	41.2	0/176(20)	0/67(7)	0/16(0)
TPMT	R215H	1	0.012	1	1	0.005	1	23.4	1	0.008	1	45	0/176(4)	0/68(1)	0/16(0)
TPMT	c.626-1G>A	1	0	1	1	0	1	22.8	1	0.001	1	42.9	0/176(0)	0/68(0)	0/16(0)
TPMT	Y180F	NA	NA	NA	1	0	1	28.6	1	0	1	40.9	NA	NA	0/16(0)
TPMT	R163H	NA	NA	NA	1	0	1	22.6	1	0	1	39.7	NA	NA	0/16(0)
TPMT	A154T	0.999	0.024	0.646	1	0.038	1	29.1	1	0.052	1	44.2	0/175(16)	1/67(6)	0/16(0)

TPMT	G144R	NA	NA	NA	1	0	1	27.4	1	0	1	41	NA	NA	0/16(0)
TPMT	C132Y	NA	NA	NA	1	0	1	37.6	1	0	1	40.4	NA	NA	0/16(0)
TPMT	S125L	NA	NA	NA	1	0	1	37.6	1	0	1	41.4	NA	NA	0/16(0)
TPMT	K119T	NA	NA	NA	1	0.001	1	20.5	1	0	1	35.8	NA	NA	0/16(0)
TPMT	A80P	1	0.002	1	1	0.003	1	23.2	1	0.001	1	40.8	0/176(2)	0/68(0)	0/16(0)
TPMT	G71R	NA	NA	NA	1	0	1	26.9	1	0	1	42	NA	NA	0/16(0)
TPMT	L49S	NA	NA	NA	1	0	1	27	1	0	1	40.2	NA	NA	0/16(0)
TPMT	Q42E	NA	NA	NA	1	0	1	22.8	1	0	1	43.7	NA	NA	0/16(0)
TPMT	E28V	NA	NA	NA	1	0	1	22.8	1	0	1	40	NA	NA	0/16(0)
UGT1A1	**28*	0.903	0.348	0.003	0.994	0.328	0.813	35.4	1	0.294	1	26.3	12/136(57)	59/3(2)	0/16(8)
VKORC1	-1639G>A	0.997	0.277	0.017	NA	NA	NA	NA	1	0.353	1	34.6	NA	0/66(36)	NA

Supplemental Table 3. Inferred haplotype composition in patients with *CYP2D6* duplication

Shown are log2-transformed read depth ratios in patients with heterozygous genotypes and with polyploid *CYP2D6* copy number as determined by either WES or qPCR. The read depth ratios are defined as the ratio of number of reads with alternative allele over number of reads with reference allele. Among patients with diploid *CYP2D6* copy numbers, the log transformed read depth ratios are within -0.6 to 0.6 except for chr22:42526694 (P34S) (Supplemental Figure 5). In all five patients with consistent *CYP2D6* duplication by both WES and CNV (patient #1-#5), we can definitively infer their haplotype compositions. In two patients with conflicting WES and qPCR CNVs (#6 and 7), the WES read depth ratios do not support duplication as inferred by XHMM. In the other three patients (#8-10), the WES read ratios also yield ambiguity, which suggests the possible presence of a *CYP2D6/CYP2D7* hybrid. Hom_Ref and Hom_Alt indicate that the patient's DNA was homozyous for the reference or alternative allele, respectively at that variant. WES and qPCR CNV indicate the number of copies of *CYP2D6* estimated using WES vs using qPCR methods, respectively.

patient	chr22:42526694 (P34S, *4)	chr22:42524947 (1846G>A, *4)	chr22:42522613 (S486T, *2, *4)	chr22:42523943 (R296C, *2)	chr22:42524178 (2615delAAG, *9)	WES CNV	qPCR CNV	Haplotype composition	Comment
1	Hom_Ref	Hom_Ref	1.093	0.813	Hom_Ref	3N	3N	*1/*2/*2	
2	Hom_Ref	Hom_Ref	1.052	1.222	Hom_Ref	3N	3N	*1/*2/*2	
3	Hom_Ref	Hom_Ref	-1.141	-0.955	Hom_Ref	3N	3N	*1/*1/*2	
4	-0.781	-1.188	Hom_Alt	0.595	Hom_Ref	3N	3N	*2/*2/*4	
5	-0.933	-1.322	-1.000	Ref	Hom_Ref	3N	3N	*1/*1/*4	
6	-1.585	0.084	0.119	Hom_Ref	0.237	3N	2N	*4/*9 (2N)	WES read depth ratios do not support 3N
7	0.152	0.096	Hom_Alt	-0.215	Hom_Ref	3N	2N	*2/*4 (2N)	WES read depth ratios do not support 3N
8	1.424	0.678	-0.556	Hom_Ref	Hom_Ref	3N	2/3/3N	*1/*4/*4(?N)	WES read depth ratios yield ambiguity
9	0.663	0.898	0.239	Hom_Ref	Hom_Ref	2N	2/3/2N	*1/*4/*4(?N)	WES read depth ratios yield ambiguity
10	0.382	0.765	-0.243	Hom_Ref	Hom_Ref	3N	2/3/3N	*1/*4(?N)	WES read depth ratios yield ambiguity

Supplemental Table 4. Coverage of coding regions of CPIC important genes by WES

* WES or WGS coverage of exonic region is calculated as % of exonic nucleotides that were interrogated at >=10X in 95% of patients. *UGT1A1* data is based on the first exon that is unique to *UGT1A1*.

Gene	WES Average Read Depth (n=636)	WES Coverage of Exonic region *	WGS Average Read Depth (n=68)	WGS Coverage of Exonic region*
CFTR	54	96.7%	37.4	100%
CYP2C19	56	99.0%	36.2	100%
CYP2C9	57	98.7%	36.6	100%
CYP2D6	123.5	98.3%	24.9	75.2%
CYP3A5	55	98.0%	37.0	100%
DPYD	59	99.3%	35.4	98.7%
G6PD	56	90.3%	15.7	41.5%
HLA-B	78	92.0%	19.7	44.5%
IFNL3	136	100%	25.5	84.4%
SLCO1B1	42	93.1%	37.5	98.2%
TPMT	60	100%	40.2	100%
UGT1A1	67	86.0%	33.9	99.4%
VKORC1	61	77.6%	23.2	64.8%

Supplemental Table 5. Coverage of exonic regions of CPIC important genes by WES or WGS by exon

gene	refseq	Exon	chr	fstart	fend	WES		WGS	
						Average Coverage	% samples with coverage >= 10X	Average Coverage	% samples with coverage >= 10X
CFTR	NM_000492	1	7	117120148	117120201	36.7	100%	24.1	100%
CFTR	NM_000492	2	7	117144306	117144417	48.3	100%	37.8	100%
CFTR	NM_000492	3	7	117149087	117149196	63.7	100%	38.8	100%
CFTR	NM_000492	4	7	117170952	117171168	88.5	100%	37.5	100%
CFTR	NM_000492	5	7	117174329	117174419	50.7	100%	42.3	100%
CFTR	NM_000492	6	7	117175301	117175465	70.6	100%	34.2	100%
CFTR	NM_000492	7	7	117176601	117176727	47.6	100%	40.6	100%
CFTR	NM_000492	8	7	117180153	117180400	33.8	99%	35.3	100%
CFTR	NM_000492	9	7	117182069	117182162	63.3	100%	40.2	100%
CFTR	NM_000492	10	7	117188694	117188877	97.0	100%	53.7	100%
CFTR	NM_000492	11	7	117199517	117199709	34.9	100%	38.8	100%
CFTR	NM_000492	12	7	117227792	117227887	68.6	100%	36.5	100%
CFTR	NM_000492	13	7	117230406	117230493	69.8	100%	41.4	100%
CFTR	NM_000492	14	7	117231987	117232711	58.0	100%	37.2	100%
CFTR	NM_000492	15	7	117234983	117235112	28.9	99%	38.0	100%
CFTR	NM_000492	16	7	117242879	117242917	43.8	100%	35.7	100%
CFTR	NM_000492	17	7	117243585	117243836	72.7	100%	36.2	100%
CFTR	NM_000492	18	7	117246727	117246807	96.3	100%	40.9	100%
CFTR	NM_000492	19	7	117250572	117250723	71.7	100%	35.5	100%
CFTR	NM_000492	20	7	117251634	117251862	54.5	100%	34.3	100%
CFTR	NM_000492	21	7	117254666	117254767	62.2	100%	37.1	100%
CFTR	NM_000492	22	7	117267575	117267824	59.9	100%	37.7	100%
CFTR	NM_000492	23	7	117282491	117282647	37.7	100%	35.1	100%
CFTR	NM_000492	24	7	117292895	117292985	53.6	100%	36.8	100%
CFTR	NM_000492	25	7	117304741	117304914	62.7	100%	33.4	100%
CFTR	NM_000492	26	7	117305512	117305618	59.4	100%	39.5	100%
CFTR	NM_000492	27	7	117306961	117307162	54.2	100%	31.7	100%
CYP2C19	NM_000769	1	10	96522462	96522630	76.7	100%	38.2	100%
CYP2C19	NM_000769	2	10	96534814	96534977	77.5	100%	33.7	100%
CYP2C19	NM_000769	3	10	96535146	96535296	89.0	100%	31.7	100%
CYP2C19	NM_000769	4	10	96540255	96540416	37.4	100%	38.7	100%
CYP2C19	NM_000769	5	10	96541577	96541754	41.0	100%	40.4	100%
CYP2C19	NM_000769	6	10	96580252	96580394	80.4	100%	37.3	100%
CYP2C19	NM_000769	7	10	96602593	96602781	32.9	100%	32.3	100%
CYP2C19	NM_000769	8	10	96609673	96609815	41.5	100%	37.9	100%
CYP2C19	NM_000769	9	10	96612489	96612671	110.1	100%	36.0	100%
CYP2C9	NM_000771	1	10	96698439	96698607	107.4	100%	36.3	100%
CYP2C9	NM_000771	2	10	96701614	96701777	92.3	100%	38.4	100%
CYP2C9	NM_000771	3	10	96701948	96702098	83.5	100%	32.1	100%
CYP2C9	NM_000771	4	10	96707535	96707696	34.8	100%	38.8	100%
CYP2C9	NM_000771	5	10	96708864	96709041	44.8	100%	41.9	100%
CYP2C9	NM_000771	6	10	96731860	96732002	64.9	100%	37.4	100%
CYP2C9	NM_000771	7	10	96740939	96741127	32.0	100%	31.6	100%
CYP2C9	NM_000771	8	10	96745789	96745931	42.8	100%	38.6	100%
CYP2C9	NM_000771	9	10	96748603	96748785	121.3	100%	34.1	100%
CYP2D6	NM_000106	1	22	42526613	42526793	69.3	95.9%	24.7	97%
CYP2D6	NM_000106	2	22	42525739	42525911	53.8	62.9%	12.3	48%
CYP2D6	NM_000106	3	22	42525034	42525187	271.3	84.1%	18.8	78%
CYP2D6	NM_000106	4	22	42524785	42524946	247.4	98.2%	27.0	98%

CYP2D6	NM_000106	5	22	42524175	42524352	93.8	96.7%	27.9	95%
CYP2D6	NM_000106	6	22	42523843	42523985	92.1	97.0%	27.0	97%
CYP2D6	NM_000106	7	22	42523448	42523636	163.8	98.0%	34.1	97%
CYP2D6	NM_000106	8	22	42522852	42522994	203.2	96.0%	25.6	97%
CYP2D6	NM_000106	9	22	42522575	42522754	194.9	97.5%	26.4	98%
CYP3A5	NM_000777	1	7	99277448	99277519	47.0	100%	31.5	100%
CYP3A5	NM_000777	2	7	99273737	99273831	75.7	100%	36.7	100%
CYP3A5	NM_000777	3	7	99272155	99272208	41.5	100%	41.0	100%
CYP3A5	NM_000777	4	7	99270202	99270302	43.7	100%	34.9	100%
CYP3A5	NM_000777	5	7	99264574	99264688	56.1	100%	37.6	100%
CYP3A5	NM_000777	6	7	99264223	99264312	52.6	100%	33.7	100%
CYP3A5	NM_000777	7	7	99262788	99262937	106.1	100%	35.7	100%
CYP3A5	NM_000777	8	7	99261590	99261718	62.2	100%	42.4	100%
CYP3A5	NM_000777	9	7	99260438	99260505	61.9	100%	36.0	100%
CYP3A5	NM_000777	10	7	99258121	99258282	74.3	100%	34.9	100%
CYP3A5	NM_000777	11	7	99250175	99250402	29.5	100%	36.4	100%
CYP3A5	NM_000777	12	7	99247695	99247855	59.0	100%	40.4	100%
CYP3A5	NM_000777	13	7	99245927	99246023	57.7	100%	40.1	100%
DPYD	NM_000110	1	1	98386439	98386478	81.3	71%	13.7	59%
DPYD	NM_000110	2	1	98348819	98348930	40.4	100%	35.8	100%
DPYD	NM_000110	3	1	98293669	98293752	112.8	100%	37.3	100%
DPYD	NM_000110	4	1	98205947	98206035	31.7	100%	38.8	100%
DPYD	NM_000110	5	1	98187065	98187227	84.8	100%	34.5	100%
DPYD	NM_000110	6	1	98164906	98165103	75.2	100%	35.4	100%
DPYD	NM_000110	7	1	98157272	98157354	43.9	100%	37.6	100%
DPYD	NM_000110	8	1	98144650	98144738	56.8	100%	41.1	100%
DPYD	NM_000110	9	1	98060614	98060722	36.6	100%	38.3	100%
DPYD	NM_000110	10	1	98058773	98058943	69.8	100%	33.8	100%
DPYD	NM_000110	11	1	98039315	98039526	39.4	100%	37.5	100%
DPYD	NM_000110	12	1	98015115	98015300	78.6	100%	36.6	100%
DPYD	NM_000110	13	1	97981281	97981497	54.3	100%	35.0	100%
DPYD	NM_000110	14	1	97915614	97915779	38.4	100%	38.5	100%
DPYD	NM_000110	15	1	97847948	97848017	52.7	100%	39.0	100%
DPYD	NM_000110	16	1	97839116	97839200	87.4	100%	34.7	100%
DPYD	NM_000110	17	1	97771732	97771853	71.8	100%	32.7	100%
DPYD	NM_000110	18	1	97770814	97770934	53.1	100%	32.1	100%
DPYD	NM_000110	19	1	97700407	97700550	56.4	100%	33.0	100%
DPYD	NM_000110	20	1	97658624	97658804	74.5	100%	35.9	100%
DPYD	NM_000110	21	1	97564044	97564188	66.1	100%	40.6	100%
DPYD	NM_000110	22	1	97547885	97548026	53.9	100%	39.8	100%
DPYD	NM_000110	23	1	97544531	97544702	136.8	100%	33.3	100%
G6PD	NM_000402	1	X	153775003	153775085	6.7	11.9%	3.1	5%
G6PD	NM_000402	2	X	153774250	153774378	54.2	93.5%	20.4	89%
G6PD	NM_000402	3	X	153764355	153764393	154.3	87.3%	18.5	81%
G6PD	NM_000402	4	X	153764151	153764260	156.8	85.9%	17.8	83%
G6PD	NM_000402	5	X	153763382	153763600	61.9	86.9%	18.0	84%
G6PD	NM_000402	6	X	153762552	153762711	54.7	86.6%	18.3	79%
G6PD	NM_000402	7	X	153762249	153762375	35.5	92.4%	21.0	87%
G6PD	NM_000402	8	X	153761790	153761884	60.8	88.2%	18.5	84%
G6PD	NM_000402	9	X	153761156	153761343	55.7	86.4%	17.5	79%
G6PD	NM_000402	10	X	153760781	153761017	102.7	82.2%	16.4	75%
G6PD	NM_000402	11	X	153760600	153760677	152.0	78.5%	15.2	67%
G6PD	NM_000402	12	X	153760402	153760495	102.2	61.4%	12.1	56%
G6PD	NM_000402	13	X	153760214	153760305	37.9	31.9%	7.7	27%
HLA-B	NM_005514	1	6	31324862	31324935	131.9	65.5%	12.5	56%
HLA-B	NM_005514	2	6	31324464	31324734	86.5	60.1%	11.2	51%
HLA-B	NM_005514	3	6	31323943	31324219	46.8	65.3%	12.0	56%

HLA-B	NM_005514	4	6	31323093	31323369	112.8	100%	31.7	100%
HLA-B	NM_005514	5	6	31322883	31323000	72.9	100%	30.1	100%
HLA-B	NM_005514	6	6	31322409	31322442	87.9	100%	25.3	100%
HLA-B	NM_005514	7	6	31322259	31322303	53.3	89.3%	15.4	83%
IFNL3	NM_172139	1	19	39735427	39735607	373.2	99.4%	28.6	98%
IFNL3	NM_172139	2	19	39735056	39735134	142.3	98.5%	23.7	100%
IFNL3	NM_172139	3	19	39734647	39734797	135.4	97.0%	24.0	95%
IFNL3	NM_172139	4	19	39734463	39734547	161.4	90.5%	23.3	87%
IFNL3	NM_172139	5	19	39734271	39734370	133.7	100%	27.7	100%
SLCO1B1	NM_006446	1	12	21294508	21294592	42.0	100%	40.4	100%
SLCO1B1	NM_006446	2	12	21325583	21325725	58.5	100%	39.7	100%
SLCO1B1	NM_006446	3	12	21327510	21327643	35.8	100%	35.1	100%
SLCO1B1	NM_006446	4	12	21329709	21329831	43.6	100%	40.4	100%
SLCO1B1	NM_006446	5	12	21331509	21331656	90.5	100%	38.5	100%
SLCO1B1	NM_006446	6	12	21331855	21331954	78.1	100%	38.6	100%
SLCO1B1	NM_006446	7	12	21349879	21350122	21.5	95.9%	39.2	100%
SLCO1B1	NM_006446	8	12	21353441	21353606	48.5	100%	41.3	100%
SLCO1B1	NM_006446	9	12	21355424	21355620	37.8	100%	39.0	100%
SLCO1B1	NM_006446	10	12	21358801	21358967	40.5	100%	39.3	100%
SLCO1B1	NM_006446	11	12	21370052	21370237	36.1	100%	40.2	100%
SLCO1B1	NM_006446	12	12	21375233	21375298	28.7	91.7%	15.9	92%
SLCO1B1	NM_006446	13	12	21377655	21377773	63.3	100%	36.6	100%
SLCO1B1	NM_006446	14	12	21391912	21392123	63.6	100%	40.5	100%
TPMT	NM_000367	1	6	18149218	18149358	78.3	100%	37.0	100%
TPMT	NM_000367	2	6	18148053	18148146	54.8	100%	41.3	100%
TPMT	NM_000367	3	6	18143826	18143959	50.3	100%	36.9	100%
TPMT	NM_000367	4	6	18139895	18139948	70.6	100%	38.1	100%
TPMT	NM_000367	5	6	18139193	18139268	51.5	100%	43.1	100%
TPMT	NM_000367	6	6	18134034	18134120	67.2	100%	41.3	100%
TPMT	NM_000367	7	6	18132363	18132408	50.9	100%	41.4	100%
TPMT	NM_000367	8	6	18130898	18131011	82.2	100%	42.3	100%
UGT1A1	NM_000463	1	2	234668933	234669797	67.0	100%	32.2	100%
VKORC1	NM_024006	1	16	31105877	31106050	60.6	80.1%	17.1	76%
VKORC1	NM_024006	2	16	31104632	31104742	15.5	96.8%	21.0	98%
VKORC1	NM_024006	3	16	31102454	31102663	119.3	100%	31.3	100%

Supplemental Table 6. Coding variants discovered by WES or WGS that were not included among CPIC important variants

6A. Coding variants discovered by WES that were not included among CPIC important variants. ExonicFunc.refGene and AA.Change (amino acid substitution) are based on annotation from Refseq release 69 (genome assembly GRCh37/hg19) ; snp138 provides the rs ID number for each variant based on build 138 of dbSNP; ExAC.maf is the minor allele frequency among all samples (multiple races) based on http://exac.broadinstitute.org/ (version 0.3); CADD Score is the estimated Combined Annotation Dependent Depletion score based on http://cadd.gs.washington.edu/ (v1.3), higher CADD score indicate possible damaging variants.

Gene refGene	chr.pos	Ref	Alt	ExonicFunc.refGene	AA.Change	snp138	ExAC.maf	CADD Score
CFTR	chr7:117149143	C	T	nonsynonymous SNV	p.R74W	rs115545701	0.001723	19.66
CFTR	chr7:117149147	G	A	nonsynonymous SNV	p.R75Q	rs1800076	0.01536	34
CFTR	chr7:117149189	A	G	nonsynonymous SNV	p.Y89C		8.26E-06	19.35
CFTR	chr7:117171029	G	A	nonsynonymous SNV	p.R117H	rs78655421	0.001537	22.4
CFTR	chr7:117171097	C	T	nonsynonymous SNV	p.P140S	rs145900055	6.68E-05	29.4
CFTR	chr7:117171122	T	C	nonsynonymous SNV	p.I148T	rs35516286	0.001871	25
CFTR	chr7:117174330	A	G	nonsynonymous SNV	p.T164A	rs200885306	2.65E-05	10.84
CFTR	chr7:117174349	G	A	nonsynonymous SNV	p.R170H	rs1800079	0.000481	23.7
CFTR	chr7:117174411	T	G	nonsynonymous SNV	p.F191V	rs141482808	8.46E-06	23.5
CFTR	chr7:117176664	T	C	nonsynonymous SNV	p.I269T	rs201016820	8.87E-05	22.6
CFTR	chr7:117176711	A	T	nonsynonymous SNV	p.I285F	rs151073129	0.0004093	23.2
CFTR	chr7:117180173	C	T	nonsynonymous SNV	p.R297W		8.41E-05	20.5
CFTR	chr7:117180324	G	C	nonsynonymous SNV	p.R347P	rs77932196	8.24E-06	27.3
CFTR	chr7:117180338	C	T	nonsynonymous SNV	p.R352W	rs193922497	0.0004698	20.9
CFTR	chr7:117199533	G	A	nonsynonymous SNV	p.V470M	rs213950	0.4829	2.095
CFTR	chr7:117199562	G	C	nonsynonymous SNV	p.E479D		2.47E-05	14.17
CFTR	chr7:117199648	T	G	nonsynonymous SNV	p.F508C	rs74571530	0.0009611	22.4
CFTR	chr7:117199663	A	G	nonsynonymous SNV	p.D513G		NA	21.5
CFTR	chr7:117227832	G	T	stopgain SNV	p.G542X	rs113993959	0.0002649	29.2
CFTR	chr7:117227874	A	G	nonsynonymous SNV	p.I556V	rs75789129	0.00291	12.91
CFTR	chr7:117230454	G	C	nonsynonymous SNV	p.G576A	rs1800098	0.005167	15.81
CFTR	chr7:117232086	G	A	nonsynonymous SNV	p.G622D	rs121908759	0.0001335	26
CFTR	chr7:117232223	C	T	nonsynonymous SNV	p.R668C	rs1800100	0.006151	16.66
CFTR	chr7:117232266	-	A	frameshift insertion	p.T682fs		5.85E-05	NA
CFTR	chr7:117232300	T	G	nonsynonymous SNV	p.F693L	rs145540754	0.0001088	8.771
CFTR	chr7:117232374	C	G	nonsynonymous SNV	p.P718R	rs142432539	2.49E-05	9.041
CFTR	chr7:117232394	G	A	nonsynonymous SNV	p.E725K	rs199791061	9.12E-05	35
CFTR	chr7:117232481	G	A	nonsynonymous SNV	p.V754M	rs150157202	0.001954	0.769
CFTR	chr7:117232642	A	G	nonsynonymous SNV	p.I807M	rs1800103	0.0007237	17.82
CFTR	chr7:117232671	G	T	nonsynonymous SNV	p.G817V	rs148604667	8.15E-05	0.227
CFTR	chr7:117234995	T	G	nonsynonymous SNV	p.F834L	rs200735475	0.0002558	8.424
CFTR	chr7:117243784	G	A	nonsynonymous SNV	p.M952I		3.30E-05	25.6
CFTR	chr7:117250575	G	C	nonsynonymous SNV	p.L997F	rs1800111	0.002104	16.06
CFTR	chr7:117251649	T	G	nonsynonymous SNV	p.F1052V		0.0006578	25.1
CFTR	chr7:117251700	G	A	nonsynonymous SNV	p.G1069R	rs200321110	0.0002335	11.74
CFTR	chr7:117251704	G	A	nonsynonymous SNV	p.R1070Q	rs78769542	0.0008077	34
CFTR	chr7:117251751	A	T	nonsynonymous SNV	p.T1086S	rs373043500	NA	22.4
CFTR	chr7:117254753	G	C	nonsynonymous SNV	p.D1152H		0.0002644	22.8
CFTR	chr7:117267592	G	T	nonsynonymous SNV	p.R1162L	rs1800120	0.0006808	32

CFTR	chr7:117267779	T	A	nonsynonymous SNV	p.N1224K	rs371475225	0.0002154	5.556
CFTR	chr7:117267812	T	G	nonsynonymous SNV	p.S1235R	rs34911792	0.004992	12.5
CFTR	chr7:117282582	G	A	nonsynonymous SNV	p.D1270N	rs11971167	0.001463	33
CFTR	chr7:117305608	A	C	nonsynonymous SNV	p.Q1411P	rs150177304	1.66E-05	19.42
CFTR	chr7:117307052	G	A	nonsynonymous SNV	p.D1445N	rs148783445	0.0004711	32
CYP2C19	chr10:96522517	A	C	nonsynonymous SNV	p.I19L	rs17882687	0.002127	0.012
CYP2C19	chr10:96522547	C	T	nonsynonymous SNV	p.L29F		4.95E-05	2.751
CYP2C19	chr10:96534863	C	T	nonsynonymous SNV	p.R73C	rs145328984	0.0002553	12.9
CYP2C19	chr10:96534887	G	A	nonsynonymous SNV	p.E81K	rs149072229	0.0003871	6.735
CYP2C19	chr10:96534922	G	C	nonsynonymous SNV	p.E92D	rs17878459	0.0236	2.054
CYP2C19	chr10:96535180	A	C	nonsynonymous SNV	p.E122A	rs17885179	0.0009637	17.51
CYP2C19	chr10:96535246	G	A	nonsynonymous SNV	p.R144H	rs17884712	0.001079	17.88
CYP2C19	chr10:96540292	C	T	nonsynonymous SNV	p.A173V	rs61311738	0.005818	16.17
CYP2C19	chr10:96541615	C	T	nonsynonymous SNV	p.P227L	rs6413438	0.000448	17.99
CYP2C19	chr10:96602623	G	A	nonsynonymous SNV	p.V331I	rs3758581	0.06242	0.001
CYP2C19	chr10:96609752	C	T	nonsynonymous SNV	p.R410C	rs17879685	0.001517	4.573
CYP2C19	chr10:96609793	C	A	nonsynonymous SNV	p.N423K		NA	5.789
CYP2C19	chr10:96612493	A	T	nonsynonymous SNV	p.K432I	rs146991374	0.000264	12.77
CYP2C9	chr10:96698447	C	A	nonsynonymous SNV	p.S3Y		1.65E-05	7.786
CYP2C9	chr10:96701988	G	T	nonsynonymous SNV	p.R124L	rs12414460	4.95E-05	23
CYP2C9	chr10:96702011	C	T	nonsynonymous SNV	p.R132W	rs199523631	0.0002804	18.39
CYP2C9	chr10:96707581	A	G	nonsynonymous SNV	p.N176S		NA	19.94
CYP2C9	chr10:96708974	A	G	nonsynonymous SNV	p.H251R	rs2256871	0.006715	23.9
CYP2C9	chr10:96741056	G	A	nonsynonymous SNV	p.D360N		8.25E-06	9.298
CYP2D6	chr22:42522601	T	C	nonsynonymous SNV	p.Y490C	rs199722016	0.000394	11.92
CYP2D6	chr22:42522650	G	A	nonsynonymous SNV	p.R474W		3.85E-05	16.17
CYP2D6	chr22:42523532	-	CA	frameshift insertion	p.Q364fs		0.0001986	NA
CYP2D6	chr22:42523568	G	C	nonsynonymous SNV	p.H352D		NA	5.746
CYP2D6	chr22:42523613	C	T	nonsynonymous SNV	p.D337N	rs78209835	0.003382	13.7
CYP2D6	chr22:42524219	G	T	nonsynonymous SNV	p.P267H	rs148769737	0.0002567	14.57
CYP2D6	chr22:42524310	C	A	nonsynonymous SNV	p.A237S	rs28371717	0.00754	11.43
CYP2D6	chr22:42525077	C	T	nonsynonymous SNV	p.E155K	rs28371710	0.003873	10.34
CYP2D6	chr22:42525778	G	T	nonsynonymous SNV	p.P105H	rs147149624	8.90E-06	11.57
CYP2D6	chr22:42525801	G	C	nonsynonymous SNV	p.D97E	rs76802407	0.0002136	14.29
CYP2D6	chr22:42525862	G	-	frameshift deletion	p.P77fs		3.77E-05	NA
CYP2D6	chr22:42526664	C	T	nonsynonymous SNV	p.G44S	rs146838345	9.68E-06	21.9
CYP2D6	chr22:42526712	G	A	nonsynonymous SNV	p.R28C	rs138100349	0.003579	14.77
CYP2D6	chr22:42526717	C	T	nonsynonymous SNV	p.R26H	rs28371696	0.003407	14.41
CYP2D6	chr22:42526763	C	T	nonsynonymous SNV	p.V11M	rs72552262	0.05301	3.418
CYP2D6	chr22:42526775	C	T	nonsynonymous SNV	p.V7M	rs72549358	0.00328	1.817
CYP3A5	chr7:99245981	T	C	nonsynonymous SNV	p.K486E		8.25E-06	14.32
CYP3A5	chr7:99247736	AC	A	frameshift deletion	p.V458fs		NA	NA
CYP3A5	chr7:99250236	G	T	nonsynonymous SNV	p.T398N	rs28365083	0.003535	5.859
CYP3A5	chr7:99261610	C	T	nonsynonymous SNV	p.R260H	rs376773432	6.61E-05	11
CYP3A5	chr7:99270222	G	T	nonsynonymous SNV	p.S100Y	rs41279857	0.00159	13.45
CYP3A5	chr7:99273810	-	C	frameshift insertion	p.G31fs	rs200579169	0.00747	NA
CYP3A5	chr7:99273815	G	A	nonsynonymous SNV	p.H30Y	rs28383468	0.007471	0.239
DPYD	chr1:97544543	G	T	nonsynonymous SNV	p.P1023T	rs114096998	0.003428	13.21
DPYD	chr1:97544549	C	G	nonsynonymous SNV	p.V1021L	rs148799944	7.42E-05	11.25
DPYD	chr1:97544558	G	C	nonsynonymous SNV	p.P1018A		NA	17.5
DPYD	chr1:97544695	T	C	nonsynonymous SNV	p.Q972R	rs145529148	0.000239	8.974
DPYD	chr1:97564058	A	G	nonsynonymous SNV	p.I918T		1.65E-05	9.733
DPYD	chr1:97700493	G	C	nonsynonymous SNV	p.P786R		8.27E-06	23.8
DPYD	chr1:97770919	A	C	nonsynonymous SNV	p.V732G	rs60511679	0.0001981	16.04
DPYD	chr1:97770920	C	T	nonsynonymous SNV	p.V732I	rs1801160	0.04647	23.5

DPYD	chr1:97847962	G	A	nonsynonymous SNV	p.A654V		NA	11.37
DPYD	chr1:97848017	T	G	nonsynonymous SNV	p.I636L	rs55971861	0.0001483	12
DPYD	chr1:97915655	C	T	nonsynonymous SNV	p.C622Y	rs201433243	8.24E-05	16.67
DPYD	chr1:97981395	T	C	nonsynonymous SNV	p.I543V	rs1801159	0.193	12.85
DPYD	chr1:97981407	C	T	nonsynonymous SNV	p.G539R	rs142619737	0.0002568	18.57
DPYD	chr1:97981421	C	T	nonsynonymous SNV	p.S534N	rs1801158	0.01416	18.66
DPYD	chr1:98015193	C	T	nonsynonymous SNV	p.V483I	rs141439344	8.25E-05	6.853
DPYD	chr1:98015282	G	C	nonsynonymous SNV	p.P453R	rs144395748	0.0001268	23.4
DPYD	chr1:98039437	C	T	nonsynonymous SNV	p.M406I	rs61622928	0.006046	10.26
DPYD	chr1:98144726	T	C	nonsynonymous SNV	p.K259E	rs45589337	0.01022	14.46
DPYD	chr1:98164983	A	T	nonsynonymous SNV	p.C202S		NA	25
DPYD	chr1:98165030	T	C	nonsynonymous SNV	p.Y186C	rs115232898	0.00234	18.78
DPYD	chr1:98165091	T	C	nonsynonymous SNV	p.M166V	rs2297595	0.08637	18.97
DPYD	chr1:98186465	G	C	nonsynonymous SNV	p.F167L	rs72977734	0.001666	11.22
DPYD	chr1:98187098	T	C	nonsynonymous SNV	p.N151D	rs200562975	0.001115	15.03
DPYD	chr1:98187190	T	C	nonsynonymous SNV	p.N120S		8.28E-06	25.5
DPYD	chr1:98293683	G	A	stopgain SNV	p.R74X	rs189768576	0.0001077	35
DPYD	chr1:98293709	G	A	nonsynonymous SNV	p.T65M		6.63E-05	17.6
DPYD	chr1:98386472	G	A	nonsynonymous SNV	p.P3S		2.37E-05	11.67
G6PD	chrX:153760649	C	G	nonsynonymous SNV	p.R439P	rs137852337	NA	24.3
G6PD	chrX:153761240	A	G	nonsynonymous SNV	p.L323P	rs76723693	0.0006526	12.79
G6PD	chrX:153761337	C	T	nonsynonymous SNV	p.V291M	rs137852327	0.0002542	18.56
G6PD	chrX:153763402	C	T	nonsynonymous SNV	p.E156K	rs137852313	0.0003083	0.012
IFNL3	chr19:39734325	G	A	nonsynonymous SNV	p.R180C	rs150748693	0.011	15.67
IFNL3	chr19:39734465	T	G	nonsynonymous SNV	p.K164T		NA	15.97
IFNL3	chr19:39734656	G	A	nonsynonymous SNV	p.R134W	rs139176035	0.0002313	7.516
IFNL3	chr19:39734673	T	C	nonsynonymous SNV	p.H128R	rs144005418	0.0002556	13.46
IFNL3	chr19:39734734	T	C	nonsynonymous SNV	p.T108A	rs148543092	0.006251	1.964
IFNL3	chr19:39734754	G	A	nonsynonymous SNV	p.T101M	rs145428712	0.001635	9.211
IFNL3	chr19:39734773	C	G	nonsynonymous SNV	p.E95Q	rs147679979	0.002381	10.53
IFNL3	chr19:39735517	G	A	nonsynonymous SNV	p.L31F	rs138893424	0.01256	9.03
SLCO1B1	chr12:21325668	C	T	nonsynonymous SNV	p.R57W	rs139257324	0.0001077	16.43
SLCO1B1	chr12:21325714	G	A	nonsynonymous SNV	p.S72N		8.77E-06	17.4
SLCO1B1	chr12:21331554	A	G	nonsynonymous SNV	p.M176V		NA	0.132
SLCO1B1	chr12:21331860	A	G	nonsynonymous SNV	p.I211M	rs201722521	0.004007	14.53
SLCO1B1	chr12:21331891	A	G	nonsynonymous SNV	p.I222V	rs79135870	0.0009899	2.147
SLCO1B1	chr12:21349885	A	G	nonsynonymous SNV	p.I245V	rs11045852	0.007622	0.162
SLCO1B1	chr12:21349910	G	A	nonsynonymous SNV	p.R253Q	rs11045853	0.0004202	10.34
SLCO1B1	chr12:21355487	T	G	nonsynonymous SNV	p.F400V		NA	14.53
SLCO1B1	chr12:21355489	C	G	nonsynonymous SNV	p.F400L	rs59113707	0.004341	9.49
SLCO1B1	chr12:21355598	G	A	nonsynonymous SNV	p.G437R	rs142965323	0.0002003	14.27
SLCO1B1	chr12:21358965	A	G	nonsynonymous SNV	p.I499V	rs74064213	0.002482	1.35
SLCO1B1	chr12:21375289	C	T	stopgain SNV	p.R580X	rs71581941	0.001639	37
SLCO1B1	chr12:21391951	CATCA	-	frameshift deletion	p.635_636del		NA	NA
SLCO1B1	chr12:21392079	C	T	nonsynonymous SNV	p.H678Y	rs200995543	0.0002487	4.423
SLCO1B1	chr12:21392092	C	T	nonsynonymous SNV	p.S682F	rs140790673	0.0001077	5.851
TPMT	chr6:18130925	T	C	nonsynonymous SNV	p.K238E	rs150900439	2.48E-05	15.16
TPMT	chr6:18130960	C	T	nonsynonymous SNV	p.R226Q	rs139392616	4.13E-05	14.53
TPMT	chr6:18134078	C	A	nonsynonymous SNV	p.Q179H	rs6921269	0.001929	8.314
UGT1A1	chr2:234669058	G	A	nonsynonymous SNV	p.S42N		2.48E-05	14.98
UGT1A1	chr2:234669094	G	T	nonsynonymous SNV	p.G54V		8.24E-06	33
UGT1A1	chr2:234669144	G	A	nonsynonymous SNV	p.G71R	rs4148323	0.02066	12.79
UGT1A1	chr2:234669256	G	A	nonsynonymous SNV	p.R108H		NA	15.4
UGT1A1	chr2:234669259	T	C	nonsynonymous SNV	p.V109A	rs144217005	0.0002969	14.38
UGT1A1	chr2:234669405	C	T	nonsynonymous SNV	p.P158S		NA	8.91

UGT1A1	chr2:234669681	T	C	nonsynonymous SNV	p.S250P	rs57307513	0.0002718	9.383
VKORC1	chr16:31102589	G	A	nonsynonymous SNV	p.P83L	rs7200749	0.01909	21.4
VKORC1	chr16:31104714	G	A	nonsynonymous SNV	p.H68Y	rs145273772	0.0004706	6.188
VKORC1	chr16:31105945	C	A	nonsynonymous SNV	p.D36Y	rs61742245	0.002159	17.49

Supplemental Table 6B. Coding variants discovered by WGS that were not included among CPIC important variants.

Gene refGene	chr.pos	Ref	Alt	ExonicFunc.refGene	AA Change	snp138	ExAC.maf	CADD Score
CFTR	chr7:117144344	C	T	nonsynonymous SNV	p.R31C	rs1800073	0.001679	25.6
CFTR	chr7:117149143	C	T	nonsynonymous SNV	p.R74W	rs115545701	0.001723	19.66
CFTR	chr7:117149144	G	A	nonsynonymous SNV	p.R74Q	rs142540482	0.0001897	15.06
CFTR	chr7:117149147	G	A	nonsynonymous SNV	p.R75Q	rs1800076	0.01536	34
CFTR	chr7:117171029	G	A	nonsynonymous SNV	p.R117H	rs78655421	0.001537	22.4
CFTR	chr7:117171122	T	C	nonsynonymous SNV	p.I148T	rs35516286	0.001871	25
CFTR	chr7:117180174	G	A	nonsynonymous SNV	p.R297Q	rs143486492	0.0004948	20.8
CFTR	chr7:117188736	C	A	nonsynonymous SNV	p.N417K	rs4727853	NA	0.059
CFTR	chr7:117188750	C	T	nonsynonymous SNV	p.S422F	rs201880593	NA	3.962
CFTR	chr7:117188797	A	G	nonsynonymous SNV	p.T438A	rs201434579	NA	10.88
CFTR	chr7:117188877	G	T	nonsynonymous SNV	p.K464N		NA	18.01
CFTR	chr7:117199533	G	A	nonsynonymous SNV	p.V470M	rs213950	0.4829	2.095
CFTR	chr7:117250575	G	C	nonsynonymous SNV	p.L997F	rs1800111	0.002104	16.06
CFTR	chr7:117267812	T	G	nonsynonymous SNV	p.S1235R	rs34911792	0.004992	12.5
CFTR	chr7:117282582	G	A	nonsynonymous SNV	p.D1270N	rs11971167	0.001463	33
CYP2C19	chr10:96534922	G	C	nonsynonymous SNV	p.E92D	rs17878459	0.0236	2.054
CYP2C19	chr10:96535264	G	A	nonsynonymous SNV	p.R150H	rs58973490	0.002652	4.412
CYP2C19	chr10:96602623	G	A	nonsynonymous SNV	p.V331I	rs3758581	0.06242	0.001
CYP2C19	chr10:96602635	C	T	nonsynonymous SNV	p.R335W		4.94E-05	13.06
CYP2C19	chr10:96602674	A	T	nonsynonymous SNV	p.T348S		8.24E-06	17.02
CYP2C19	chr10:96609752	C	T	nonsynonymous SNV	p.R410C	rs17879685	0.001517	4.573
CYP2C9	chr10:96708974	A	G	nonsynonymous SNV	p.H251R	rs2256871	0.006715	23.9
CYP2C9	chr10:96740948	CA	C	frameshift deletion	p.Q324fs		3.30E-05	NA
CYP2D6	chr22:42522698	T	C	nonsynonymous SNV	p.T407A	rs375715419	NA	16.55
CYP2D6	chr22:42523505	C	T	nonsynonymous SNV	p.G322S	rs150552908	NA	11.82
CYP2D6	chr22:42523514	C	T	nonsynonymous SNV	p.V319I	rs61745683	NA	6.769
CYP2D6	chr22:42523528	C	T	nonsynonymous SNV	p.R314H	rs1058172	0.1211	34
CYP2D6	chr22:42523597	A	G	nonsynonymous SNV	p.V291A		NA	3.038
CYP2D6	chr22:42523613	C	T	nonsynonymous SNV	p.D286N	rs78209835	0.003382	13.7
CYP2D6	chr22:42523636	C	A	nonsynonymous SNV	p.R278L	rs3915951	NA	14.89
CYP2D6	chr22:42524219	G	T	nonsynonymous SNV	p.P216H	rs148769737	0.0002567	14.57
CYP2D6	chr22:42524310	C	A	nonsynonymous SNV	p.A186S	rs28371717	0.00754	11.43
CYP2D6	chr22:42524316	C	T	nonsynonymous SNV	p.A184T		NA	13.98
CYP2D6	chr22:42524327	A	G	nonsynonymous SNV	p.L180P	rs17002853	0.0002071	12.07
CYP2D6	chr22:42524817	C	T	nonsynonymous SNV	p.G161E	rs139779104	0.007325	3.567
CYP2D6	chr22:42524838	A	G	nonsynonymous SNV	p.L154P		NA	17.12

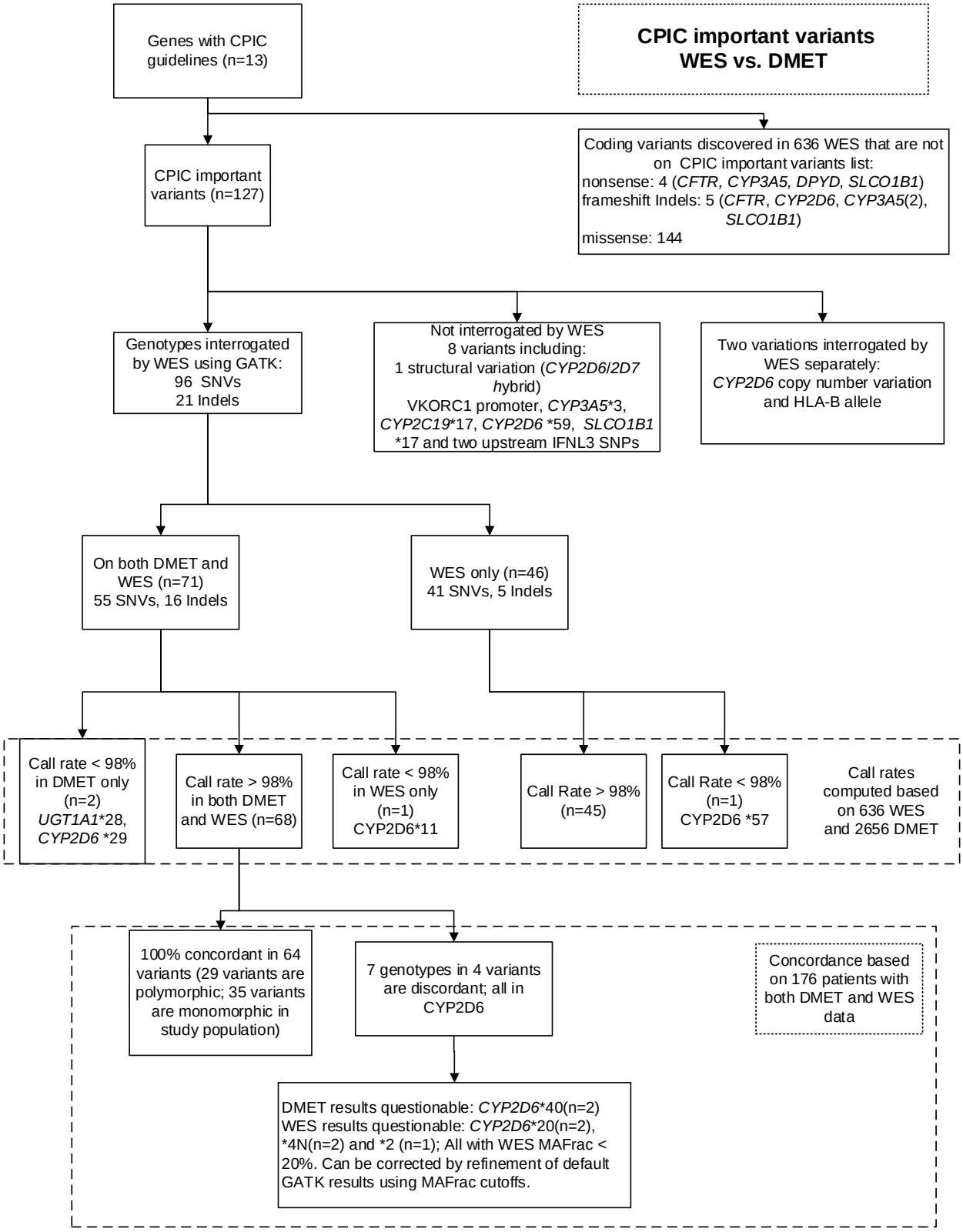
CYP2D6	chr22:42525077	C	T	nonsynonymous SNV	p.E155K	rs28371710	0.003873	10.34
CYP2D6	chr22:42525089	G	C	nonsynonymous SNV	p.Q151E	rs78482768	0.002392	0.009
CYP2D6	chr22:42525811	T	C	nonsynonymous SNV	p.H94R	rs28371704	NA	0.424
CYP2D6	chr22:42525821	G	T	nonsynonymous SNV	p.L91M	rs28371703	NA	14.36
CYP2D6	chr22:42526717	C	T	nonsynonymous SNV	p.R26H	rs28371696	0.003407	14.41
CYP2D6	chr22:42526763	C	T	nonsynonymous SNV	p.V11M	rs72552262	0.05301	3.418
CYP2D6	chr22:42526775	C	T	nonsynonymous SNV	p.V7M	rs72549358	0.00328	1.817
CYP3A5	chr7:99247736	AC	A	frameshift deletion	p.V458fs		0.00117	NA
CYP3A5	chr7:99269397	T	C	stoploss SNV	p.X141W	rs6977165	0.04571	0.019
DPYD	chr1:97544543	G	T	nonsynonymous SNV	p.P1023T	rs114096998	0.003428	13.21
DPYD	chr1:97770920	C	T	nonsynonymous SNV	p.V732I	rs1801160	0.04647	23.5
DPYD	chr1:97848017	T	G	nonsynonymous SNV	p.I636L	rs55971861	0.0001483	12
DPYD	chr1:97981395	T	C	nonsynonymous SNV	p.I543V	rs1801159	0.193	12.85
DPYD	chr1:97981421	C	T	nonsynonymous SNV	p.S534N	rs1801158	0.01416	18.66
DPYD	chr1:98165030	T	C	nonsynonymous SNV	p.Y186C	rs115232898	0.00234	18.78
DPYD	chr1:98165091	T	C	nonsynonymous SNV	p.M166V	rs2297595	0.08637	18.97
G6PD	chrX:153762615	G	C	nonsynonymous SNV	p.D224E	rs145247580	0.0004003	9.442
IFNL3	chr19:39734325	G	A	nonsynonymous SNV	p.R180C	rs150748693	0.011	15.67
IFNL3	chr19:39734352	C	T	nonsynonymous SNV	p.E171K	rs62120527	NA	15.48
IFNL3	chr19:39734490	G	A	nonsynonymous SNV	p.H156Y	rs139076671	NA	17.47
IFNL3	chr19:39735106	T	C	nonsynonymous SNV	p.K70R	rs8103142	0.2787	3.478
IFNL3	chr19:39735127	G	A	nonsynonymous SNV	p.S63L	rs140585624	0.0002665	14.46
IFNL3	chr19:39735517	G	A	nonsynonymous SNV	p.L31F	rs138893424	0.01256	9.03
IFNL3	chr19:39735520	C	A	nonsynonymous SNV	p.A30S		NA	8.855
IFNL3	chr19:39735549	C	G	nonsynonymous SNV	p.G20A	rs148017150	0.006512	11.73
SLCO1B1	chr12:21355489	C	G	nonsynonymous SNV	p.F400L	rs59113707	0.004341	9.49
UGT1A1	chr2:234669144	G	A	nonsynonymous SNV	p.G71R	rs4148323	0.02066	12.79
UGT1A1	chr2:234669441	T	C	nonsynonymous SNV	p.F170L		NA	16.07
VKORC1	chr16:31102589	G	A	nonsynonymous SNV	p.P83L	rs7200749	0.01909	21.4
VKORC1	chr16:31104720	C	T	nonsynonymous SNV	p.V66M	rs72547529	0.0002643	32

Supplemental Table 7. Number of coding variations observed in exomes of unrelated individuals (n=60,706) in CPIC important genes as reported by ExAC database (http://exac.broadinstitute.org/ version 0.3).

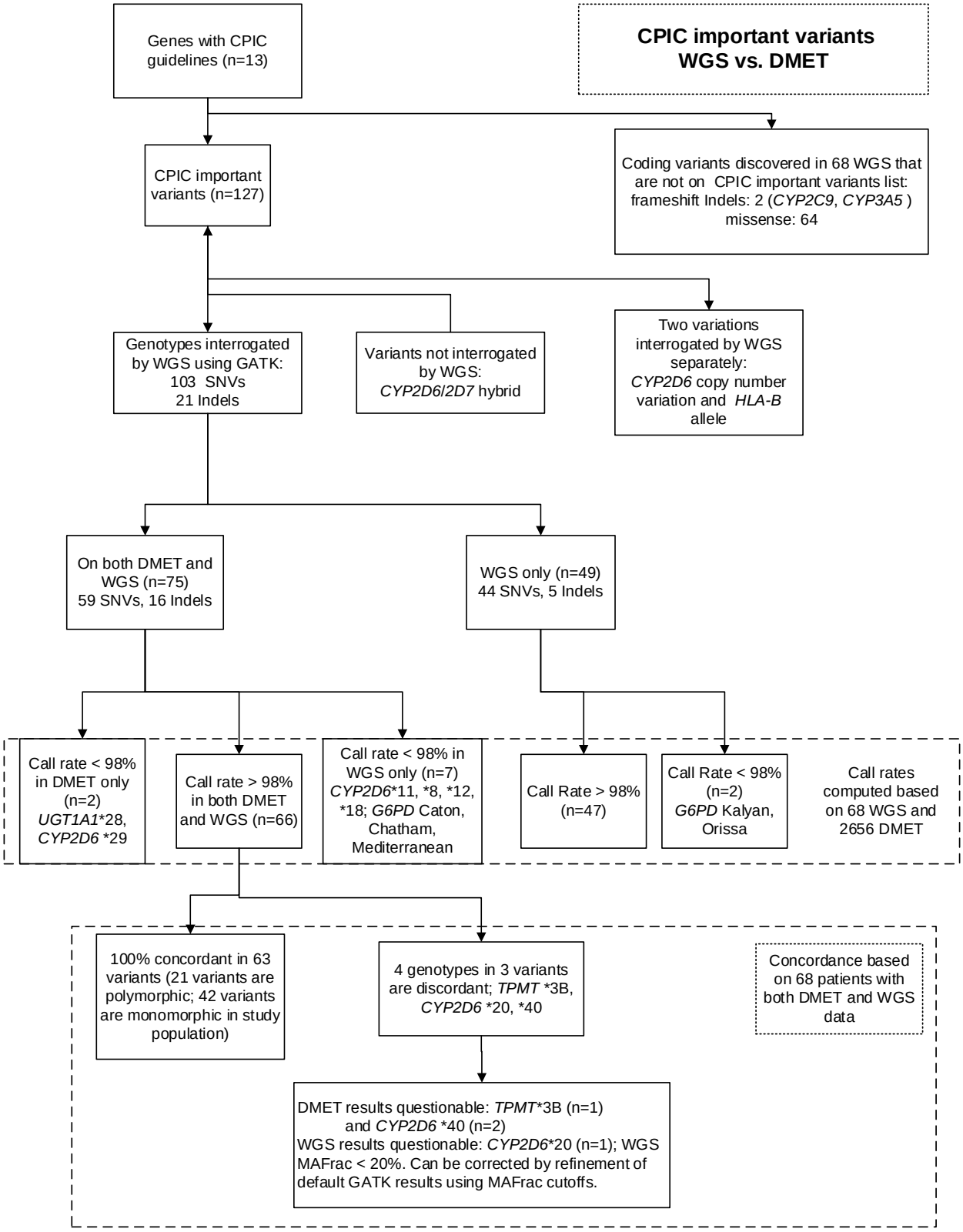
Listed are 12 CPIC important genes (excluding *HLA*-B) and all coding variants reported by ExAC, including CPIC important variants. Loss of function variants include "stop gained" and "frameshift" variants.

Gene	Base pairs of coding region	frameshift	inframe deletion	inframe insertion	initiator codon	missense	splice acceptor	splice donor	stop gained	stop lost	Total	Total (loss of function variants)	Sum of MAF for Loss of function variants
CFTR	4443	33	5	2	2	688	11	11	35		787	68	0.24%
CYP2C19	1473	9			2	258	6	3	7	1	286	16	0.58%
CYP2C9	1473	10			1	225	3	3	7		249	17	0.11%
CYP2D6	1494	11	4	2		246	1	1	13	1	279	24	2.30%
CYP3A5	1509	14	1	1	1	157	3	4	12	2	195	26	1.90%
DPYD	3078	13		1	1	393	5	8	11		432	24	0.05%
G6PD	1638	1				118		1	2		122	3	0.05%
IFNL3	1089	1	1		1	81	3	1	3		91	4	0.01%
SLCO1B1	591	19	2		2	278	1	10	16		328	35	0.23%
TPMT	2076	1			1	81	4	1	4		92	5	0.02%
UGT1A1	738	36	6		4	680	1	5	34		766	70	0.54%
VKORC1	864	3			1	127	1	1	6		139	9	0.03%
Total		151	19	6	16	3332	39	49	150	4	3766	301	6.05%

Supplemental Figure 1

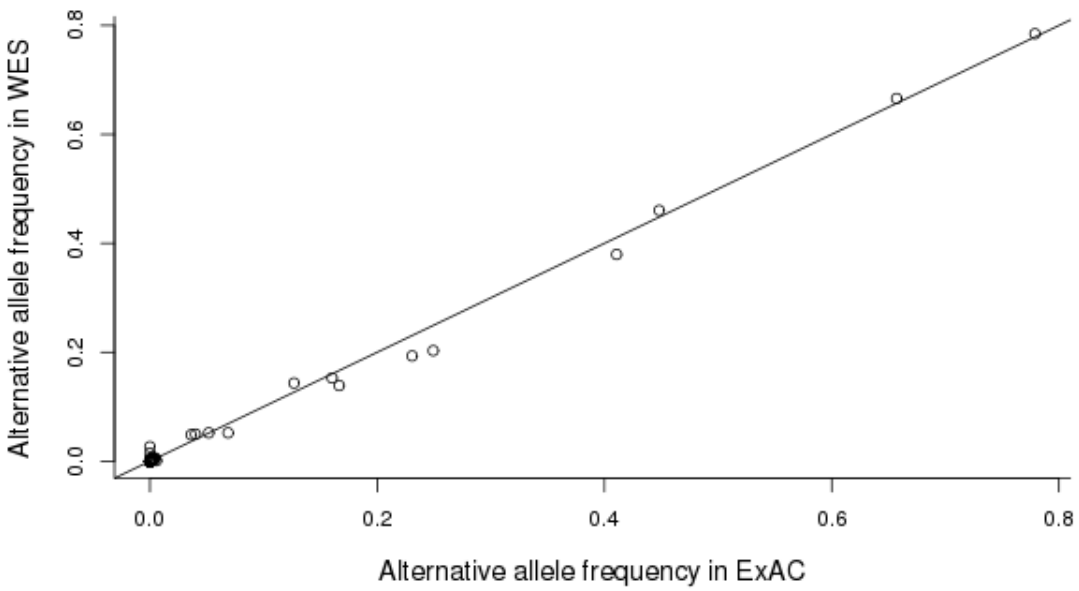


Supplemental Figure 2

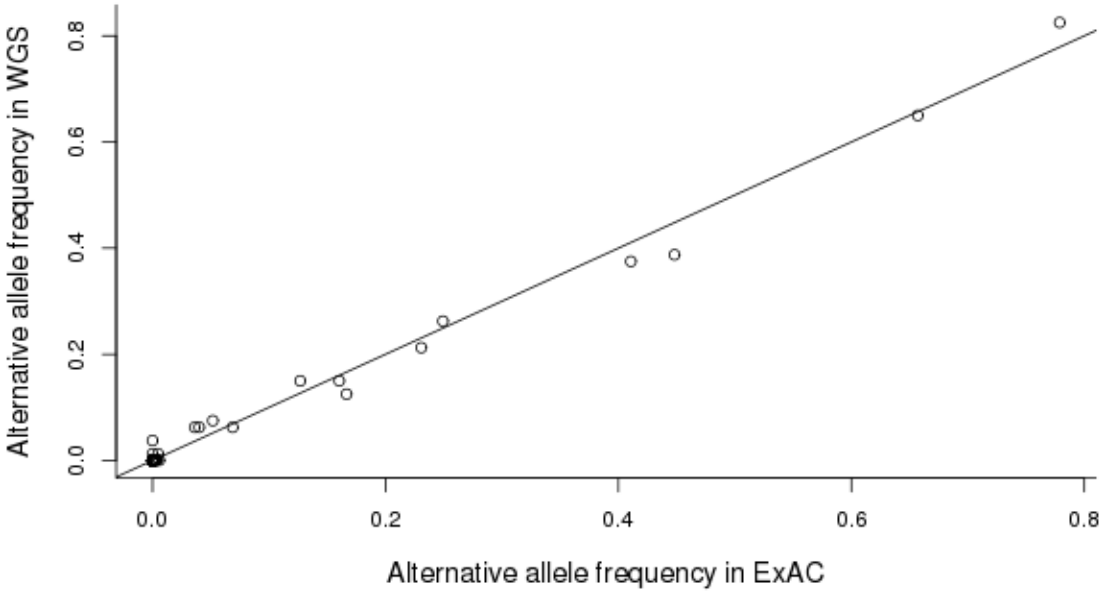


Supplemental Figure 3

A)

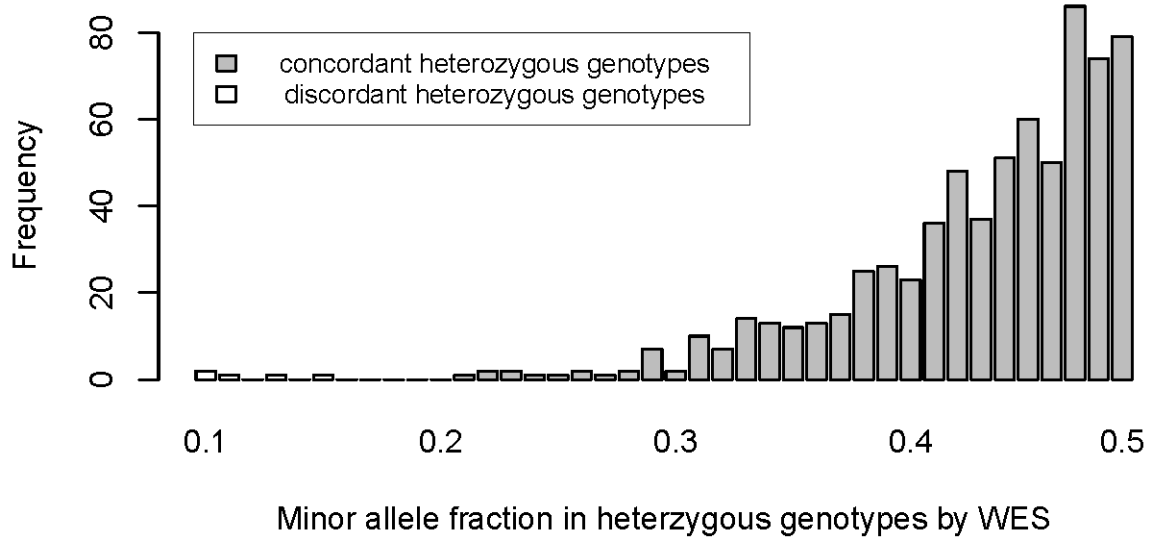


B)

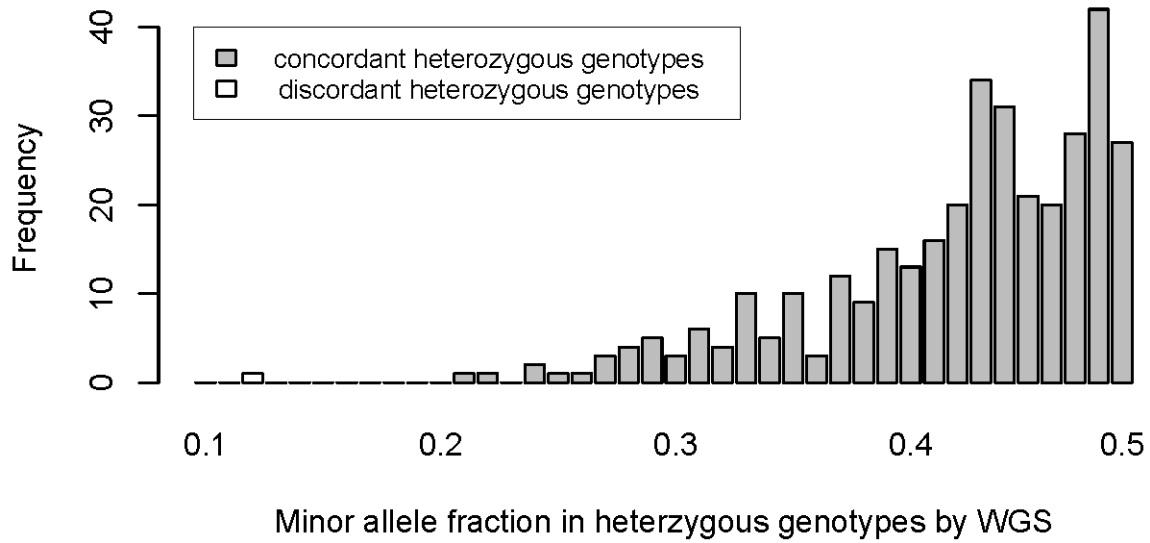


Supplemental Figure 4

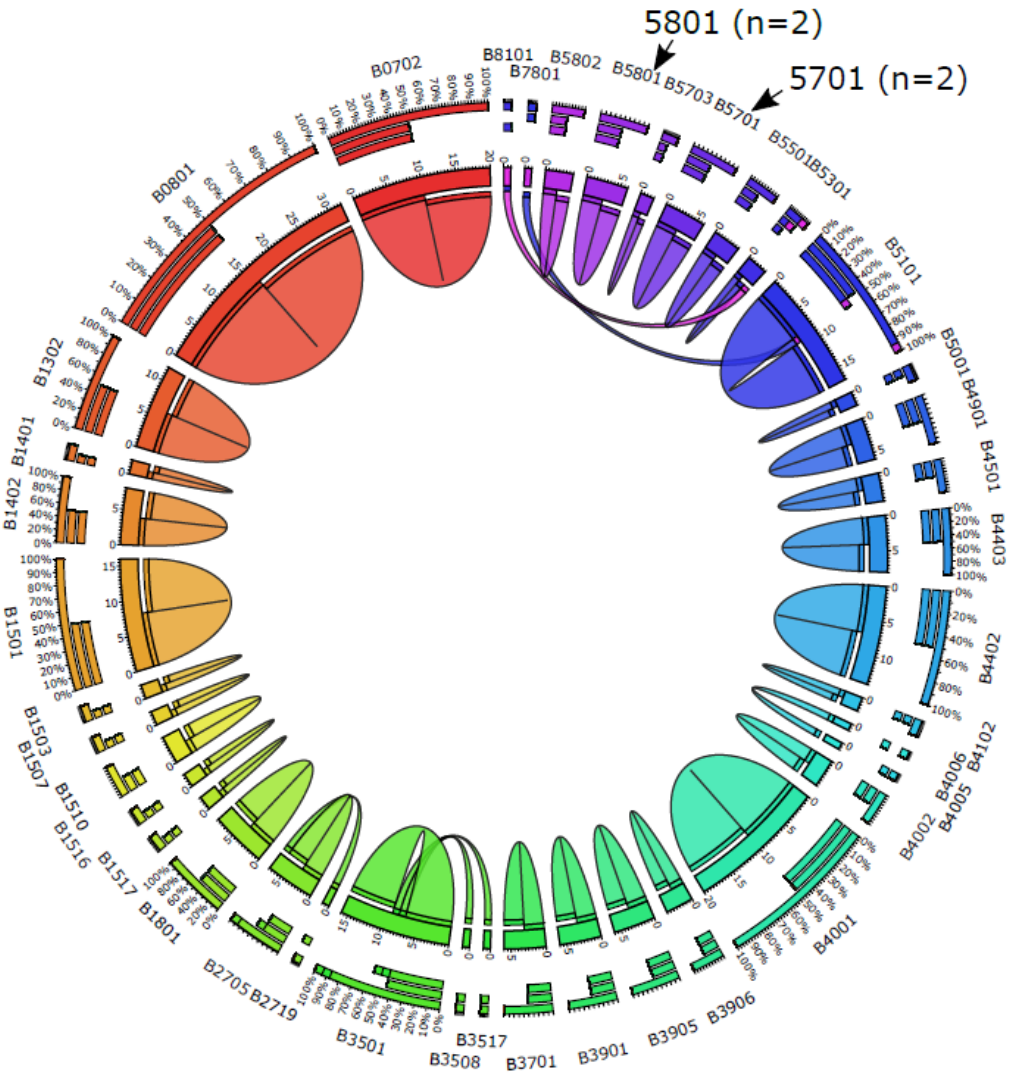
A)



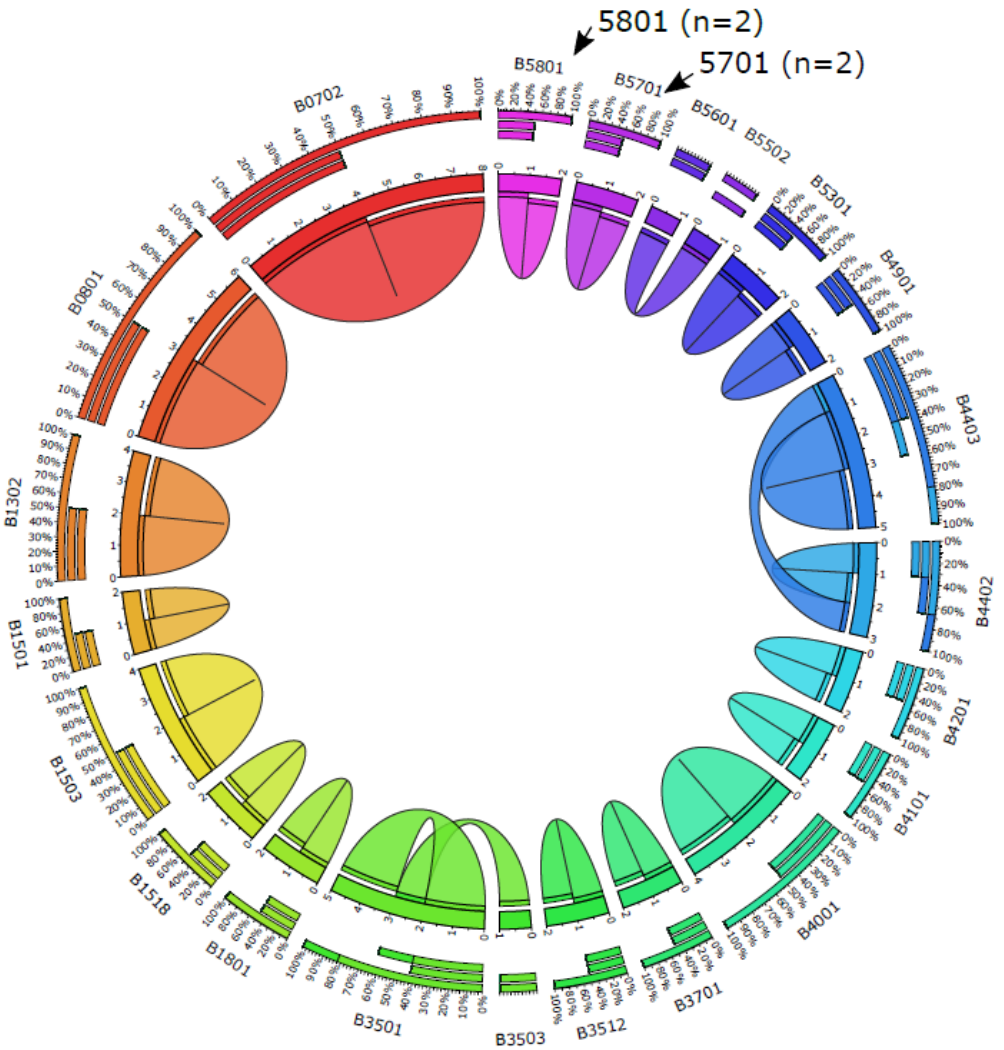
B)



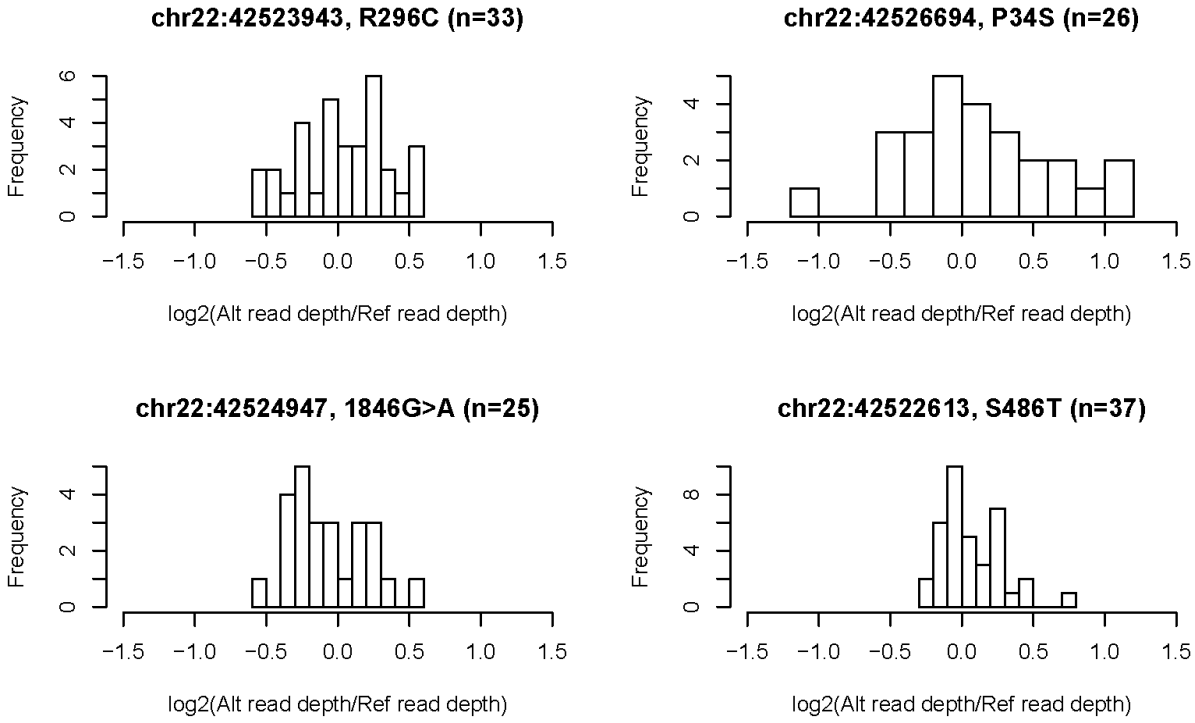
Supplemental Figure 5A



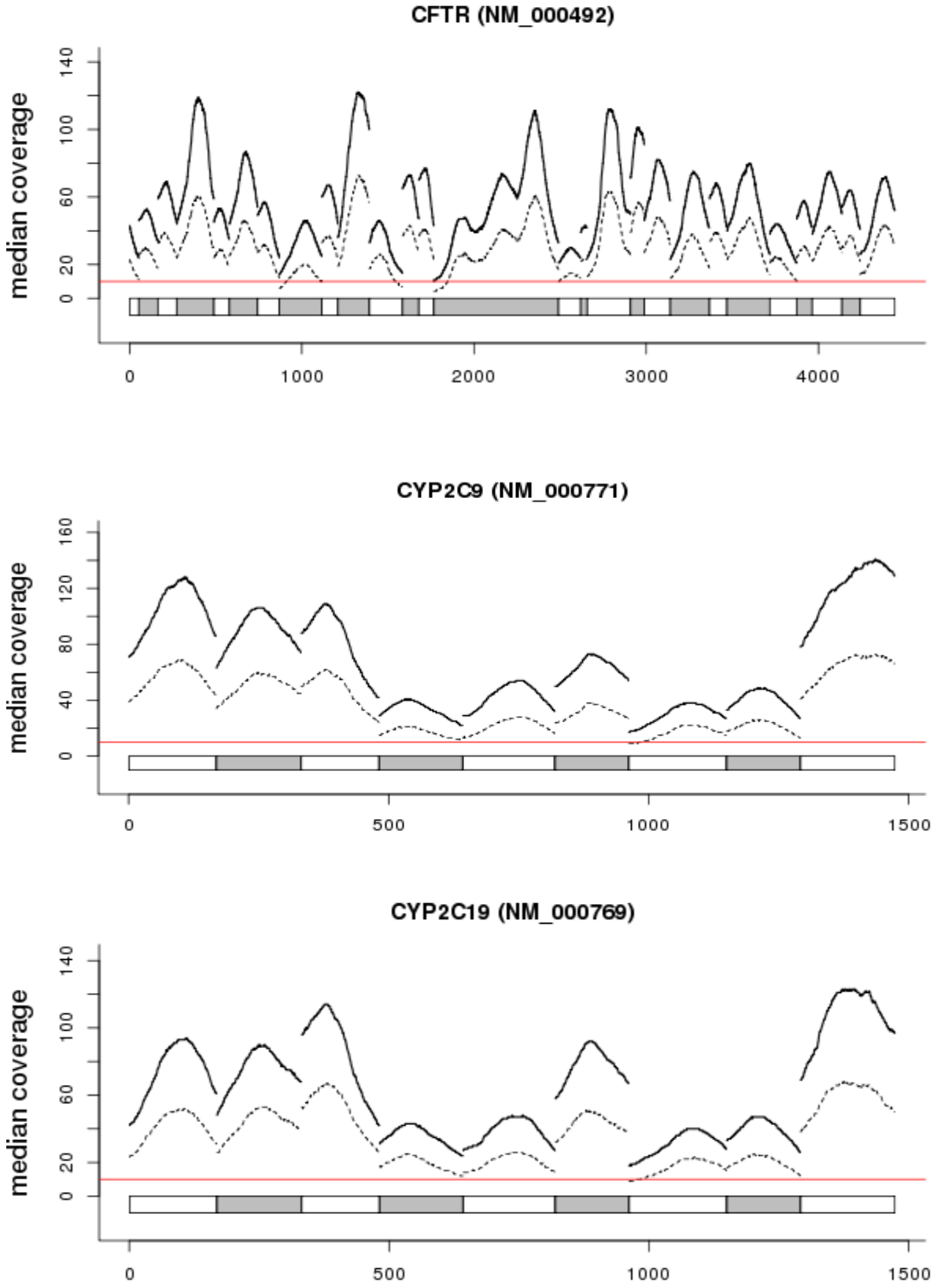
Supplemental Figure 5B

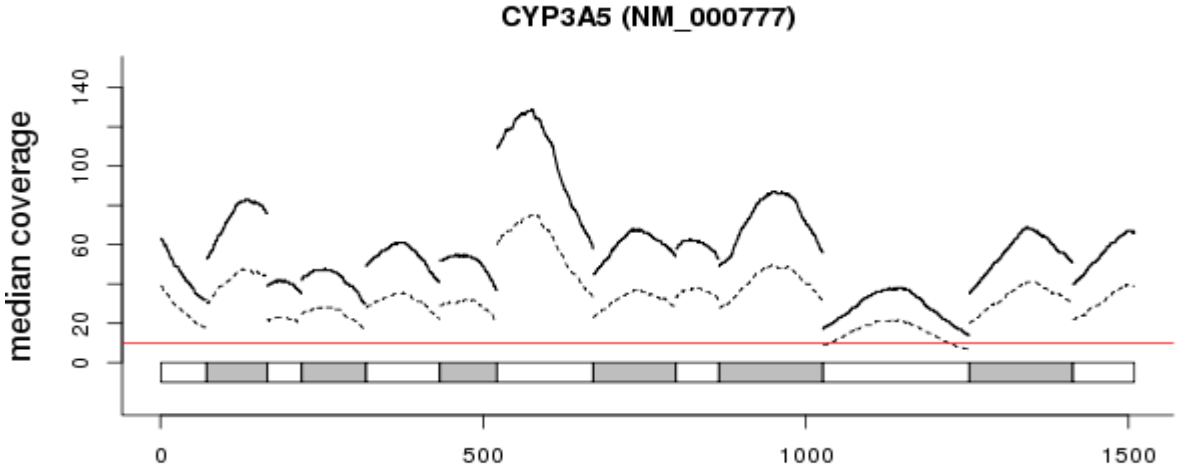


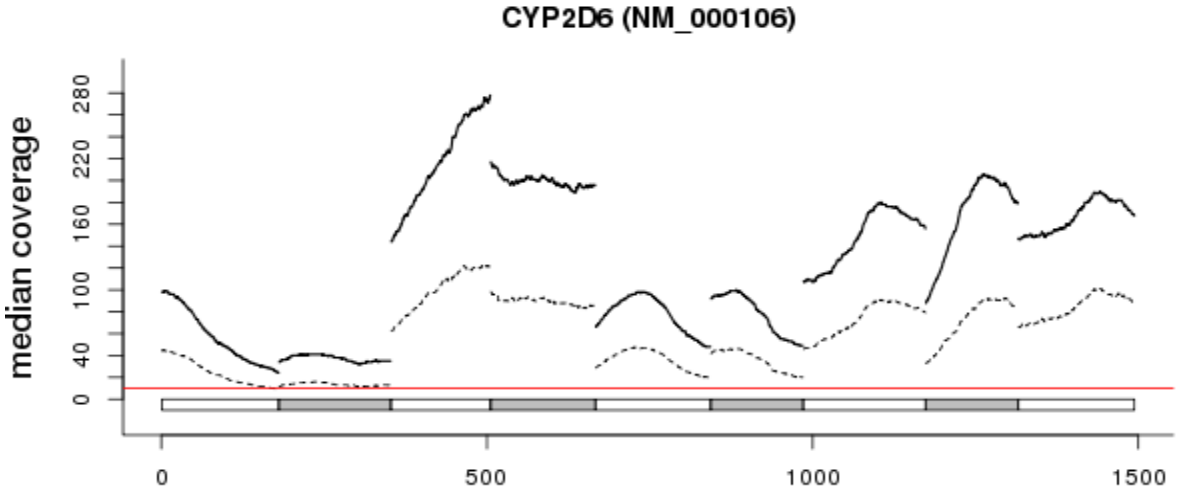
Supplemental Figure 6

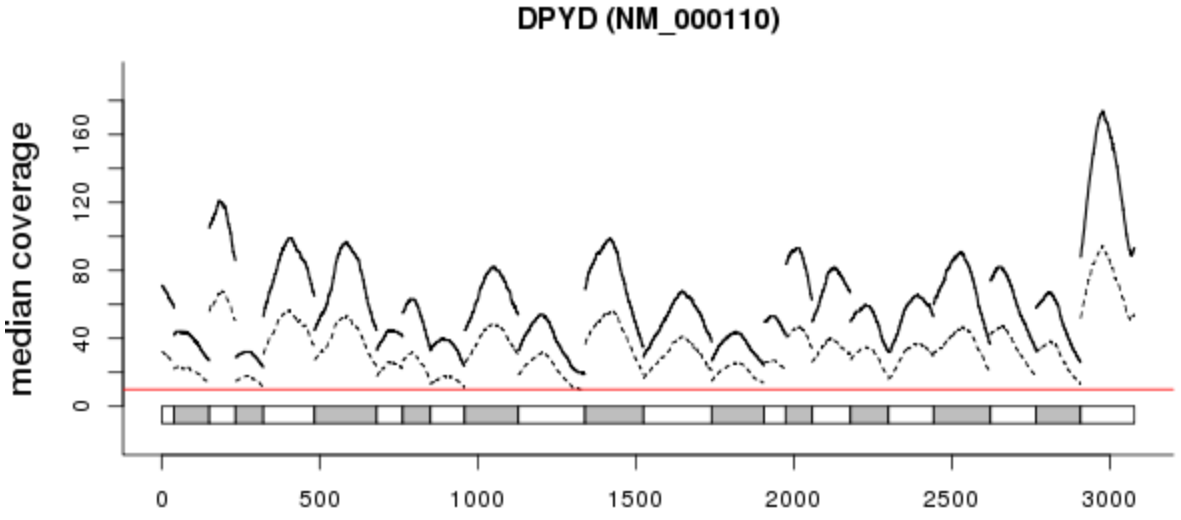


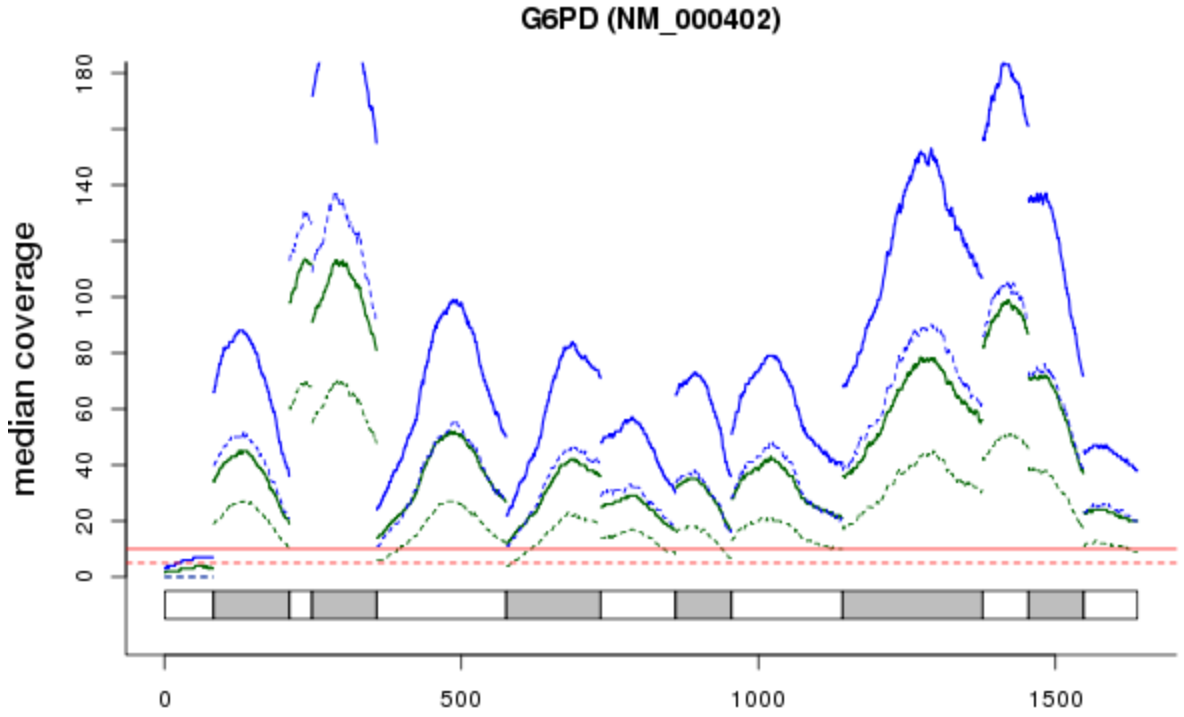
Supplemental Figure 7

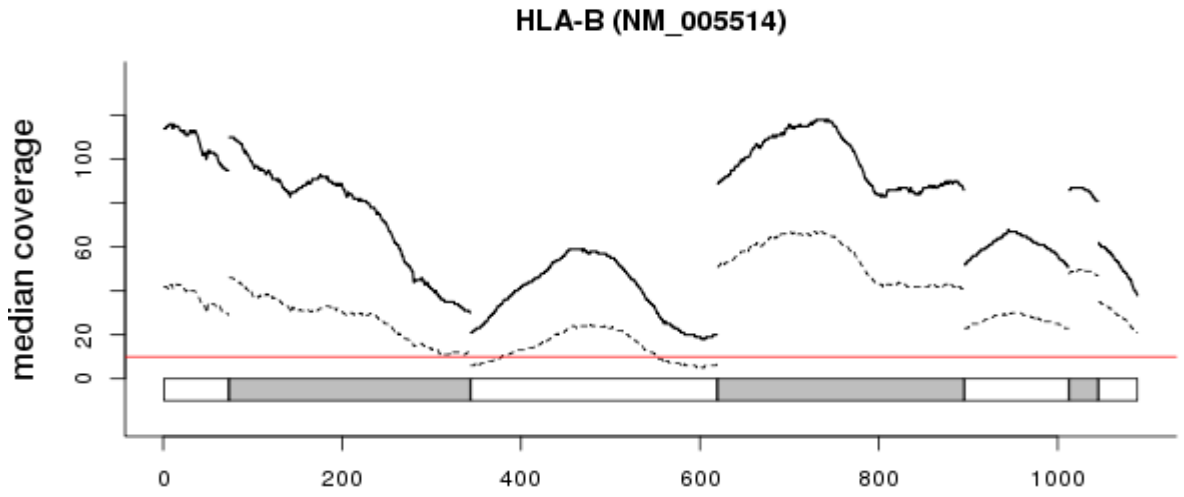


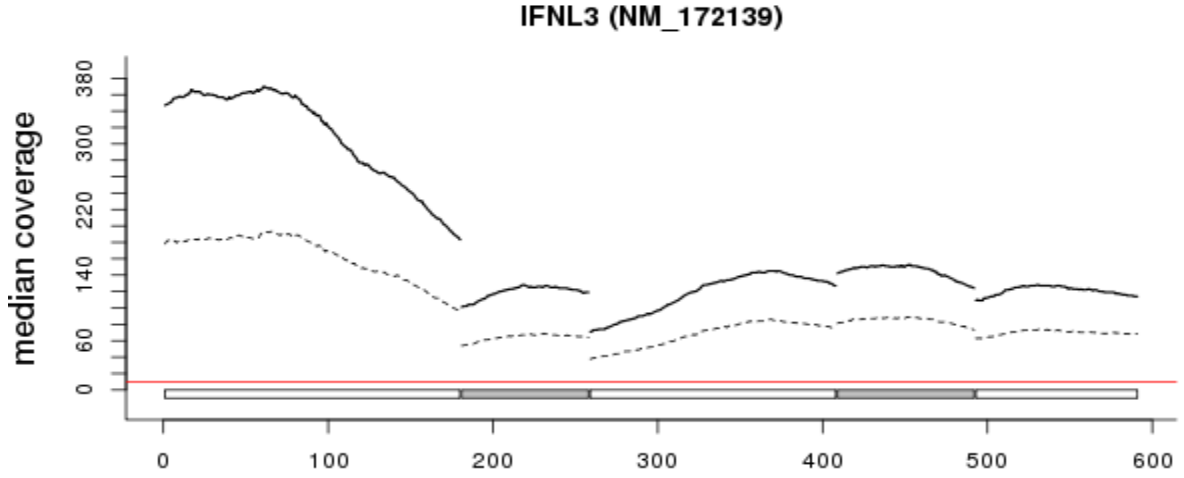

CYP3A5 (NM_000777)
median coverage
0
20
60
100
140
0
500
1000
1500

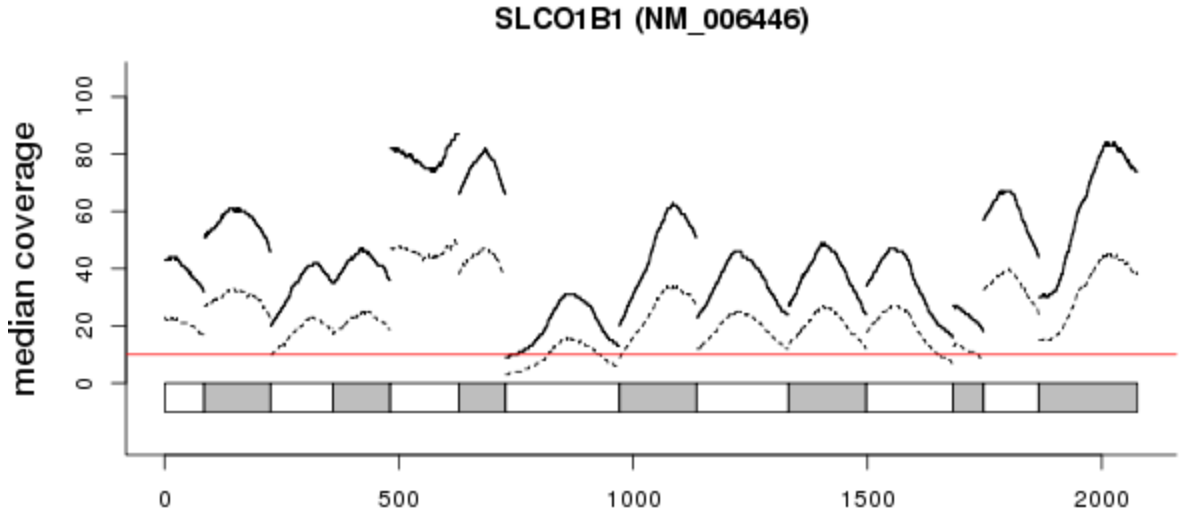

CYP2D6 (NM_000106)
median coverage
0
40
100
160
220
280
0
500
1000
1500

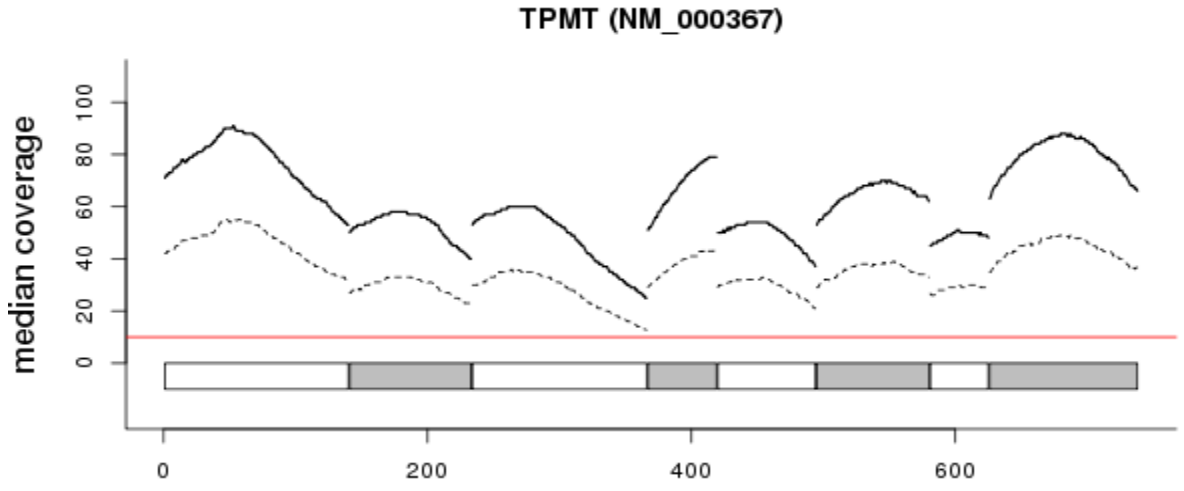

DPYD (NM_000110)
median coverage
0
40
80
120
160
0
500
1000
1500
2000
2500
3000

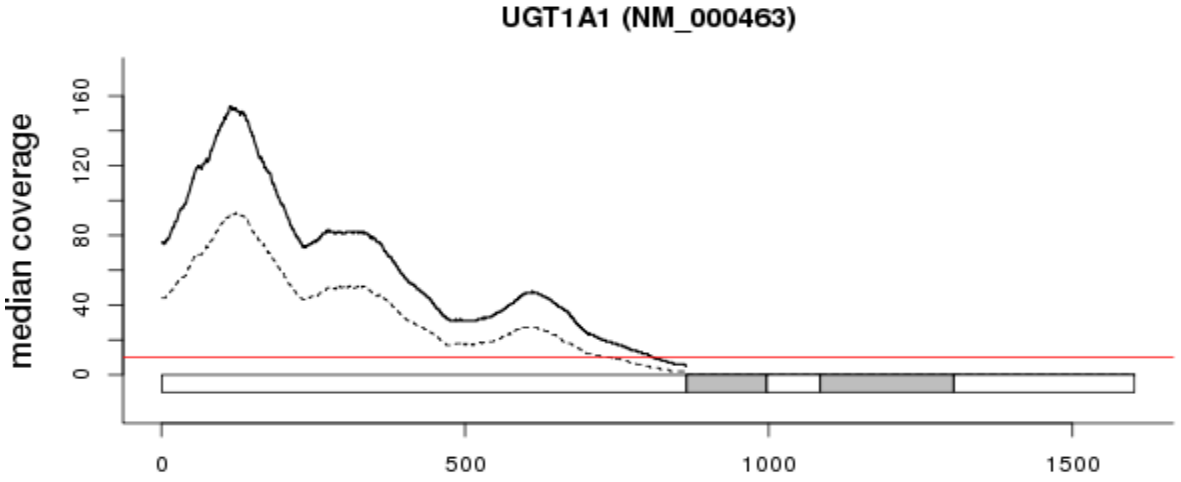

G6PD (NM_000402)
median coverage
0
20
40
60
80
100
140
180
0
500
1000
1500

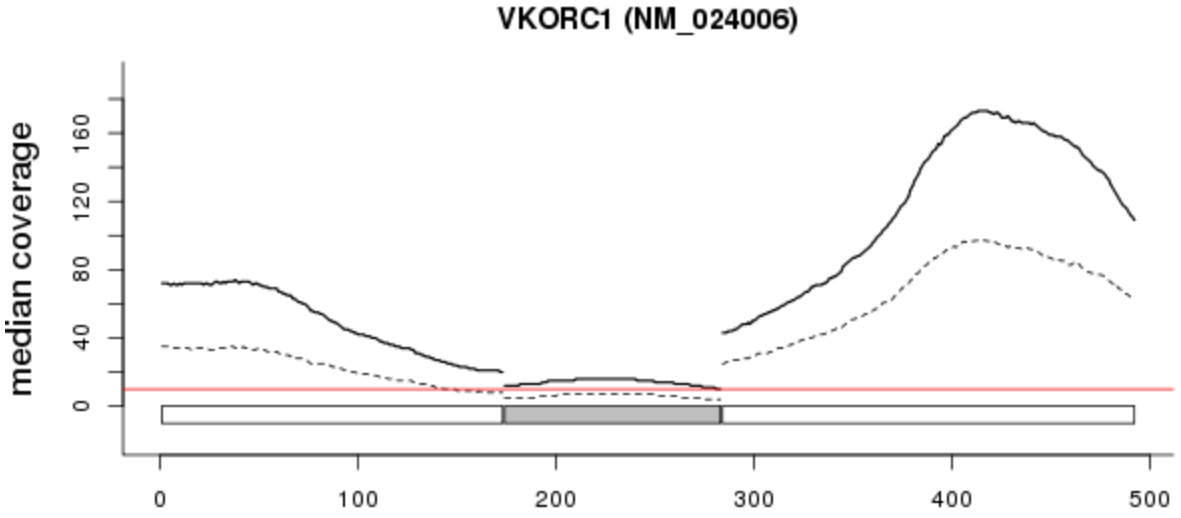

HLA-B (NM_005514)
median coverage
0
20
60
100
0
200
400
600
800
1000


IFNL3 (NM_172139)
median coverage
0
60
140
220
300
380
0
100
200
300
400
500
600

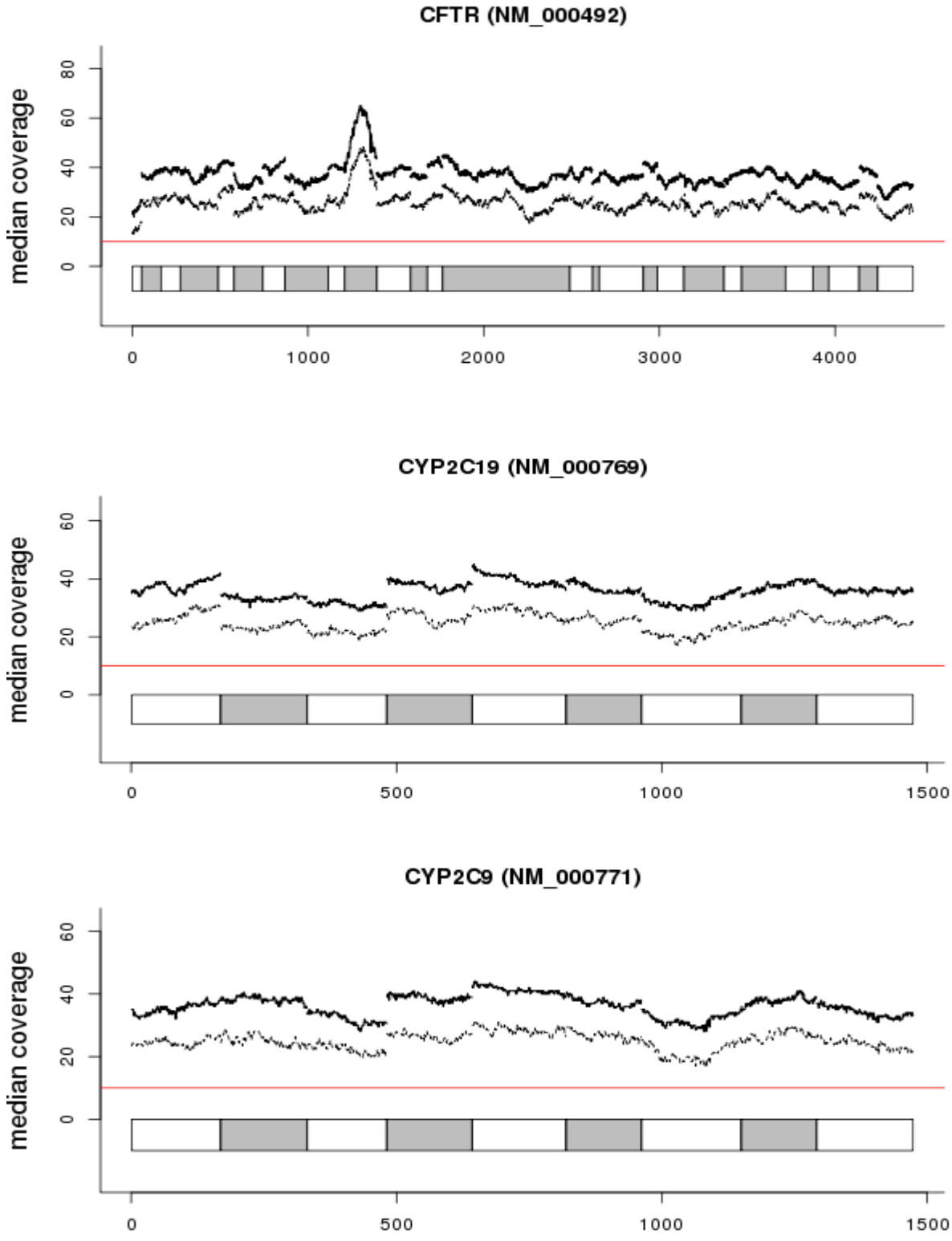

SLCO1B1 (NM_006446)
median coverage
0
20
40
60
80
100
0
500
1000
1500
2000

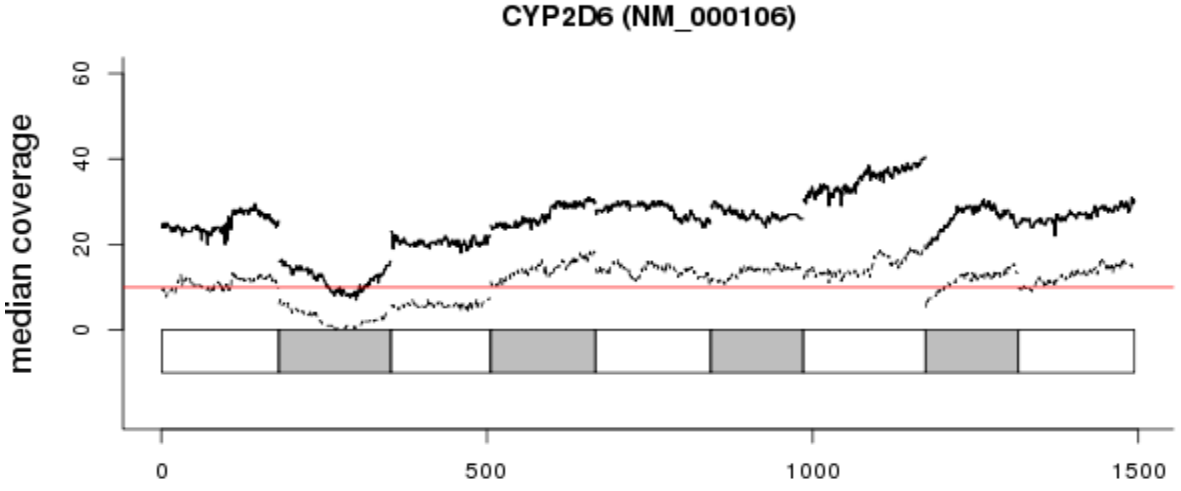

TPMT (NM_000367)
median coverage
0
20
40
60
80
100
0
200
400
600

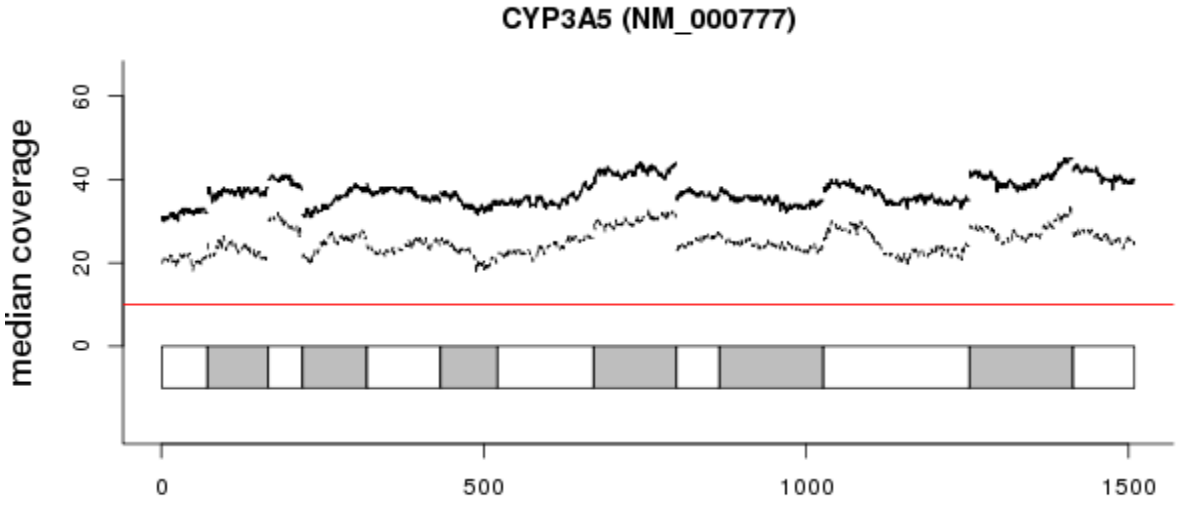

UGT1A1 (NM_000463)
median coverage
0
40
80
120
160
0
500
1000
1500

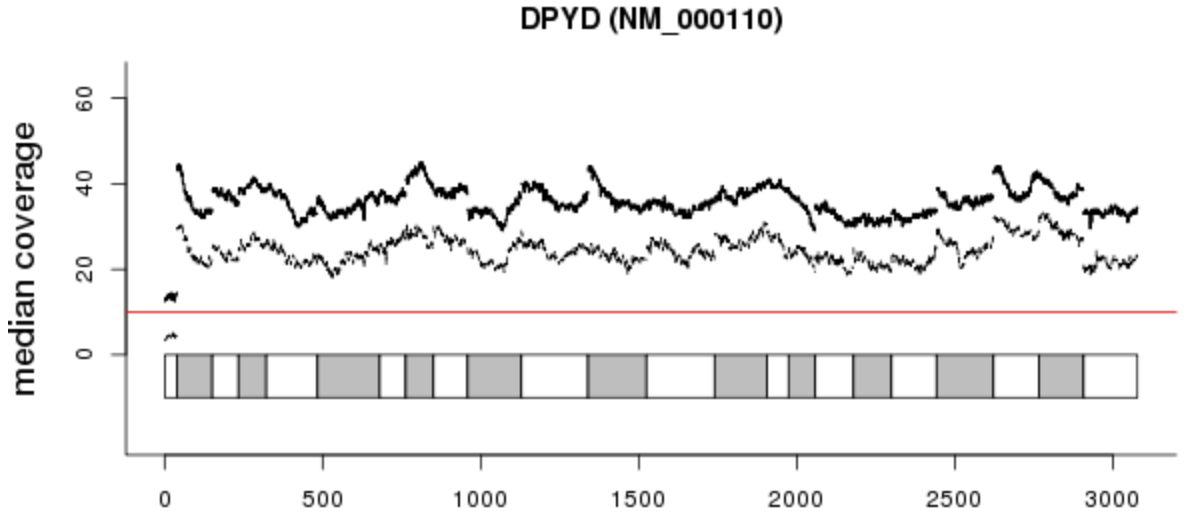

VKORC1 (NM_024006)
median coverage
0
40
80
120
160
0
100
200
300
400
500

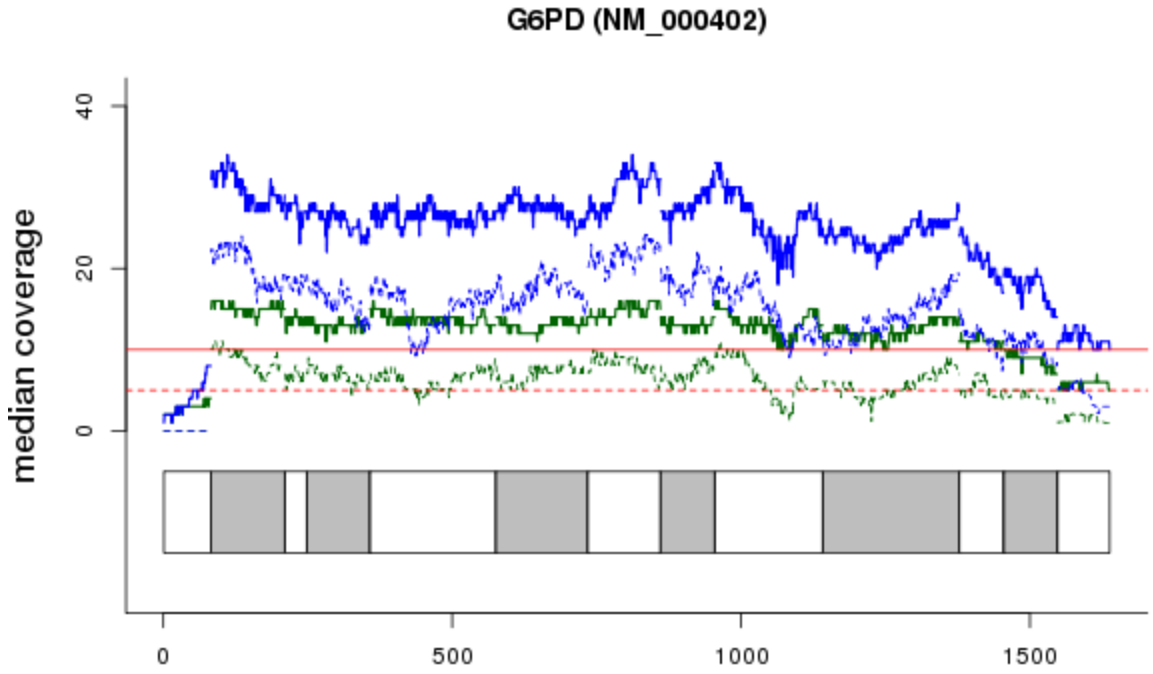
Supplemental Figure 8

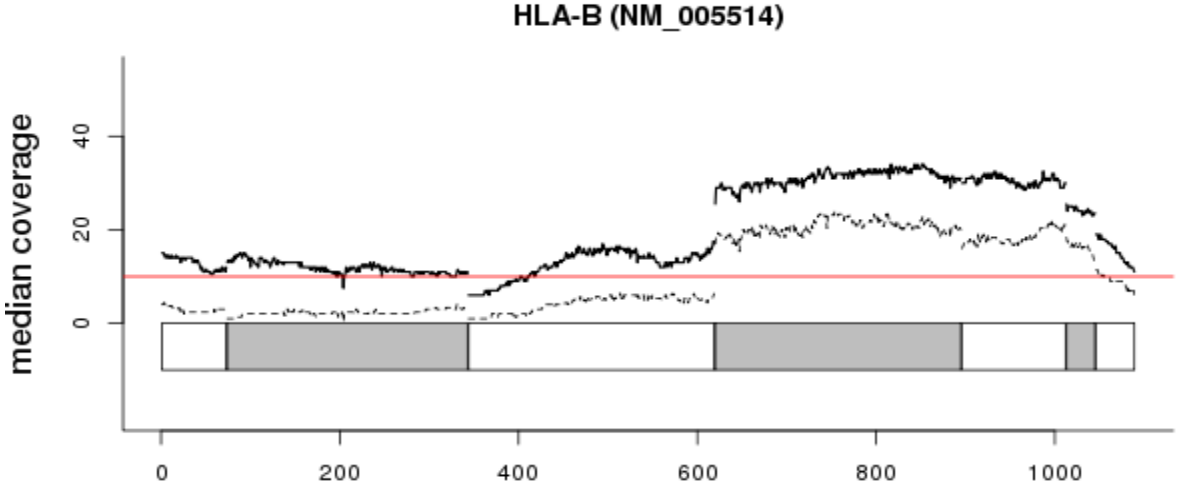


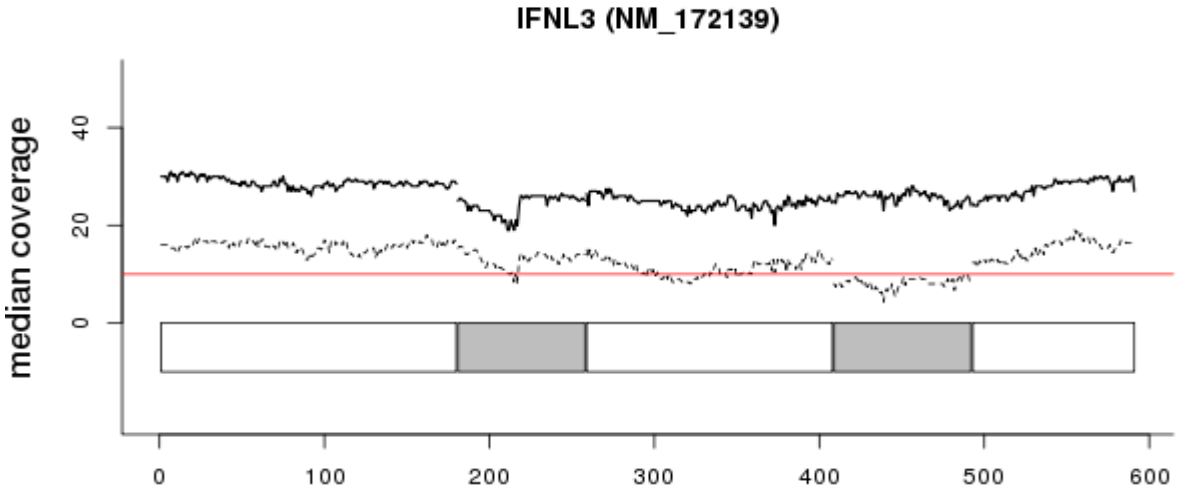

CYP2D6 (NM_000106)
median coverage
0
20
40
60
0
500
1000
1500

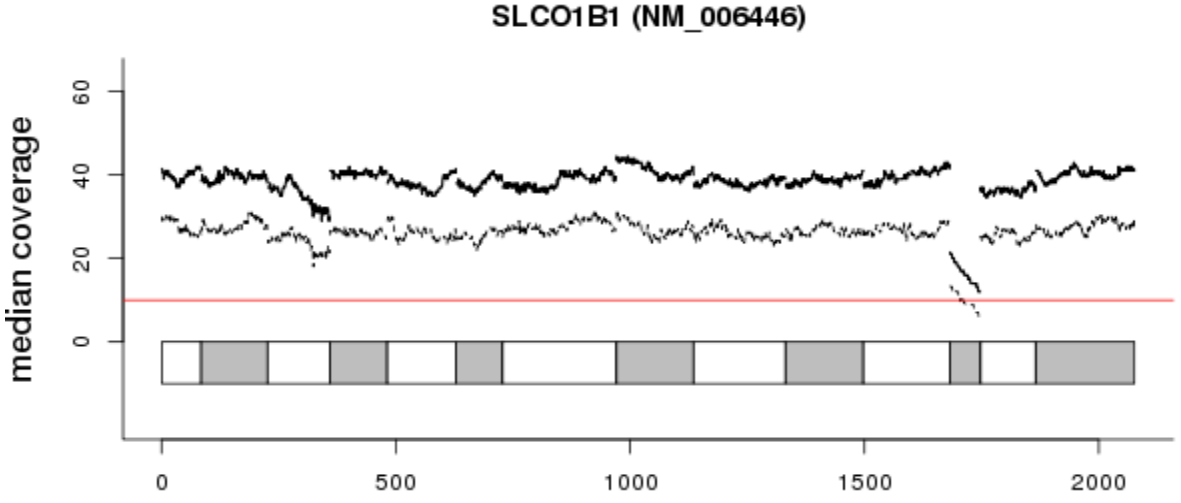

CYP3A5 (NM_000777)
median coverage
0
20
40
60
0
500
1000
1500

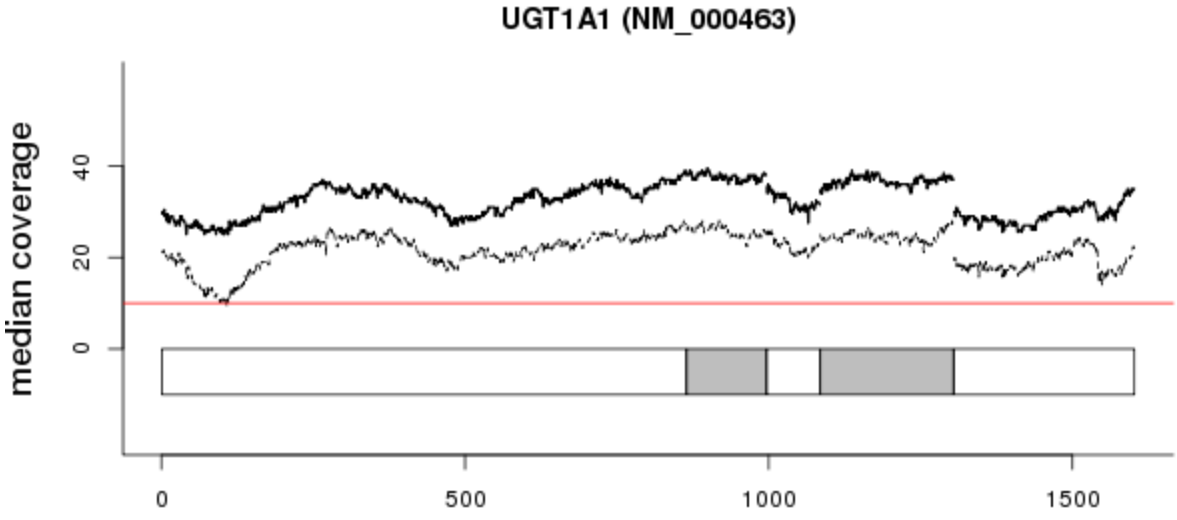

DPYD (NM_000110)
median coverage
0
20
40
60
0
500
1000
1500
2000
2500
3000

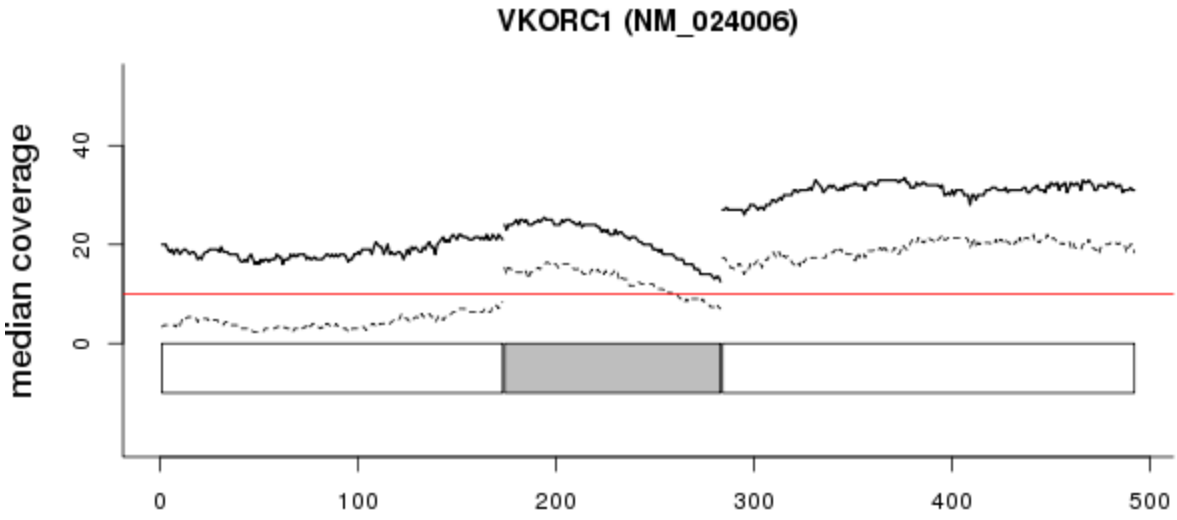

G6PD (NM_000402)
median coverage
0
20
40
0
500
1000
1500


HLA-B (NM_005514)
median coverage
0
20
40
0
200
400
600
800
1000


IFNL3 (NM_172139)
median coverage
0
20
40
0
100
200
300
400
500
600


SLCO1B1 (NM_006446)
median coverage
0
20
40
60
0
500
1000
1500
2000


UGT1A1 (NM_000463)
median coverage
0
20
40
0
500
1000
1500


VKORC1 (NM_024006)
median coverage
0
20
40
0
100
200
300
400
500

Supplemental Figure 9