Supplementary Materials

Supplementary Methods

Haplotype associations with remission

Haplotype analysis was performed with SNPs across the 5’-flanking region (5’-FR) and intron 1 for their possible association with remission in STAR*D WNH subjects. Score tests implemented in the haploStats R package (Schaid et al. Am. J. Human Genet. 70:425-434, 2002), with an additive haplotype effect model, were used to perform these analyses. A separate analysis included SNPs in the proximal promoter for S-COMT (intron 2) plus rs4680 (the common functional Val108/158Met polymorphism). Finally, a three-locus haplotype (rs737865 + rs4680 + rs165599) that has been referred to as the “Shifman haplotype” (Shifman et al., Am. J. Hum. Genet. 71:1296-1302, 2002), was also assessed for its possible association with remission. These haplotype analyses were performed only for the WNH subjects because of the relatively small number of subjects of other ethnic groups.

Supplementary Results

Association of remission with COMT haplotypes

COMT linkage disequilibrium (LD) structure in WNH patients was determined using the Haploview 3.3 program for the 23 genotyped *COMT* SNPs in the 1235 WNH STAR*D subjects studied. Figure 1B shows that at least two major “haplotype blocks” were observed in these DNA samples, a pattern similar to that observed previously during our resequencing study of 60 DNA samples from Caucasian subjects (Ji et al., Cancer Res. 68:5997-6005, 2008). This structure also suggested that SNPs genotyped within the 5’-FR and intron 1, the region containing the distal promoter for MB-COMT, are in strong LD. Rs13306278 mapped to this “haplotype block” and is indicated in Figure 1B with a red box.

Based on the *COMT* haplotype structure as well as the biological importance of MB-COMT in brain (Axelrod and Tomchick, J. Biol. Chem. 233:702-705, 1958), haplotype association analyses were performed separately for SNPs located in the distal promoter (5’-FR + intron 1) and in the proximal promoter (intron 2) plus the heavily studied Val108/158Met polymorphism (rs4680). The distal promoter haplotype analysis results are summarized in Supplementary Table 4. There was strong evidence (global simulation *P*-value = 0.026) that haplotypes in this region were associated with remission in WNH subjects. Most significant were Haplotype No. 1 (*P*-value = 0.029) and a rare haplotype, Haplotype No. 9 (*P*-value =

0.00045). Haplotype No. 1, present in 13% of the WNH subjects, was associated with decreased remission during SSRI therapy. Because this haplotype contains the rs13306278 variant nucleotide, the variant that we found to be associated with a decrease in remission during the single SNP analysis, the haplotype effect shown in Table 2 is most likely driven by this SNP. Haplotype analysis for the proximal promoter plus the Val108/158Met polymorphism did not yield significant observations, suggesting that this region is less important for variation in remission during SSRI therapy than is the distal promoter. We also assessed a possible effect of the 3-locus (rs737866 + rs4680 + rs165599) “Shifman haplotype”. We did not observe a significant association of this haplotype with remission in the STAR*D WNH subjects.

Supplementary Table 1

Single SNP associations for the subset of patients who remained in the study for ≥ 6 weeks and were not found to be non-compliant.

		WNH					Black					WH				
		Association			MAF		Association			MAF		Association			MAF	
SNP	rs#	P-value*	OR (allelic)	95% CI	NonremittersN = 553	Remitters N = 521	P-value*	OR (allelic)	95% CI	Nonremitters N = 144	Remitters N = 89	P-value*	OR (allelic)	95% CI	Nonremitters N = 122	Remitters N = 74
5'-FR(706)	rs4646310	0.15	1.17	0.95, 1.45	0.18	0.20	0.74	0.90	0.47, 1.71	0.10	0.09	0.50	0.78	0.38, 1.60	0.10	0.08
5'-FR(-628)	rs2020917	0.06	0.83	0.69, 1.01	0.29	0.25	0.80	1.08	0.60, 1.95	0.10	0.11	0.11	0.65	0.38, 1.11	0.22	0.15
5'-FR(-485)	rs13306278	0.02	0.73	0.57, 0.94	0.15	0.12	0.20	2.20	0.66, 7.35	0.01	0.03	0.17	0.55	0.23, 1.31	0.09	0.05
Intron1(99)	rs45454096	0.42	1.19	0.78, 1.81	0.04	0.05	0.56	0.74	0.27, 2.03	0.05	0.03	0.84	1.1	0.45, 2.69	0.05	0.05
Intron1(689)	rs737866	0.06	0.83	0.69, 1.01	0.29	0.25	0.59	1.16	0.68, 1.98	0.13	0.15	0.09	0.63	0.37, 1.08	0.22	0.15
Intron1(1987)	rs933271	0.03	1.23	1.02, 1.48	0.26	0.30	0.32	0.82	0.56, 1.21	0.41	0.36	0.46	0.85	0.56, 1.30	0.44	0.40
Intron1(8218)	rs5993883	0.92	1.01	0.85, 1.20	0.49	0.49	0.41	0.85	0.58, 1.25	0.48	0.44	0.04	0.65	0.43, 0.98	0.45	0.34
Intron1(15757)	rs740603	0.12	0.87	0.74, 1.03	0.47	0.49	0.20	1.29	0.88, 1.90	0.43	0.49	0.06	0.68	0.46 1.01	0.46	0.36
Intron2(201)	rs165722	0.47	0.94	0.81, 1.11	0.47	0.46	0.40	1.16	0.82, 1.64	0.48	0.48	0.12	0.71	0.46 1.10	0.37	0.45
Intron2(832)	rs3810595	0.15	0.88	0.74, 1.05	0.40	0.37	0.55	0.90	0.63, 1.28	0.38	0.35	0.07	0.66	0.42, 1.03	0.36	0.27
Intron2(935)	rs11569716	0.53	0.63	0.15, 2.67	0.00	0.00	0.40	1.30	0.70, 2.43	0.09	0.11	0.91	1.11	0.18, 6.79	0.01	0.01
Exon3(186)	rs4633	0.58	1.05	0.89, 1.24	0.47	0.46	0.11	0.72	0.48, 1.08	0.35	0.28	0.13	1.4	0.90, 2.17	0.36	0.43
Exon4(304)	rs5031015	N/A	N/A	N/A	0.00	0.00	0.61	0.65	0.12, 3.44	0.02	0.01	N/A	N/A	N/A	0.00	0.00
Exon4(408)	rs4818	0.13	0.88	0.74, 1.04	0.39	0.36	0.75	0.93	0.61, 1.43	0.22	0.21	0.05	0.62	0.39, 1.00	0.33	0.23
Exon4(472)	rs4680	0.56	1.05	0.89, 1.24	0.48	0.46	0.46	0.86	0.58, 1.28	0.30	0.27	0.10	1.44	0.93, 2.24	0.35	0.43
Exon5(597)	rs769224	0.83	1.06	0.62, 1.84	0.02	0.03	0.45	1.26	0.69, 2.29	0.10	0.12	0.18	0.35	0.07, 1.66	0.04	0.01
Intron5(75)	rs4646315	0.66	1.05	0.84, 1.32	0.17	0.18	0.07	0.58	0.33, 1.04	0.16	0.09	0.29	1.29	0.81, 2.07	0.22	0.27
Intron5(310)	rs4646316	0.68	0.96	0.79, 1.17	0.24	0.23	0.21	1.33	0.85, 2.08	0.17	0.22	0.08	0.6	0.35, 1.05	0.23	0.15
Intron5(739)	rs165774	0.69	1.04	0.87, 1.23	0.33	0.33	0.41	0.83	0.53 1.30	0.22	0.19	0.37	1.26	0.76, 2.10	0.15	0.19
Intron5(1354)	rs174696	0.07	1.21	0.98, 1.49	0.20	0.24	0.86	1.03	0.72, 1.50	0.43	0.42	0.85	1.04	0.70, 1.54	0.48	0.47
Intron5(3870)	rs9332377	0.35	0.90	0.71, 1.13	0.16	0.15	0.53	1.14	0.75, 1.75	0.32	0.35	0.10	0.56	0.28, 1.12	0.14	0.09
3'-FR(23)	rs9332381	0.03	1.58	1.05, 2.39	0.04	0.06	0.93	0.98	0.64, 1.51	0.26	0.26	0.31	0.59	0.21, 1.64	0.06	0.03
3'-FR(1338)	rs165599	0.61	1.05	0.87, 1.26	0.31	0.32	0.46	1.16	0.78, 1.72	0.33	0.29	0.19	0.75	0.49, 1.15	0.48	0.41

NOTE: The 5'-FR(-485) SNP that was pursued in our replication study and the heavily studied Val158/108Met SNP (rs4680) are "boxed".

Abbreviations: MAF, minor allele frequency; OR, odds ratios; WNH, White Non-Hispanic; WH, White Hispanic.

*Trend test p-value assuming a log-additive allele effect, not adjusted for multiple comparisons.

Supplementary Table 2: Single SNP associations with remission, after accounting for the effects of "tolerance", days in study and dose.

SNP	rs#	WNH			Black			WH		
		P1	P2	P3	P1	P2	P3	P1	P2	P3
5'-FR(706)	rs4646310	0.236	0.292	0.441	0.801	0.499	0.410	0.525	0.940	0.361
5'-FR(-628)	rs2020917	0.060	0.097	0.151	0.833	0.874	0.514	0.147	0.230	0.337
5'-FR(-485)	rs13306278	0.038	0.016	0.003	0.360	0.415	0.124	0.125	0.309	0.303
Intron1(99)	rs45454096	0.566	0.878	0.878	0.560	0.604	0.432	0.930	0.448	0.473
Intron1(689)	rs737866	0.058	0.100	0.150	0.862	0.995	0.818	0.127	0.153	0.252
Intron1(1987)	rs933271	0.091	0.176	0.324	0.265	0.486	0.687	0.405	0.738	0.289
Intron1(8218)	rs5993883	0.892	0.897	0.797	0.131	0.378	0.542	0.055	0.187	0.062
Intron1(15757)	rs740603	0.098	0.155	0.131	0.145	0.303	0.180	0.064	0.213	0.107
Intron2(201)	rs165722	0.374	0.513	0.575	0.441	0.444	0.112	0.090	0.091	0.072
Intron2(832)	rs3810595	0.119	0.116	0.217	0.491	0.322	0.809	0.085	0.074	0.096
Intron2(935)	rs11569716	0.525	0.369	0.694	0.717	0.946	0.713	0.976	0.915	0.700
Exon3(186)	rs4633	0.469	0.620	0.714	0.083	0.181	0.096	0.092	0.090	0.038
Exon4(304)	rs5031015	N/A	N/A	N/A	0.517	0.759	0.766	N/A	N/A	N/A
Exon4(408)	rs4818	0.119	0.116	0.200	0.850	0.767	0.783	0.069	0.064	0.070
Exon4(472)	rs4680	0.449	0.560	0.657	0.354	0.407	0.310	0.061	0.085	0.032
Exon5(597)	rs769224	0.493	0.855	0.924	0.395	0.339	0.435	0.145	0.159	0.086
Intron5(75)	rs4646315	0.680	0.291	0.207	0.084	0.098	0.059	0.125	0.228	0.041
Intron5(310)	rs4646316	0.466	0.273	0.347	0.142	0.187	0.283	0.116	0.063	0.051
Intron5(739)	rs165774	0.643	0.911	0.674	0.360	0.292	0.397	0.322	0.316	0.524
Intron5(1354)	rs174696	0.152	0.050	0.136	0.825	0.554	0.600	0.901	0.952	0.870
Intron5(3870)	rs9332377	0.693	0.873	0.734	0.761	0.607	0.659	0.089	0.168	0.295
3'-FR(23)	rs9332381	0.006	0.081	0.457	0.584	0.487	0.514	0.156	0.279	0.043
3'-FR(1338)	rs165599	0.352	0.208	0.399	0.970	0.956	0.760	0.061	0.203	0.074

NOTE: The 5'-FR(-485) SNP that was pursued in our replication study and the heavily studied Val158/108Met SNP (rs4680) are "boxed".

Abbreviations: WNH, White Non-Hispanic; WH, White Hispanic.

P1, p-value for log-additive effect of SNP

P2, p-value for log-additive effect of SNP, after accounting for the effect of tolerance

P3, p-value for log-additive effect of SNP, after accounting for the effect of tolerance, dose, and days in study (these are main contributors to remission)

Supplementary Table 3: Association between change in QIDS-C16 scale as a quantitive trait outcome ("remission") with *COMT* genotypes.

SNP	rs#	WNH	Black	WH
		P	P	P
5'-FR(706)	rs4646310	0.433	0.573	0.606
5'-FR(-628)	rs2020917	0.158	0.935	0.082
5'-FR(-485)	rs13306278	0.695	0.761	0.253
Intron1(99)	rs45454096	0.794	0.224	0.656
Intron1(689)	rs737866	0.111	0.875	0.071
Intron1(1987)	rs933271	0.374	0.221	0.540
Intron1(8218)	rs5993883	0.634	0.149	0.355
Intron1(15757)	rs740603	0.133	0.051	0.377
Intron2(201)	rs165722	0.780	0.218	0.168
Intron2(832)	rs3810595	0.504	0.621	0.459
Intron2(935)	rs11569716	0.973	0.666	0.985
Exon3(186)	rs4633	0.841	0.013	0.145
Exon4(304)	rs5031015	N/A	0.908	N/A
Exon4(408)	rs4818	0.447	0.829	0.412
Exon4(472)	rs4680	0.878	0.246	0.076
Exon5(597)	rs769224	0.477	0.152	0.396
Intron5(75)	rs4646315	0.286	0.254	0.186
Intron5(310)	rs4646316	0.965	0.051	0.126
Intron5(739)	rs165774	0.598	0.376	0.341
Intron5(1354)	rs174696	0.190	0.537	0.701
Intron5(3870)	rs9332377	0.891	0.089	0.112
3'-FR(23)	rs9332381	0.001	0.739	0.646
3'-FR(1338)	rs165599	0.250	0.984	0.117

NOTE: The 5'FR(-485) SNP that was pursued in our replication study and the heavily studied Val158/108Met SNP (rs4680) are "boxed".
The 3'-FR(23) SNP was also "boxed" since it was significantly associated with outcome in this test.
P, p-value for 1 df (log-additive model) test adjusted for baseline QIDS
Abbreviations: WNH, White Non-Hispanic; WH, White Hispanic.

Supplementary Table 4. Association of *COMT* distal promoter haplotypes with remission in WNH STAR*D subjects.

	COMT Distal Promoter Haplotypes										
Hap ID #	5'-FR(706)	5'-FR(-628)	5'-FR(-485)	Intron1(99)	Intron1(689)	Intron1(1987)	Intron1(8218)	Intron1(15757)	Hap-Frequency	Hap-Score	Sim *P* -value
1	G	T	T	G	G	T	G	G	0.13	-2.18	0.0289
2	G	C	C	G	A	T	T	G	0.03	-1.21	0.2190
3	A	C	C	G	A	C	G	G	0.15	-0.64	0.5242
4	G	C	C	G	A	C	T	G	0.01	-0.05	0.9588
5	G	T	C	G	G	T	G	G	0.13	0.04	0.9666
6	G	C	C	G	A	C	T	A	0.04	0.47	0.6321
7	G	C	C	G	A	T	T	A	0.40	0.55	0.5888
8	G	C	C	A	A	C	G	G	0.04	0.89	0.3714
9	A	C	C	G	A	C	G	A	0.03	3.51	0.0002

Haplotypes significantly associated with remission in STAR*D WNH subjects are highlighted in gray.

Global simulation *P*-value = 0.026.

Max-Stat simulation *P*-value = 0.004.