

Supplementary Material

**Effect of genetic variability in the *CYP4F2*, *CYP4F11* and *CYP4F12*
genes on liver mRNA levels and warfarin response**

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Supplementary figures, tables, and text

Supplementary Figure 1. Genomic structure of the *CYP4F* gene cluster encompassing *CYP4F2*, *CYP4F3*, *CYP4F8*, *CYP4F11* and *CYP4F12*.

Supplementary Figure 2. Genotype-phenotype correlation.

Supplementary Figure 3. GeneGo graphic illustrating the interaction of nuclear factors with *CYP4F2*, *CYP4F11* and *CYP4F12* genes.

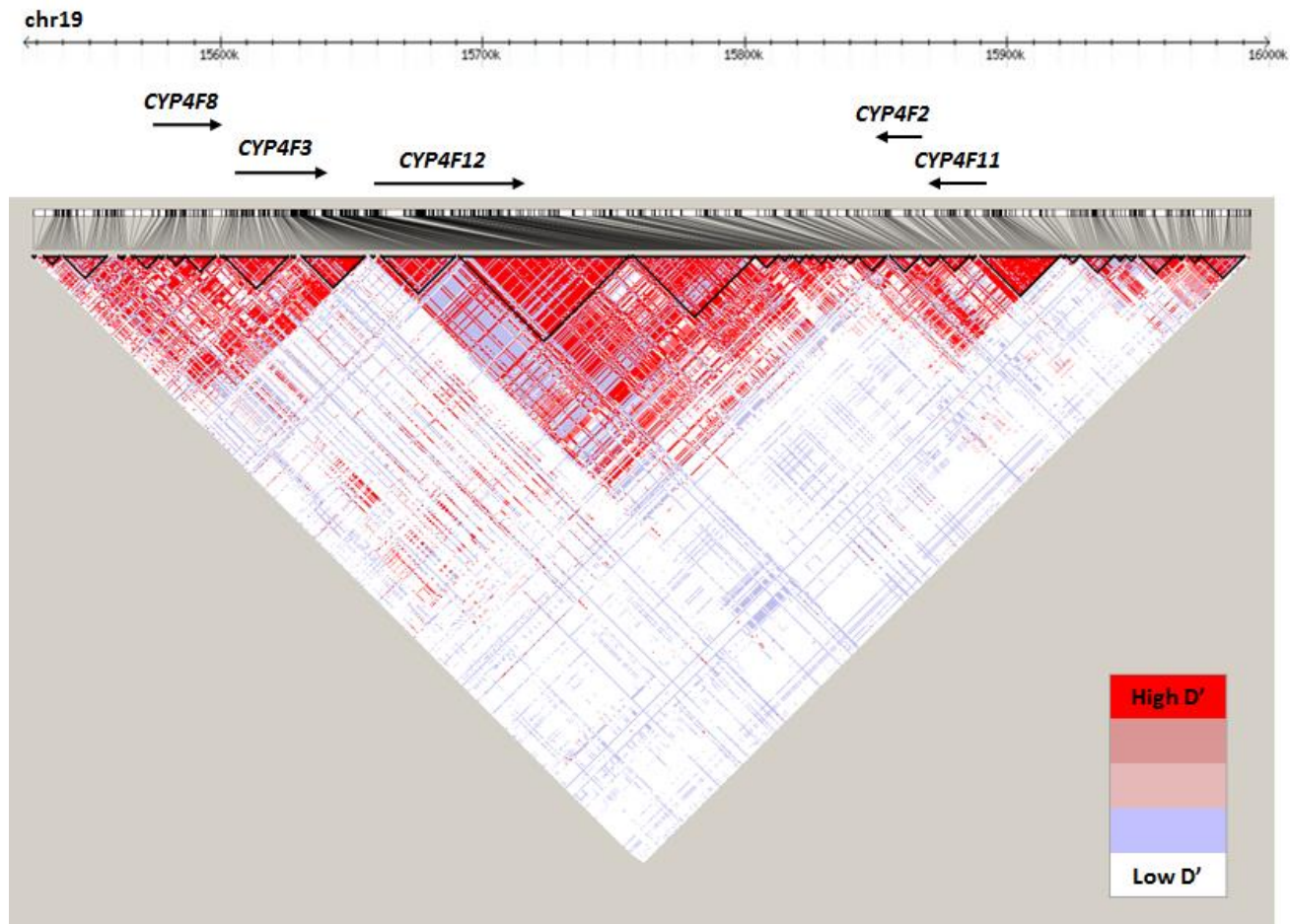
Supplementary Table 1. Characteristics and allele frequencies of *CYP4F2*, *CYP4F11* and *CYP4F12* SNPs investigated in our study.

Supplementary Table 2. Tagging SNPs across the *CYP4F12-CYP4F2-CYP4F11* locus ($r^2 \geq 0.9$).

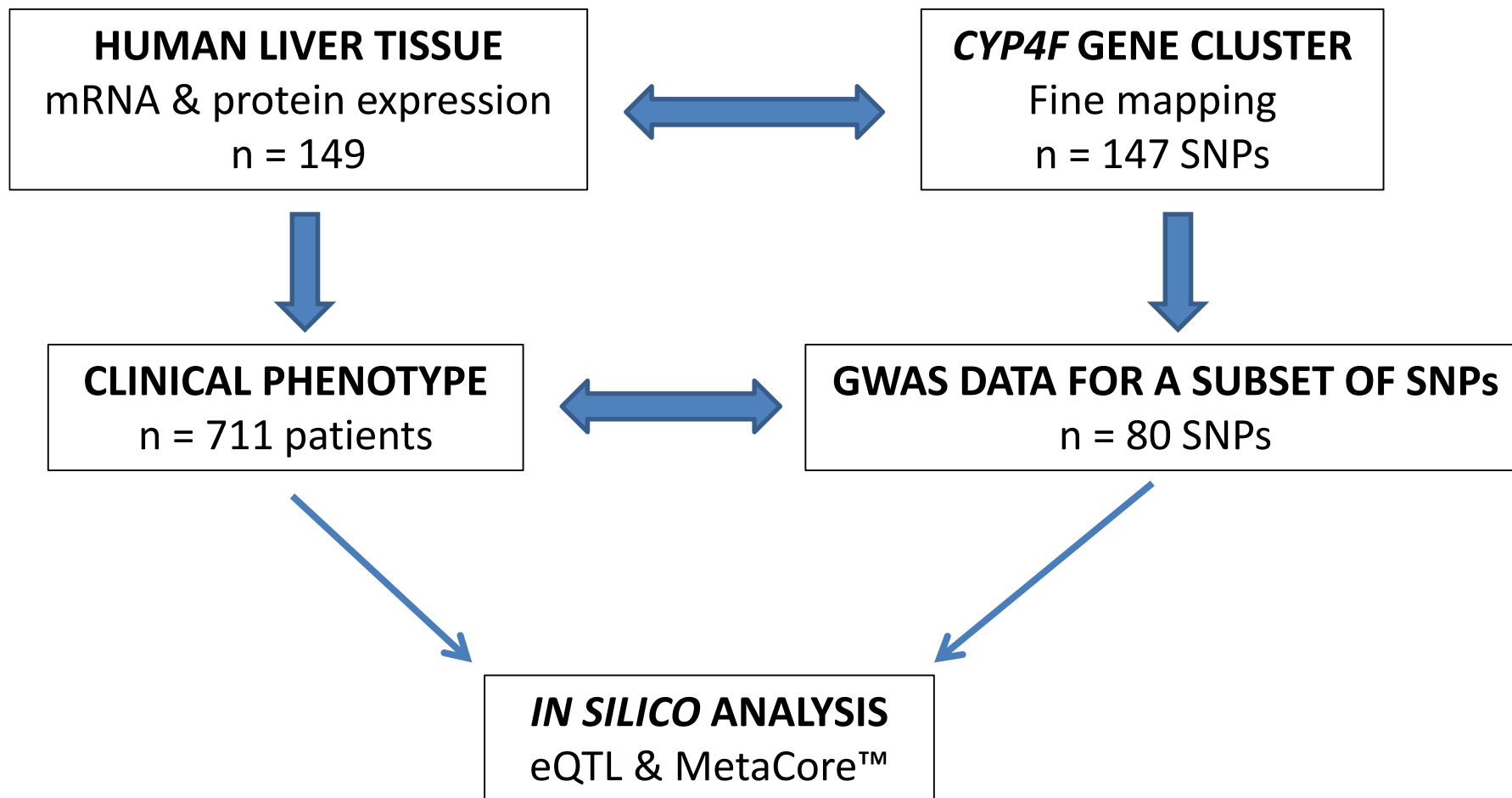
Supplementary Table 3. Significant univariate associations with warfarin stable dose.

Supplementary Results

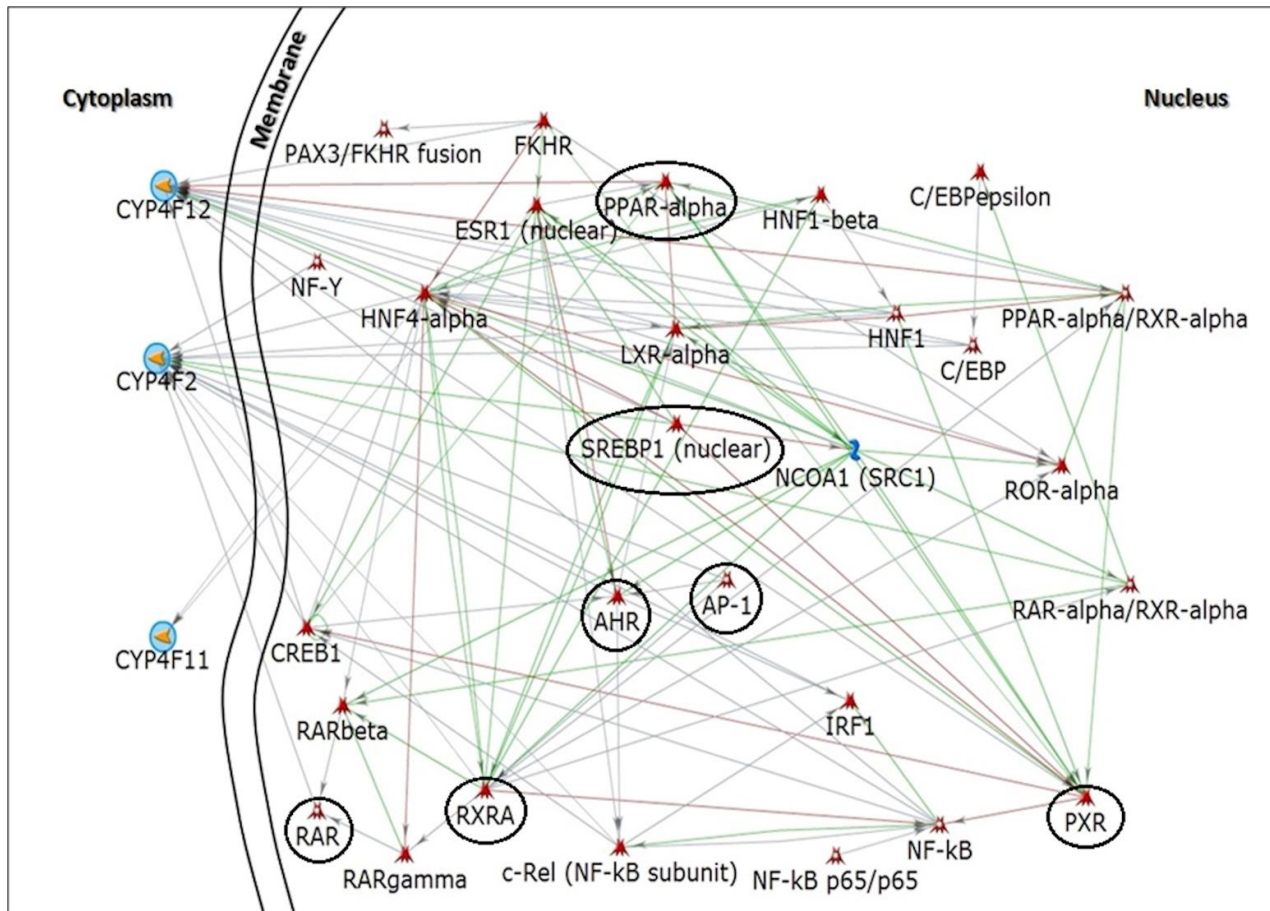
Supplementary Discussion



Supplementary Figure 1. Genomic structure of the *CYP4F* gene cluster encompassing *CYP4F2*, *CYP4F3*, *CYP4F8*, *CYP4F11* and *CYP4F12*. LD pattern and haplotype blocks were generated using HaploView version 4.2 based on the CEU population genotype data on chromosome 19p13 region 15529000 – 16040000, obtained from HapMap data release 27, NCBI build 36 assembly.



Supplementary Figure 2. Genotype-phenotype correlation.



Supplementary Figure 3. GeneGo graphic illustrating the interaction of nuclear factors with *CYP4F2*, *CYP4F11* and *CYP4F12* genes. Each connection represents a direct, experimentally confirmed, physical interaction between the objects.

Supplementary Table 1. Characteristics and allele frequencies of *CYP4F2*, *CYP4F11* and *CYP4F12* SNPs investigated in our study.

Gene	SNP	Chromosomal Position	SNP Alleles	SNP Location and Function	HWE <i>P</i> -Value	% Call Rate	MAF (our study)	MAF (public database)*
CYP4F12	rs10854147	15642995	A > G	5' near gene	0.798	100	0.077	0.116
CYP4F12	rs10854148	15643025	C > T	5' near gene	0.798	100	0.077	0.116
CYP4F12	rs7245534	15643098	T > C	5' near gene	0.798	100	0.077	0.083
CYP4F12	rs16980695	15643275	A > T	5' near gene	0.095	93.3	0.241	0.263
CYP4F12	rs3813137	15643397	C > T	5' near gene	1.000	99.3	0.041	0.054
CYP4F12	rs10405688 ^b	15643494	A > G	5' near gene	0.000	0	0.000	0.089
CYP4F12	rs12977005	15643668	A > G	5' near gene	0.736	92.6	0.083	0.116
CYP4F12	rs4347744	15643859	C > G	5' near gene	1.000	96.6	0.069	0.127
CYP4F12	rs4331436	15643897	C > T	5' near gene	0.595	98.7	0.088	0.116
CYP4F12	rs7248804 ^c	15644051	A > G	5' near gene	7.584E-42	95.3	0.500	0.117
CYP4F12	rs2176917	15644236	A > G	5' near gene	0.731	100	0.081	0.130
CYP4F12	rs2139749 ^b	15644378	C > T	5' near gene	1.682E-24	56.4	0.500	0.000
CYP4F12	rs17641206 ^b	15645152	T > C	Intron 1	1.000	83.2	0.077	0.216
CYP4F12	rs10414690	15645195	C > G	Intron 1	0.670	100	0.091	0.102
CYP4F12	rs16995376	15645377	C > T	Exon 2, Missense, Pro13Leu	0.106	100	0.232	0.250
CYP4F12	rs16995378 ^b	15645386	T > C	Exon 2, Missense, Met16Thr	0.407	61.1	0.126	0.096
CYP4F12	rs9305063	15646525	T > C	Intron 2	0.798	100	0.077	0.102
CYP4F12	rs10410157	15646622	C > T	Intron 2	0.798	100	0.077	0.112
CYP4F12	rs610142 ^a	15649930	A > T	Intron 2	1.000	100	0.000	0.000
CYP4F12	rs609636	15650098	C > T	Exon 3, Missense, Asp76Asn	0.776	97.3	0.079	0.117
CYP4F12	rs609290	15650140	C > T	Exon 3, Missense, Val90Ile	0.798	100	0.077	0.110
CYP4F12	rs17682485	15650698	G > A	Intron 3	0.890	100	0.419	0.398
CYP4F12	rs12460703	15650776	A > G	Intron 3	0.963	100	0.490	0.500
CYP4F12	rs675326	15651144	G > A	Intron 3	1.000	98.7	0.003	0.000
CYP4F12	rs16980704 ^b	15651531	T > C	Intron 3	0.221	80.5	0.242	0.267
CYP4F12	rs677139 ^a	15651547	A > G	Intron 3	1.000	100	0.000	0.000
CYP4F12	rs688468 ^a	15651752	A > G	Intron 3	1.000	100	0.000	0.000
CYP4F12	rs2074568	15652132	T > A	Intron 4	0.792	100	0.218	0.164
CYP4F12	rs10409750	15652606	A > G	Intron 5	0.569	100	0.433	0.397
CYP4F12	rs10415331	15652617	C > T	Intron 5	0.709	97.3	0.083	0.121
CYP4F12	rs595381 ^a	15652809	C > G	Intron 5	1.000	100	0.000	0.000
CYP4F12	rs673020 ^b	15653081	G > A	Intron 5	1.000	75.8	0.018	0.000

CYP4F12	rs672645 ^a	15653127	A > G	Intron 5	1.000	100	0.000	0.000
CYP4F12	rs672555 ^b	15653185	C > A	Intron 5	1.000	88.6	0.057	0.008
CYP4F12	rs11085969	15653546	G > A	Intron 5	0.870	99.3	0.236	0.203
CYP4F12	rs12151032	15653566	C > T	Intron 5	0.156	100	0.242	0.268
CYP4F12	rs610652 ^a	15653900	C > T	Intron 5	1.000	100	0.000	0.000
CYP4F12	rs2285888 ^b	15654235	C > T	Exon 6, Missense, Arg188Cys	0.009	83.9	0.360	0.483
CYP4F12	rs2285890	15654415	C > T	Intron 6	1.000	100	0.030	0.061
CYP4F12	rs57578760 ^a	15655463	G > C	Exon 7, Missense, Val270Leu	1.000	100	0.000	NA
CYP4F12	rs628603 ^a	15655595	A > G	Intron 7	1.000	100	0.000	0.000
CYP4F12	rs2074569 ^a	15655727	C > T	Intron 7	1.000	100	0.000	0.000
CYP4F12	rs630133 ^a	15655769	C > T	Intron 7	1.000	96	0.000	0.000
CYP4F12	rs629748 ^a	15655843	A > G	Intron 7	1.000	100	0.000	0.000
CYP4F12	rs640169 ^a	15655885	A > G	Intron 7	1.000	100	0.000	0.000
CYP4F12	rs616745 ^a	15656420	C > T	Intron 7	1.000	100	0.000	0.000
CYP4F12	rs633929 ^b	15657441	A > G	Intron 9	1.000	6.7	0.000	0.000
CYP4F12	rs17682497 ^b	15657542	C > T	Intron 9	0.094	87.9	0.206	0.200
CYP4F12	rs659825 ^a	15657584	A > T	Intron 9	1.000	100	0.000	0.018
CYP4F12	rs659447	15657662	C > T	Intron 9	1.000	96.6	0.031	0.051
CYP4F12	rs11085971	15657813	G > T	Intron 9	1.000	92.6	0.152	0.067
CYP4F12	rs10420354	15657946	C > T	Intron 9	0.252	100	0.158	0.085
CYP4F12	rs642322	15659173	C > G	Intron 9	0.188	100	0.238	0.250
CYP4F12	rs631279	15659334	T > C	Intron 9	0.188	100	0.238	0.268
CYP4F12	rs627753 ^b	15660130	T > C	Intron 9	0.617	61.1	0.192	0.248
CYP4F12	rs10410357	15661331	A > G	Intron 9	0.252	100	0.158	0.083
CYP4F12	rs4109350	15661921	C > T	Intron 9	0.234	98	0.236	0.264
CYP4F12	rs11879787	15662454	A > G	Intron 9	0.676	100	0.242	0.186
CYP4F12	rs613503 ^a	15663113	C > T	Intron 9	1.000	96.6	0.000	0.000
CYP4F12	rs680681	15663148	T > C	Intron 9	0.188	100	0.238	0.242
CYP4F12	rs615392 ^c	15663595	C > T	Intron 9	9.050E-05	91.3	0.346	0.264
CYP4F12	rs627971	15664094	T > C	Intron 9	0.778	100	0.490	0.491
CYP4F12	rs665872	15664106	C > T	Intron 9	0.649	97.3	0.493	0.470
CYP4F12	rs629651 ^b	15664417	G > T	Intron 9	7.171E-05	83.9	0.376	0.458
CYP4F12	rs4808362	15664892	G > A	Intron 9	0.902	98.7	0.497	0.483
CYP4F12	rs651109	15665158	G > A	Intron 9	1.000	100	0.067	0.067
CYP4F12	rs59302543 ^a	15667846	A > G	Exon 10, Missense, Ile406Val	1.000	100	0.000	NA

CYP4F12	rs687774 ^b	15668062	C > T	Intron 11	0.665	65.8	0.235	0.225
CYP4F12	rs688231	15668157	A > G	Intron 11	0.188	100	0.238	0.225
CYP4F12	rs688256	15668175	G > C	Intron 11	0.188	100	0.238	0.242
CYP4F12	rs688755	15668305	T > C	Exon 12, Synonymous, Pro460Pro	0.188	100	0.238	0.258
CYP4F12	rs61391486 ^a	15668720	A > G	Exon 13, Missense, Asn467Ser	1.000	100	0.000	NA
CYP4F12	rs593818	15668884	G > A	Exon 13, Missense, Gly522Ser	0.844	99.3	0.486	0.492
CYP4F12	rs594255	15668984	G > A	3' UTR	0.188	100	0.238	0.242
CYP4F12	rs611848	15669379	C > T	3' near gene	0.778	100	0.490	0.486
CYP4F12	rs624512	15669890	G > A	3' near gene	0.188	100	0.238	0.258
CYP4F12	rs12976669	15671312	A > C	3' near gene	0.283	100	0.272	0.250
CYP4F12	rs7255335	15672079	G > C	3' near gene	0.283	100	0.272	0.228
CYP4F12	rs2886476	15672717	T > G	3' near gene	0.283	100	0.272	0.254
CYP4F12	rs670476	15674467	A > G	3' near gene	0.118	95.3	0.268	0.322
CYP4F12	rs590828	15674919	T > C	3' near gene	1.000	98.7	0.480	0.450
-	rs4808369	15691869	T > G	Intergenic, between CYP4F12 and CYP4F2	0.283	100	0.272	0.233
-	rs7252197	15696098	T > G	Intergenic, between CYP4F12 and CYP4F2	1.000	100	0.087	0.110
-	rs4433928	15699690	G > A	Intergenic, between CYP4F12 and CYP4F2	0.744	99.3	0.470	0.500
-	rs16980800	15706047	A > G	Intergenic, between CYP4F12 and CYP4F2	0.546	100	0.285	0.297
-	rs2240228	15713872	G > A	Intergenic, between CYP4F12 and CYP4F2	0.001	94.6	0.241	0.300
-	rs2079234	15718510	G > T	Intergenic, between CYP4F12 and CYP4F2	0.691	100	0.466	0.392
-	rs11666521	15722672	T > C	Intergenic, between CYP4F12 and CYP4F2	0.966	100	0.268	0.233
-	rs10423986	15727655	C > T	Intergenic, between CYP4F12 and CYP4F2	0.731	100	0.081	0.092
-	rs2189784	15820200	G > A	Downstream of CYP4F2	0.216	100	0.433	0.381
-	rs2079288	15825203	T > C	Downstream of CYP4F2	0.240	100	0.205	0.217
-	rs7252046	15832473	T > C	Downstream of CYP4F2	0.957	100	0.336	0.325
-	rs12610189	15839641	T > G	Downstream of CYP4F2	0.881	100	0.359	0.300
CYP4F2	rs3093216	15848737	T > C	3' near gene	0.708	100	0.362	0.300
CYP4F2	rs3093212 ^b	15848966	A > A	3' near gene	0.000	0	0.000	0.475
CYP4F2	rs3093211 ^c	15848967	C > T	3' near gene	6.069E-44	100	0.500	0.200
CYP4F2	rs3093210 ^c	15849401	G > A	3' near gene	1.718E-07	100	0.238	0.142
CYP4F2	rs3093209	15849420	C > G	3' near gene	0.708	100	0.362	0.347
CYP4F2	rs3093208 ^a	15849582	T > C	3' near gene	1.000	100	0.000	0.000
CYP4F2	rs3093207	15849658	A > G	3' near gene	0.708	100	0.362	0.300
CYP4F2	rs17756654	15849725	C > A	3' near gene	1.000	100	0.044	0.033
CYP4F2	rs3093206	15849753	AA > DEL	3' near gene	0.095	100	0.383	0.217
CYP4F2	rs1272	15850040	G > C	Exon 13	0.581	100	0.275	0.180
CYP4F2	rs3093204	15850167	G > A	Exon 13	1.000	100	0.057	0.065
CYP4F2	rs3093203	15850184	C > T	Exon 13	0.791	99.3	0.260	0.292

CYP4F2	rs1126433 ^c	15850405	A > G	Exon 13	2.236E-28	100	0.453	0.477
CYP4F2	rs3093201 ^a	15850454	T > C	Exon 13	1.000	100	0.000	0.000
CYP4F2	rs3093200	15850589	C > A	Exon 13, Missense, Met519Leu	1.000	100	0.057	0.083
CYP4F2	rs3093199 ^b	15850871	A > T	Intron 12	0.000	0	0.000	0.284
CYP4F2	rs3093198	15851048	C > T	Intron 12	1.000	100	0.332	0.340
CYP4F2	rs3093197 ^a	15851128	A > T	Intron 12	1.000	100	0.000	0.000
CYP4F2	rs2108622	15851431	C > T	Exon 11, Missense, Met433Val	1.000	100	0.289	0.233
CYP4F2	rs3093195	15852433	G > A	Intron 9	0.856	100	0.262	0.325
CYP4F2	rs3093227	15852520	G > T	Intron 9	1.000	100	0.010	0.023
CYP4F2	rs3093194	15852676	G > A	Intron 9	0.856	100	0.262	0.332
CYP4F2	rs3093193	15852914	G > C	Intron 9	0.708	100	0.362	0.333
CYP4F2	rs3093192 ^a	15853319	C > T	Intron 9	1.000	100	0.000	0.000
CYP4F2	rs12984060	15853553	G > A	Intron 9	0.884	100	0.376	0.375
CYP4F2	rs3093226 ^b	15853780	T > T	Intron 9	0.000	0	0.000	0.071
CYP4F2	rs2886296	15855478	A > T	Intron 9	0.493	100	0.094	0.065
CYP4F2	rs3093184 ^b	15855730	C > T	Intron 9	0.022	19.5	0.328	0.329
CYP4F2	rs3093180	15856148	C > T	Intron 9	1.000	100	0.171	0.153
CYP4F2	rs3093173	15856788	G > A	Intron 9	1.000	100	0.168	0.095
CYP4F2	rs3093170	15856974	T > G	Intron 9	0.002	100	0.487	0.432
CYP4F2	rs3093169	15857008	G > A	Intron 9	0.032	100	0.154	0.139
CYP4F2	rs3093168	15857245	C > T	Intron 9	0.644	100	0.393	0.345
CYP4F2	rs3093167	15857292	T > C	Intron 9	1.000	100	0.168	0.109
CYP4F2	rs3093166	15857349	A > T	Intron 9	0.644	100	0.393	0.345
CYP4F2	rs3093163 ^a	15857497	G > A	Intron 9	1.000	100	0.000	0.000
CYP4F2	rs2074900	15857820	G > A	Exon 9, Synonymous, His343His	0.002	100	0.225	0.325
CYP4F2	rs3093160	15857907	G > A	Intron 8	1.000	100	0.168	0.109
CYP4F2	rs2074901	15858422	A > C	Intron 7	1.000	100	0.168	0.100
CYP4F2	rs1558139	15858564	A > G	Intron 7	0.002	100	0.487	0.433
CYP4F2	rs3093158 ^b	15861166	A > G	Intron 8	6.418E-06	48.3	0.417	0.286
CYP4F2	rs3093156	15861609	A:T	Intron 6	0.709	98.7	0.442	0.433
CYP4F2	rs3093150	15862629	C > T	Intron 5	0.867	100	0.074	0.045
CYP4F2	rs3093145	15862852	C:A	Intron 5	0.593	100	0.443	0.441
CYP4F2	rs3093144	15863297	G > A	Intron 5	1.000	100	0.185	0.224
CYP4F2	rs3093141 ^a	15863521	C > T	Intron 5	1.000	100	0.000	0.000
CYP4F2	rs3093135	15865371	T > A	Intron 3	1.000	100	0.168	0.118
CYP4F2	rs3093134	15865396	G > C	Intron 3	1.000	100	0.168	0.114
CYP4F2	rs2006193	15865800	C > A	Intron 3	0.040	100	0.151	0.142

CYP4F2	rs2365178	15866003	G > A	Intron 3	1.000	100	0.168	0.114
CYP4F2	rs3093129	15866019	A > G	Intron 3	1.000	100	0.168	0.114
CYP4F2	rs3093128	15866104	G > A	Intron 3	1.000	100	0.168	0.142
CYP4F2	rs3093126 ^a	15866160	A > G	Intron 3	1.000	100	0.000	0.000
CYP4F2	rs2016503	15866185	T > C	Intron 3	0.890	100	0.181	0.109
CYP4F2	rs3093124	15866232	T > C	Intron 3	1.000	99.3	0.169	0.109
CYP4F2	rs3093122 ^b	15866276	C > G	Intron 3	1.000	3.4	0.100	0.109
CYP4F2	rs3093121	15866277	C > A	Intron 3	1.000	100	0.168	0.109
CYP4F2	rs736089 ^b	15866300	A > G	Intron 3	0.588	43	0.133	0.000
CYP4F2	rs2215092	15866521	G > T	Intron 3	0.867	100	0.074	0.043
CYP4F2	rs3093116	15866574	G > A	Intron 3	1.000	100	0.168	0.109
CYP4F2	rs3093115	15866615	T > A	Intron 3	1.000	100	0.168	0.114
CYP4F2	rs984692	15867074	T > A	Intron 3	0.676	100	0.242	0.208
CYP4F2	rs3093114	15867413	C > T	Exon 3, Synonymous, Ala82Ala	1.000	100	0.168	0.114
CYP4F2	rs3093113 ^a	15867545	A > G	Intron 2	1.000	100	0.000	0.000
CYP4F2	rs3093112	15867611	A > G	Intron 2	1.000	100	0.168	0.114
CYP4F2	rs3093110	15868784	T > C	Intron 2	1.000	100	0.168	0.109
CYP4F2	rs2074902 ^c	15869099	C > T	Intron 2	8.325E-38	100	0.487	0.180
CYP4F2	rs3093106	15869257	A > G	Exon 2, Synonymous, Pro55Pro	1.000	100	0.168	0.109
CYP4F2	rs3093105 ^c	15869388	G > T	Exon 2, Missense, Gly12Trp	8.325E-38	100	0.487	0.109
CYP4F2	rs3093103	15869434	T > C	Intron 1	1.000	100	0.168	0.109
CYP4F2	rs3093100	15869469	G > C	Intron 1	1.000	100	0.168	0.139
CYP4F2	rs3093098	15869512	T > C	Intron 1	0.871	100	0.171	0.128
CYP4F2	rs3093097	15869690	CA > DEL	Intron 1	0.748	100	0.282	NA
CYP4F2	rs3093092 ^c	15870127	C > A	3' near gene	1.000E-04	96.6	0.212	0.142
CYP4F2	rs3093091 ^a	15870133	C > T	3' near gene	1.000	100	0.000	0.222
CYP4F2	rs3761014	15872763	C > G	3' near gene	1.000	100	0.185	0.207
CYP4F11	rs2018460	15873757	G > A	3' near gene	1.000	100	0.185	0.217
CYP4F11	rs2365177	15880408	T > G	3' near gene	1.000	95.3	0.035	0.042
CYP4F11	rs8102331 ^b	15883144	G > A	3' near gene	1.000	82.6	0.069	0.333
CYP4F11	rs12459933	15884116	T > C	3' near gene	0.460	99.3	0.365	0.308
CYP4F11	rs12610962	15884377	G > A	3' UTR	0.268	100	0.500	0.483
CYP4F11	rs1060467	15885538	T > C	3' UTR	0.692	99.3	0.334	0.425
CYP4F11	rs1064796	15885662	G > C	Exon 12, Synonymous, Thr485Thr	0.524	94	0.282	0.283
CYP4F11	rs2072269	15885739	G > A	Intron 11	0.203	100	0.497	0.467
CYP4F11	rs1060463 ^b	15886176	G > A	Exon 11, Missense, Asn446Asp	8.314E-06	67.8	0.381	0.392
CYP4F11	rs12977516	15886919	G > C	Intron 8	0.450	96.6	0.420	0.491

CYP4F11	rs12971888	15887204	G > A	Intron 8	0.782	100	0.440	0.417
CYP4F11	rs6512074	15887894	A > G	Intron 8	0.496	92.6	0.471	0.361
CYP4F11	rs6512075	15888067	C > T	Intron 8	0.677	99.3	0.449	0.382
CYP4F11	rs7253051	15888131	G > C	Intron 8	0.600	100	0.426	0.486
CYP4F11	rs1471112	15891458	T > G	Intron 8	1.000	100	0.265	0.242
CYP4F11	rs12978309	15892188	T > A	Intron 8	0.782	100	0.440	0.361
CYP4F11	rs11086012	15893643	C > A	Intron 8	0.966	100	0.268	0.283
CYP4F11	rs4808409 ^b	15894379	G > T	Intron 6	0.008	73.8	0.445	0.492
CYP4F11	rs3746152	15895519	T > A	Intron 6	1.000	100	0.037	0.025
CYP4F11	rs8104361 ^b	15895714	A > G	Exon 6, Missense, Arg276Cys	1.000	48.3	0.014	0.258
CYP4F11	rs7249167	15898359	G > A	Intron 4	0.603	100	0.174	0.167
CYP4F11	rs2305804	15899365	G > C	Intron 2	0.094	96.6	0.125	0.121
CYP4F11	rs3765071	15901034	G > A	Intron 2	1.000	96.6	0.441	0.361
CYP4F11	rs3765070 ^b	15901292	C > T	Exon 2, Synonymous, Ile106Ile	0.318	83.9	0.428	0.397
CYP4F11	rs2305801 ^b	15906141	G > A	Exon 1, Synonymous, Gly26Gly	0.207	74.5	0.135	0.250
CYP4F11	rs2305800	15906294	T > C	5' UTR	0.807	100	0.262	0.190
CYP4F11	rs11879253 ^b	15906491	G > C	5' UTR	0.163	68.5	0.147	0.250
CYP4F11	rs12985091	15906749	G > A	5' near gene	0.417	96	0.392	0.481
CYP4F11	rs3826950	15906891	C > T	5' near gene	0.871	99.3	0.260	0.192
CYP4F11	rs3810428	15907478	C > A	5' near gene	0.019	99.3	0.240	0.145
CYP4F11	rs3810427	15907650	G > T	5' near gene	0.509	100	0.406	0.492
CYP4F11	rs16980968	15907925	C > T	5' near gene	1.000	89.9	0.015	NA
CYP4F11	rs12460831	15908758	T > C	5' near gene	0.818	96	0.266	0.186
CYP4F11	rs2116951	15908806	A > G	5' near gene	1.000	100	0.040	0.018
CYP4F11	rs11670533	15911160	G > A	5' near gene	0.337	99.3	0.341	0.308
CYP4F11	rs4375789	15912804	G > A	5' near gene	1.000	98.7	0.265	0.173
CYP4F11	rs2116952	15913255	C > T	5' near gene	0.015	99.3	0.101	0.125
CYP4F11	rs2163859	15914143	C > A	5' near gene	1.000	100	0.265	0.192
-	rs12327750 ^c	15916687	T > C	Upstream of CYP4F11	1.784E-41	98.7	0.497	0.195
-	rs10500211	15919348	A > T	Upstream of CYP4F11	0.895	96	0.164	0.125
-	rs17641489 ^c	15920483	A > G	Upstream of CYP4F11	2.411E-43	98.7	0.500	0.052

Chromosomal positions are given in base pairs from the p-telomere of chromosome 19, as per HapMap Data release 27, March 2008, NCBI B36 assembly, dbSNP b126.

^a SNPs were monomorphic.

^b SNPs gave <90% call rate.

^c SNPs were not in HWE.

*Frequency data were compiled from HapMap R27 and NCBI dbSNP b126 databases.

Supplementary Table 2. Tagging SNPs across the *CYP4F12-CYP4F2-CYP4F11* locus ($r^2 \geq 0.9$).

Tagging SNP	Tagged SNPs	Gene	Chromosomal Location	Localisation
rs3093209	rs3093209	<i>CYP4F2</i>	15849420	3' near gene
	rs12610189	<i>CYP4F2</i>	15839641	Downstream of <i>CYP4F2</i>
	rs3093216	<i>CYP4F2</i>	15848737	3' near gene
	rs3093207	<i>CYP4F2</i>	15849658	3' near gene
	rs3093206	<i>CYP4F2</i>	15849753	3' near gene
	rs3093193	<i>CYP4F2</i>	15852914	Intron 9
rs3093173	rs3093173	<i>CYP4F2</i>	15856788	Intron 9
	rs3093180	<i>CYP4F2</i>	15856148	Intron 9
	rs3093167	<i>CYP4F2</i>	15857292	Intron 9
	rs3093160	<i>CYP4F2</i>	15857907	Intron 8
	rs2074901	<i>CYP4F2</i>	15858422	Intron 7
	rs3093135	<i>CYP4F2</i>	15865371	Intron 3
	rs3093134	<i>CYP4F2</i>	15865396	Intron 3
	rs2365178	<i>CYP4F2</i>	15866003	Intron 3
	rs3093129	<i>CYP4F2</i>	15866019	Intron 3
	rs3093128	<i>CYP4F2</i>	15866104	Intron 3
	rs3093124	<i>CYP4F2</i>	15866232	Intron 3
	rs3093121	<i>CYP4F2</i>	15866277	Intron 3
	rs3093116	<i>CYP4F2</i>	15866574	Intron 3
	rs3093115	<i>CYP4F2</i>	15866615	Intron 3
	rs3093114	<i>CYP4F2</i>	15867413	Exon 3, Synonymous, Ala82Ala
	rs3093112	<i>CYP4F2</i>	15867611	Intron 2
	rs3093110	<i>CYP4F2</i>	15868784	Intron 2
	rs3093106	<i>CYP4F2</i>	15869257	Exon 2, Synonymous, Pro55Pro
	rs3093103	<i>CYP4F2</i>	15869434	Intron 1
	rs3093100	<i>CYP4F2</i>	15869469	Intron 1
rs3093098	<i>CYP4F2</i>	15869512	Intron 1	
rs3093169	rs3093169	<i>CYP4F2</i>	15865800	Intron 3
	rs2006193	<i>CYP4F2</i>	15857008	Intron 9
rs12977516	rs12977516	<i>CYP4F11</i>	15886919	Intron 8
	rs7253051	<i>CYP4F11</i>	15888131	Intron 8
rs627971	rs627971	<i>CYP4F12</i>	15664094	Intron 9
	rs665872	<i>CYP4F12</i>	15664106	Intron 9
	rs4808362	<i>CYP4F12</i>	15664892	Intron 9
	rs593818	<i>CYP4F12</i>	15668884	Exon 13, Missense, Gly522Ser
	rs611848	<i>CYP4F12</i>	15669379	3' near gene
rs2886476	rs2886476	<i>CYP4F12</i>	15672717	3' near gene
	rs12976669	<i>CYP4F12</i>	15671312	3' near gene
	rs7255335	<i>CYP4F12</i>	15672079	3' near gene
	rs4808369	-	15691869	Intergenic, between <i>CYP4F12</i> and <i>CYP4F2</i>

Chromosomal positions are given in base pairs from the p-telomere of chromosome 19, as per HapMap Data release 27, NCBI B36 assembly, dbSNP b126.

Supplementary Table 3. Significant univariate associations with warfarin stable dose.

Variable	P
Age	3.96E-07
BMI	9.10E-05
Baseline Factor II*	1.40E-05
Gender	1.31E-04
CYP2C9*2_rs1799853	7.61E-07
CYP2C9*3_rs1057910	5.35E-08
VKORC1_rs9923231	2.15E-20

*Factor II was highly correlated with factors VII, IX, X, proteins C and S ($r > 0.6$).

Supplementary Results

Interaction between CYP4F2, CYP4F11 and CYP4F12

We used MetaCore™ to put *CYP4F2*, *CYP4F11* and *CYP4F12* into a cellular context to evaluate the significance of gene networks that these three genes participate in and to identify regulatory cascades that lead to or from these genes. , highlights the network interactions of nuclear transcriptional factors relating to the gene expression of *CYP4F2*, *CYP4F11* and *CYP4F12*. Several nuclear transcription factors including pregnane X receptor (PXR), aryl hydrocarbon receptor (AHR), activator protein 1(AP-1), peroxisome proliferator-activated receptor (PPAR) alpha, sterol regulatory element-binding protein 1 (SREBP-1), retinoid X receptor (RXR) and retinoic acid receptor (RAR) are known to be involved in the metabolism and clearance of diverse endogenous and exogenous compounds as well as gene activation (Pavek and Dvorak, 2008;Zhou et al., 2009).

Supplementary Discussion

Interaction between CYP4F2, CYP4F11 and CYP4F12

Our network analysis shows that the regulation of *CYP4F2*, *CYP4F11* and *CYP4F12* expression is co-ordinated via numerous nuclear transcription factors including AP-1, RXR, RAR and SREBP, which are also known to be involved in the regulation of a number of other P450 isoforms (Rushmore and Kong, 2002;Roth et al., 2008). This is consistent with data from various cell lines: AP-1 and RXR have been shown to regulate *CYP4F11* expression (Wang et al., 2010) in human keratinocyte-derived HaCaT cells; RXR stimulated whilst RAR repressed *CYP4F2* expression in the HepG2 cell line (Zhang et al., 2000;Zhang and Hardwick, 2000); SREBP mediated the induction of *CYP4F2* expression by statins in primary human hepatocytes and HepG2 cells (Hsu et al., 2007); and PXR has been shown to regulate *CYP4F2* expression in healthy human lymphocytes (Siest et al., 2008) and *CYP4F12* expression in primary human hepatocytes (Hariparsad et al., 2009). Further work is required to further assess the cross-regulation of the *CYP4F* genes.

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