European Journal of Human Genetics (2009) 17, 946–957

www.nature.com/ejhg

ARTICLE

Pharmacogenetics of antipsychotic response in the CATIE trial: a candidate gene analysis

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The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Phase 1 Schizophrenia trial compared the effectiveness of one typical and four atypical antipsychotic medications. Although trials such as CATIE present important opportunities for pharmacogenetics research, the very richness of the clinical data presents challenges for statistical interpretation, and in particular the risk that data mining will lead to false-positive discoveries. For this reason, it is both misleading and unhelpful to perpetuate the current practice of reporting association results for these trials one gene at a time, ignoring the fact that multiple gene-by-phenotype tests are being carried out on the same data set. On the other hand, suggestive associations in such trials may lead to new hypotheses that can be tested through both replication efforts and biological experimentation. The appropriate handling of these forms of data therefore requires dissemination of association statistics without undue emphasis on select findings. Here we attempt to illustrate this approach by presenting association statistics for 2769 polymorphisms in 118 candidate genes evaluated for 21 pharmacogenetic phenotypes. On current evidence it is impossible to know which of these associations may be real, although in total they form a valuable resource that is immediately available to the scientific community.
European Journal of Human Genetics (2009) **17,** 946–957; doi:10.1038/ejhg.2008.264; published online 21 January 2009

Keywords: schizophrenia; neurocognition; RIMS1; quetiapine; GRM8; discontinuation

Introduction

One notable result of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial of antipsychotic effectiveness in schizophrenia[1] was the high discontinuation rates among the four atypical and one typical antipsychotic drugs trialed – ranging from 64% for olanzapine to 82% for quetiapine. An even more striking outcome was the rough equivalence among the medicines in most measures when patients on each drug are considered as a group. Although current medicines therefore do not appear better or worse on average, at the individual patient level, variation in response is pronounced. A major goal of psychiatric pharmacogenetics is therefore the prediction of the drug that will work best, with the fewest side effects, for individual patients with schizophrenia.

Unfortunately, our capacity to predict therapeutic response and clinically significant side effects in individual patients is currently extremely limited. There are, for example, no effective means by which to match individual patients to medications that offer them more symptom

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Received 11 June 2008; revised 11 October 2008; accepted 9 December 2008; published online 21 January 2009

control or that reduce their chances or severity of adverse reactions. In general, studies implicating genetic variants in antipsychotic response have not been well replicated, with follow-up studies often using different genetic markers and models, testing heterogeneous study populations, and affected by a publication bias of positive findings.[2,3] There may be some cumulative evidence for associations with weight gain and tardive dyskinesia, although effect sizes are generally small.[3–6] There are examples of genetic associations with antipsychotic response that have led to the development of predictive tests: a human leukocyte antigen test that measures the risk of developing agranulocytosis when treated with clozapine,[7] and a combination of polymorphisms that can be used in certain patient groups to predict clozapine response;[8] however, both these tests are of very limited clinical utility.[5] Finally, the AmpliChip CYP450 pharmacogenetic test was hoped to help predict antipsychotic response.[9] However, a recent study showed that these genotypes cannot predict antipsychotic dose or response in real-world settings,[10] and the AmpliChip too is expected to be of little utility in antipsychotic prescribing.[11]

Here we have identified 21 response phenotypes, some of which are partially correlated, and evaluated them in the 756 CATIE participants consented for genetic studies. Although in the CATIE trial, the primary phenotype was discontinuation of treatment for any cause, we felt that this end point was too heterogeneous for a genetic study. Instead, we examined CATIE secondary outcome measures, including discontinuation due to inefficacy, weight gain and change in PANSS scores. To reduce the scope for data mining, our philosophy for defining these pharmacogenetic phenotypes was, wherever possible, to follow how CATIE investigators evaluated and reported responses in the trial. For example, a weight-gain 'case' was defined as a patient who gained 7% or more of his or her baseline body weight (cf. Lieberman *et al*.[1]). Finally, as neurocognitive impairment in schizophrenia is a significant predictor of outcome[12] and has been suggested to be a particularly suitable trait for the genetic study of schizophrenia,[13] we searched for genetic predictors of cognitive change, utilizing data from detailed cognitive assessments performed throughout the CATIE trial and reflecting various measures of verbal learning and memory, working memory, motor function, attention and executive function. All phenotypes in this paper were defined before genetic analyses were performed to prevent false positives due to unconstrained or biased data mining.

Materials and methods

A detailed description of the participants consented for genetic study is provided in Sullivan *et al*.[14] SNPs were genotyped using Illumina GoldenGate technology. For further description of the CATIE trial and participants and detailed description of gene and SNP selection, genotyping and quality control, phenotype definitions and statistical analyses, please see Supplementary Methods. All genes examined and their SNP coverage are shown in Table 1; all phenotypes and sample sizes for each association test are shown in Table 2.

Results

In total, 21 phenotypes were tested (Table 2). Two associations were significant after permutation correction for all tested SNPs (see below). No associations were significant after correction for all SNPs and all phenotypes tested ($P<9\times10^{-7}$).

Neurocognition

Study-wide significant association SNP rs7778604, located in intron 2 of the *GRM8* gene, was associated with antipsychotic-induced change in verbal memory, and this remained significant after permutation correcting for all studied SNPs (corrected $P=0.02$, uncorrected $P=0.00001$, $n=447$; Figure 1). The SNP was present in both African-American and European-American participants, and to ensure that the association was not caused by uncorrected stratification, we repeated the analysis of this phenotype with 10 axes of ancestry, instead of a single axis. The association remained significant at 0.00037 (uncorrected), but was no longer significant after correction by permutation for all tested SNPs ($P=0.58$). Those patients carrying the rarer variant ($n=97$) tended to improve in verbal memory with 8 weeks of treatment, whereas those homozygous for the common allele ($n=369$) performed worse after 8 weeks of phase 1 treatment. The associated SNP is in a highly alternatively spliced gene but has no obvious function. It is in strong linkage disequilibrium (LD) with a number of other intronic SNPs, including rs17863182, which lies in the middle of a highly conserved region 3 kb upstream from another alternative exon.

Multiple hits To identify SNPs with a general effect across cognitive domains, we first looked at the top hits associated with the principal component axis drawn from the change measures of all tests. The strongest association was with rs10954143, an intronic SNP in *GRM8* ($P=0.0003$) that was associated with many other intronic SNPs. This association seemed to be primarily driven by letter-number sequencing ($P=0.001$), continuous performance test (0.002) and mazes ($P=0.03$), so it is associated with a number of different domains. Similarly, the next strongest associated SNPs were two tightly linked SNPs in the 3′-UTR of *ADCY1*, rs2461127 and rs2471267 (each with $P=0.0005$), and these were also driven by associations in letter-number sequencing ($P=0.01$) and continuous performance ($P=0.06$), as well as verbal recall ($P=0.01$) and FAS ($P=0.06$).

Table 1 Coverage for each gene in relevant HapMap populations

Gene	No. of original tags	No. of tags passed QC	Average r^2CEU	Average r^2YRI	Gene	No. of original tags	No. of tags passed QC	Average r^2CEU	Average r^2YRI	Gene	No. of original tags	No. of tags passed QC	Average r^2CEU	Average r^2YRI
ACE	19	17	0.88	0.58	DRD5	3	2	0.00	0.00	HTR2B	9	8	0.59	0.47
ACHE	6	4	0.00	0.77	GAD1	13	12	0.84	0.52	HTR2C	36	30	0.93	0.75
ADCY1	33	25	0.76	0.62	GAD2	22	21	0.92	0.47	HTR3A	11	10	0.52	0.51
ADCY2	80	75	0.75	0.53	GLS	19	16	0.84	0.67	HTR3B	13	12	0.69	0.67
ADCY8	84	75	0.82	0.67	GLUD1	8	7	0.78	0.52	HTR4	36	33	0.81	0.58
ADCY9	44	41	0.67	0.53	GLUD2	4	1	0.00	0.00	HTR5A	11	9	0.63	0.51
ADORA2A	9	7	0.42	0.92	GLUL	8	8	0.82	0.67	HTR6	8	8	0.90	0.57
BCHE	9	8	0.77	0.56	GRIA1	49	47	0.73	0.68	HTR7	13	12	0.78	0.60
BDNF	9	8	0.80	0.59	GRIA2	14	13	0.74	0.68	MAOA	9	8	0.86	0.28
CACNG2	48	40	0.69	0.56	GRIA3	86	74	0.78	0.50	MAOB	19	19	0.71	0.60
CAMK2A	26	25	0.70	0.35	GRIA4	42	39	0.82	0.65	MTHFR	12	12	0.73	0.63
CAMK2B	21	14	0.69	0.44	GRIN1	7	6	0.34	0.43	NOTCH4	29	23	0.73	0.56
CCL2	6	4	0.92	0.63	GRIN2A	75	75	0.79	0.60	NTRK2	77	70	0.84	0.65
CHAT	22	21	0.66	0.48	GRIN2B	114	109	0.70	0.63	PPP1R1B	3	3	0.82	0.67
CHRM1	10	9	0.61	0.52	GRIN2C	8	6	0.88	0.54	PPP3R1	9	9	0.87	0.71
CHRM2	31	29	0.80	0.58	GRIN2D	16	13	0.78	0.33	PPP3R2	1	1	0.01	0.01
CHRM3	55	51	0.71	0.50	GRIN3A	42	35	0.84	0.71	PRNP	13	11	0.88	0.49
CHRM4	2	2	0.00	0.24	GRIN3B	10	7	0.55	0.52	RELN	8	6	0.20	0.13
CHRM5	11	9	0.76	0.62	GRM1	53	50	0.86	0.69	RGS9	12	9	0.82	0.52
CHRNA10	7	5	0.58	0.36	GRM2	4	3	0.00	0.00	RIMS1	71	58	0.73	0.60
CHRNA2	16	15	0.72	0.51	GRM3	33	31	0.85	0.63	SLC17A6	15	15	0.73	0.52
CHRNA3	4	4	0.78	0.39	GRM4	32	28	0.66	0.54	SLC17A7	9	7	0.50	0.15
CHRNA4	8	6	0.67	0.49	GRM5	76	73	0.82	0.60	SLC18A1	15	13	0.77	0.52
CHRNA5	12	11	0.97	0.77	GRM6	14	13	0.67	0.62	SLC18A2	17	17	0.63	0.33
CHRNA6	4	4	0.73	0.64	GRM7	200	181	0.73	0.53	SLC1A1	51	48	0.63	0.51
CHRNA7	18	17	0.70	0.45	GRM8	275	244	0.90	0.77	SLC1A2	37	35	0.86	0.55
CHRNA9	13	10	0.84	0.40	GSK3A	2	2	0.00	0.00	SLC1A3	28	27	0.60	0.48
CHRNB2	10	9	0.24	0.36	GSK3B	21	19	0.94	0.88	SLC1A6	9	8	0.56	0.51
CHRNB3	11	11	0.93	0.60	HDC	15	14	0.60	0.59	SLC6A3	19	17	0.67	0.61
CHRNB4	8	8	0.56	0.29	HNMT	17	17	0.96	0.51	SLC6A4	11	10	0.59	0.35
COMT	23	18	0.81	0.44	HRH1	7	5	0.84	0.42	SNAP25	27	25	0.69	0.44
CREB1	13	13	0.89	0.78	HRH2	10	9	0.51	0.05	SOD1	8	8	0.77	0.64
CREBBP	24	23	0.62	0.52	HRH3	8	7	0.29	0.15	SOD2	7	4	0.65	0.36
DAO	9	8	0.77	0.63	HRH4	14	12	0.57	0.52	SYT11	9	9	0.86	0.39
DBH	27	22	0.62	0.37	HTR1A	4	4	0.00	0.00	SYT4	5	4	0.37	0.61
DDC	21	17	0.71	0.62	HTR1B	10	10	1.00	1.00	TH	7	6	0.22	0.24
DRD1	8	8	0.69	0.31	HTR1D	3	3	0.00	0.00	TPH2	25	24	0.90	0.63
DRD2	25	23	0.87	0.57	HTR1E	15	14	0.76	0.72	ZDHHC8	10	7	0.48	0.47
DRD3	17	17	0.84	0.55	HTR1F	5	5	1.00	0.90					
DRD4	4	4	0.00	0.19	HTR2A	23	22	0.70	0.43					

CEU, CEPH samples from Utah; YRI, Yoruban samples from Nigeria. Displayed are both the number of original SNPs ($n = 3072$) and those remaining after poorly genotyped SNPs were removed ($n = 2769$). The average r^2 calculations were based on phase II HapMap data including only SNPs with MAF > 0.05 in one or both of the populations. For each gene, each HapMap SNP was tested against all tags for that gene, and the highest pairwise r^2 value with any tag was used to calculate the average.

Table 2 Phenotypes analyzed

Phenotype (description)	*Sample size (case–control)*	*Description*	*Statistical analysis*
Visuospatial working memory change (*computerized test of spatial working memory*)	402		
Letter/number sequencing change (*reorder auditorily presented letter-number clusters*)	442		
FAS change (*name words beginning with F, A or S*)	447		
Categories change (*name words in particular category*)	447		
Digit symbol change (*(WAIS-R) draw symbols associated with digits*)	447	Neurocognitive baseline score subtracted from score at 2 months, only for subjects who are still on phase I drug at 2 months	All drug groups analyzed together, using linear regression with additive genetic model and including the Eigenstrat axis, sex, self-described race, baseline and phase I drug as covariates
WCST perseverative error change (*sort cards by correct sorting strategy*)	421		
Mazes change (*(WISC-R), timed navigation of pencil through mazes)*	439		
Verbal change (*recall of 12 nouns verbally presented 3 times*)	447		
Continuous performance change (*detecting rapidly presented repeated numbers*)	381		
Neurocognitive change principal component 1 (PC1)	447		
PANSS total change	524	PANSS baseline score subtracted from score at 3 months, only for subjects who are still on phase I drug at 3 months. Negative score reflects improvement as the higher the PANSS score the worse the symptoms	As for cognitive change
PANSS positive change	524		
PANSS negative change	524		
PANSS general psychopathology change	524		
Weight gain quantitative	653	Maximum % weight gain at any point during phase I	As for cognitive change
Weight gain case–control	472/181	Cases gained $\geq$7% of baseline weight at any point during phase I	Logistic regression, otherwise as for cognitive change
Discontinuation olanzapine inefficacy	127/21	Phase I data only, cases defined as patients who did not continue phase I drug until the end of the trial for whom the primary reason for discontinuation was recorded as 'inadequate therapeutic effect'	Logistic regression with additive genetic model including the Eigenstrat axis, sex and race as covariates
Discontinuation perphenazine inefficacy	79/35		
Discontinuation quetiapine inefficacy	87/47		
Discontinuation risperidone inefficacy	101/40		
Discontinuation ziprasidone inefficacy	50/19		

We then looked at the uncorrected *P*-values to examine all hits in common across multiple cognitive tests (<0.05), not including PC1 (Table 3). No SNPs were associated with all nine tests. The SNP that was associated with most tests (5/9) was rs1011427, an intronic SNP in *HTR4*, and was in complete LD with another intronic SNP. *HTR4* codes for the serotonin receptor 4 subunit, and has been associated with enhanced cognition in animals.[15–17] This SNP was associated with verbal fluency categories and letters, visuospatial working memory, verbal recall and digit symbol score (Table 3). As expected, it was also associated with the PC1 measure ($P=0.006$).

Other SNPs of particular interest include an intronic SNP in *ADCY1*, rs11766222 (PC1, $P=0.002$). *ADCY1* codes for the neurospecific type I adenylyl cyclase, involved in hippocampal long-term potentiation and certain forms of learning and memory. This SNP is in complete LD ($r^2=1$) with several other SNPs surrounding exons 12, 13 and 14, and associates with verbal fluency (letters), the auditory letter-number test, the continuous performance test and mazes. Also, of interest was rs1390938 (The136Ile), a non-synonymous coding SNP in *SLC18A1*, the gene that codes for the vesicular monoamine transporter 1 (PC1, $P=0.008$). This SNP has previously been associated with bipolar disorder[18] and in this study associated with verbal fluency (categories), the auditory letter-number test, verbal recall and digit symbol. All SNPs that associated with three or more of the cognitive phenotypes are displayed in Table 3.

Top hits We next examined the strongest cognitive associations. The lowest *P*-value was for rs17866959, an intronic SNP in *GRM8* that was present only in African-American patients and associated with change in Wisconsin card sorting test (WCST) score. The *P*-value for association with change in WCST errors was $P = 8.3 \times 10^{-6}$, and considering only African-Americans, the *P*-value was 2.4×10^{-6}. Those patients carrying the variant allele all declined in WCST performance except one participant whose score did not change; however, those participants not carrying this variant tended to slightly improve in performance with treatment.

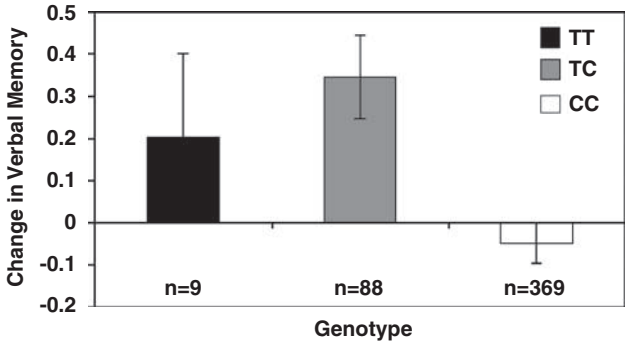

Figure 1 Association of GRM8 SNP rs7778604 with change in verbal memory ($n = 447$; uncorrected $P = 0.00001$). On average, the patients with the less common allele showed an improvement in memory, whereas the patients homozygous for the common allele did not.

The next two strongest hits, and the only others with $P < 10^{-4}$, were both intronic SNPs in *GRM7* that were associated with a change in visuospatial memory. The SNPs are rs7627369 and rs3864075, and they are in partial LD with each other ($r^2 = 0.25$ in this data set). Those individuals, both African-American and European-American, that carried the rare variant showed a stronger improvement in score across the 8 weeks of treatment (eg, rs7627369 homozygotes carrying the common variant made an average of 0.07 fewer errors *versus* those carrying the rare variant, who made 0.90 fewer errors after 8 weeks of treatment). SNP rs7627396 also associates with change in PANSS negative ($P = 0.0002$) and PANSS general psychopathology ($P = 0.0004$) scores.

We annotated the list of cognitive hits (<0.05) using WGAviewer,[19] and some of the SNPs seemed to be of particular note due to their position or the position of associated SNPs. SNPs that had a *P*-value <0.001, and also SNPs that had a *P*-value <0.01 and were located in a coding or otherwise putatively functional region of the gene, are displayed in Table 4. All SNPs with a *P*-value of association with a cognitive phenotype <0.05, along with their annotation, are displayed in Supplementary Results Table S1.

PANSS No PANSS association stood up to correction for all tested SNPs. All *P*-values described are uncorrected.

Table 3 All SNPs that associated ($P < 0.05$, uncorrected for multiple testing) with three or more of the nine cognitive phenotypes (not including PC1)

SNP	*Gene*	*Position*	*Number of hits*	*Categories (verbal fluency)*	*FAS (verbal fluency)*	*Letter/ number sequencing*	*Visuospatial working memory*	*Verbal recall*	*Continuous performance test*	*Digit symbol*	*Mazes*	*WCST perseverative errors*
rs1011427	**HTR4**	Intronic	**5**	0.0441	0.0218		0.0143	0.0446		0.03995		
rs11766222	ADCY1	Intronic	**4**		0.0275	0.0436			0.0313		0.0304	
rs339015	**GRM7**	Intronic	**4**	0.0200	0.0172	0.0116					0.0447	
rs1390938	**SLC18A1**	**Non-synonymous**	**4**	**0.0045**		**0.0014**		0.0398		0.01083		
rs1544938	ADCY2	Intronic	3		0.0295	0.0116			0.0724	0.0837		0.0056
rs919322	ADCY2	Intronic	3		0.0222	0.0316			0.0862			0.0274
rs2067477	CHRM1	Intronic	3		0.0612	0.0238		0.0442		0.01195	0.0897	
rs3920243	CHRNA7	Intronic	3			0.0762		0.0327	0.0495			**0.0017**
rs965435	CHRNA7	Upstream	3			0.0103	0.0103					0.0352
rs129968	CREBBP	Intronic	3					0.0211	**0.0033**	0.009104		
rs6539460	DAO	Intronic	3			0.0259	0.0150	0.0219				
rs324029	DRD3	Intronic	3				0.0164	0.0446				0.0239
rs3734120	HTR4	Downstream	3			0.0427			0.0448		0.0066	
rs4934292	GLUD1	Intronic	3		0.0303				0.0415	0.03173		
rs10512287	GRIN3A	Intronic	3	0.0236	0.0604				0.0230	0.01025		
rs1323423	GRIN3A	Intronic	3	0.0065	0.0387					0.03957		
rs1323426	GRIN3A	Intronic	3	0.0065	0.0387					0.03957		
rs1323427	GRIN3A	Intronic	3	0.0134		**0.0004**			0.0455			
rs1572560	GRIN3A	Intronic	3	0.0056	0.0141					0.03631		
rs2485523	GRIN3A	Intronic	3	**0.0044**	0.0152					0.04913		
rs163326	GRM7	Intronic	3	0.0590	0.0292	**0.0020**					0.0040	
rs756084	GRM7	Intronic	3				0.0090		0.0489		0.0369	
rs10954143	GRM8	Intronic	3			**0.0010**			**0.0018**		0.0289	
rs2237801	GRM8	Intronic	3					0.0411	0.0267		0.0381	
rs1187362	NTRK2	Intronic	3			0.0184			0.0384			0.0109
rs3776572	SLC1A3	Intronic	3	0.0115		0.0447		0.0279				

Highlighted in bold are *P*-values below 0.005, in light gray are borderline hits $0.1 > x > 0.05$.

Table 4 All SNPs that associated with a cognitive phenotype with a *P*-value <0.001, and all SNPs that associated with a cognitive trait with a *P*-value <0.01 that were in a putatively functional genic position

Phenotype	*SNP*	*No. of patients*	P-*value*	*Gene*	*Gene product*	*Position*
WCST perseverative errors	rs17866959	421	8.27E−06	GRM8	Metabotropic glutamate receptor 8	Intronic
Verbal recall	rs7778604	447	1.00E−05	GRM8	Metabotropic glutamate receptor 8	Intronic
Visuospatial working memory	rs7627369	402	2.90E−05	GRM7	Metabotropic glutamate receptor 7	Intronic
Visuospatial working memory	rs3864075	402	9.46E−05	GRM7	Metabotropic glutamate receptor 7	Intronic
Digit symbol	rs1491850	447	0.0001	BDNF	Brain-derived neurotrophic factor	Intergenic
Continuous performance	rs779760	381	0.0002	GRM7	Metabotropic glutamate receptor 7	Intronic
Categories (verbal fluency)	rs949731	447	0.0003	GRM7	Metabotropic glutamate receptor 7	Intronic
Change PC1	rs10954143	447	0.0003	GRM8	Metabotropic glutamate receptor 8	Intronic
Verbal recall	rs17867741	447	0.0004	GRM8	Metabotropic glutamate receptor 8	Intronic
Verbal recall	rs11563409	447	0.0004	GRM8	Metabotropic glutamate receptor 8	Intronic
Letter/number sequencing	rs1323427	442	0.0004	GRIN3A	NMDA receptor 3A	Intronic
WCST perseverative errors	rs7972662	421	0.0005	GRIN2B	NMDA receptor 2B	Intronic
Change PC1	rs2461127	447	0.0005	ADCY1	Adenylate cyclase 1	3′-UTR
Change PC1	rs2471267	447	0.0005	ADCY1	Adenylate cyclase 1	3′-UTR
WCST perseverative errors	rs10488597	421	0.0006	CHRM2	Muscarinic receptor 2	Intronic
Verbal recall	rs10512289	447	0.0006	GRIN3A	NMDA receptor 3A	Intergenic
Mazes	rs1361957	439	0.0007	GRM8	Metabotropic glutamate receptor 8	Intronic
WCST perseverative errors	rs2228703	421	0.0008	CACNG2	Stargazin	Intergenic
Continuous performance	rs1361956	381	0.0009	GRM8	Metabotropic glutamate receptor 8	Intronic
Change PC1	rs6774660	447	0.0009	GRM7	Metabotropic glutamate receptor 7	Intronic
Verbal recall	rs11563780	447	0.0009	GRM8	Metabotropic glutamate receptor 8	Intronic
FAS (verbal fluency)	rs3824519	447	0.0009	NTRK2	Neurotrophic tyrosine kinase receptor 2	Intronic
Mazes	rs10455255	439	0.001	RIMS1	RAB3A-interacting molecule 1	3′-UTR
Letter/number sequencing	rs1390938	441	0.001	SLC18A1	Vesicular monoamine transporter 1	Non-synonymous
FAS (verbal fluency)	rs707176	447	0.002	GRIA1	NMDA receptor subunit 1	Synonymous
Categories (verbal fluency)	rs1948	447	0.002	CHRNB4	Neuronal nicotinic receptor B4	3′-UTR
Change PC1	rs2067477	447	0.002	CHRM1	Muscarinic acetylcholine receptor 1	Synonymous
WCST perseverative errors	rs11575542	421	0.003	DDC	Dopa decarboxylase	Non-synonymous
WCST perseverative errors	rs3744959	421	0.003	SYT4	Synaptotagmin 4	3′-UTR
Categories (verbal fluency)	rs3743075	447	0.003	CHRNA3	Neuronal nicotinic receptor A3	Synonymous
Letter/number sequencing	rs942142	442	0.004	GRIN3A	NMDA receptor 3A	Synonymous
Letter/number sequencing	rs10512285	439	0.004	GRIN3A	NMDA receptor 3A	Synonymous
Change PC1	rs10249706	447	0.004	ADCY1	Adenylate cyclase 1	3′-UTR
Verbal recall	rs3829210	447	0.004	ADCY8	Adenylate cyclase 8	5′-UTR
Auditory letter-number test	rs10989589	442	0.004	GRIN3A	NMDA receptor 3A	Frameshift
Digit symbol	rs10225980	447	0.004	ADCY1	Adenylate cyclase 1	3′-UTR
Verbal recall	rs7301328	447	0.004	GRIN2B	NMDA receptor 2B	Synonymous
Categories (verbal fluency)	rs1390938	446	0.005	SLC18A1	Vesicular monoamine transporter 1	Non-synonymous
Continuous performance	rs2073440	381	0.005	HDC	Histidine decarboxylase	Non-synonymous
Change PC1	rs10225980	447	0.005	ADCY1	Adenylate cyclase 1	3′-UTR
FAS (verbal fluency)	rs3743075	447	0.006	CHRNA3	Neuronal nicotinic receptor A3	Synonymous

Table 4 (*Continued*)

Phenotype	*SNP*	*No. of patients*	P-*value*	*Gene*	*Gene product*	*Position*
Digit symbol	rs10249706	447	0.006	ADCY1	Adenylate cyclase 1	3′-UTR
FAS (verbal fluency)	rs1549521	447	0.006	HDC	Histidine decarboxylase	Synonymous
FAS (verbal fluency)	rs2273689	447	0.006	SLC1A2	Glutamate transporter 1	Splice site, intronic
Categories (verbal fluency)	rs3134942	447	0.006	NOTCH4	Notch4	Synonymous
WCST perseverative errors	rs11692815	421	0.006	PPP3R1	Calcineurin b, type 1	Synonymous
Verbal recall	rs2471267	447	0.007	ADCY1	Adenylate cyclase 1	3′-UTR
Mazes	rs891398	439	0.007	CHRNA2	Neuronal nicotinic receptor A2	Non-synonymous
Change PC1	rs1390938	446	0.008	SLC18A1	Vesicular monoamine transporter 1	Non-synonymous
Verbal recall	rs6280	447	0.008	DRD3	Dopamine receptor 3	Non-synonymous
WCST perseverative errors	rs3820594	421	0.008	SYT11	Synaptotagmin 11	5′-UTR
Visuospatial working memory	rs10022491	402	0.009	CHRNA9	Neuronal nicotinic receptor A9	Synonymous
Change PC1	rs11575542	447	0.009	DDC	Dopa Decarboxylase	Non-synonymous
Letter/number sequencing	rs2471267	442	0.009	ADCY1	Adenylate cyclase 1	3′-UTR
Letter/number sequencing	rs1549521	442	0.009	HDC	Histidine decarboxylase	Synonymous
Change PC1	rs7030238	446	0.009	GRIN3A	NMDA receptor 3A	3′-UTR

Table 5 SNPs that associated with PANSS total score with a *P*-value <0.01

				PANSS P-value			
SNP	*Gene*	*Gene product*	*Position*	*Positive*	*Negative*	*General psychopathology*	*Total*
rs3828628	ADCY2	Adenylate cyclase 2	Intronic	0.01	0.009	0.06	0.004
rs2241695	**CAMK2A**	**α-CaM kinase II**	**Intronic**	**0.02**	**0.001**	**0.007**	**0.0006**
rs869191	**CAMK2A**	**α-CaM kinase II**	**Intronic**	**0.03**	**0.01**	**0.002**	**0.0009**
rs4586	**CCL2**	**Small inducible cytokine A2**	**Synonymous**	**0.01**	**0.007**	**0.02**	**0.001**
rs4795893	**CCL2**	**Small inducible cytokine A2**	**7.8 kb upstream**	**0.006**	**0.1**	**0.02**	**0.004**
rs7164043	CHRNA7	Neuronal nicotinic receptor A7	Intronic	0.005	0.02	0.14	0.007
rs6808291	DRD3	Dopamine receptor D3	9 kb upstream	0.02	0.001	0.007	0.0006
rs2867383	DRD5	Dopamine receptor D5	2.3 kb downstream	0.12	0.02	0.006	0.004
rs1654670	GRIN2D	NMDA receptor 2D	Intronic	0.004	0.03	0.002	0.0005
rs362835	GRM1	Metabotropic glutamate receptor 1	Intronic	0.003	0.17	0.02	0.004
rs12275483	GRM5	Metabotropic glutamate receptor 5	Intronic	0.02	0.03	0.06	0.009
rs7733067	GRM6	Metabotropic glutamate receptor 6	3.6 kb upstream	0.006	0.15	0.03	0.007
rs7627369	GRM7	Metabotropic glutamate receptor 7	Intronic	0.09	0.0002	0.0004	0.0001
rs6774660	GRM7	Metabotropic glutamate receptor 7	Intronic	0.01	0.008	0.008	0.0009
rs17869476	GRM8	Metabotropic glutamate receptor 8	Intronic	0.004	0.34	0.009	0.005
rs1923882	HTR2A	Serotonin receptor 2A	Intronic	0.01	0.03	0.04	0.006
rs10061244	HTR4	Serotonin receptor 4	Intronic	0.09	0.06	0.004	0.004
rs1957893	PRKCH	Protein kinase C eta	Intronic	0.02	0.12	0.02	0.007
rs8103212	**SLC1A6**	**Excitatory amino-acid transporter 4**	**Intronic**	**0.006**	**0.04**	**0.02**	**0.002**
rs3746295	**SLC1A6**	**Excitatory amino-acid transporter 4**	**Synonymous**	**0.03**	**0.04**	**0.006**	**0.002**
rs3803927	SLC1A6	Excitatory amino-acid transporter 4	Intronic	0.04	0.03	0.01	0.004

Light gray coloring indicates that the SNP did not associate significantly with that test. Bold text indicates that the two same-gene SNPs are in LD ($r^2 \geq 0.5$).

Multiple hits To see if any SNP is associated with an overall improvement in symptoms, we looked first at SNPs that associated with PANSS total, and thus associated with multiple PANSS measures. Table 5 shows all 22 SNPS that are associated with PANSS total score with an uncorrected *P*-value of <0.01, along with their *P*-value for association with each of the three individual PANSS scores. The strongest PANSS total association was rs7627369, an intronic SNP in the metabotropic glutamate receptor gene *GRM7* that is of low frequency (4%) in both European- and African-Americans (and is also associated with visuospatial working memory, above). It is located in intron 8 of the gene and is associated with other SNPs in introns 8 and 9. Altogether, there were 19

participants who carried the rare allele at this locus who also had change scores for PANSS available at 3 months on the phase I drug. For each PANSS category, those with the rare allele showed greater improvement in score across the 3 months. On average, patients carrying the rare allele dropped 17.3 PANSS total points in comparison with 6.5 points dropped by patients homozygous for the common allele.

SLC1A6, a glutamate transporter gene, showed three associated SNPs but only two of the SNPs were in LD, indicating two independent hits in the same gene. One of the associated SNPs, rs3746295, is a synonymous coding SNP in the first exon.

There was another SNP located in a coding region that was associated with PANSS score. This was rs4586, in exon 2 of *CCL2* (aka *SCYA2*, *MCP1* and *MCAF*), the monocyte chemoattractant protein-1 gene. A promoter polymorphism in this gene (rs1024611) has earlier been associated with antipsychotic resistance.[20] SNP rs4586 is in LD with rs1024611 ($D' = 1.00$, $r^2 = 0.62$); therefore, it is possible that the association detected could be driven by rs1024611, which is not directly genotyped in this study.

Top hits for PANSS negative, positive and general psychosis No PANSS change hits were significant after correction for multiple testing. All of the strongest hits were in glutamate receptor genes. The overall top hit was rs7628369 (*GRM7* SNP, see above) associating with a change in PANSS negative score ($P = 0.0002$), and the next strongest was the same SNP associating with PANSS general psychosis score. After this, the strongest association was with rs2106190, a *GRM8* SNP that was associated with change in positive PANSS score at $P = 0.0008$. The next three strongest hits were all associated with change in PANSS negative score: rs2237547, in *GRM3*, $P = 0.0009$; rs10512287, in *GRIN3A*, $P = 0.0010$ and rs757656, in *GRM3*, $P = 0.0010$. All other associations were above $P = 0.001$. All PANSS change associations below 0.05, along with their locations and associated SNPs of interest, are shown in Supplementary Table S2.

Discontinuation

Study-wide significant association An SNP in intron 2 of *RIMS1*, rs502046, was associated with discontinuation from quetiapine due to inefficacy (raw *P*-value = 0.00009; study-wide corrected $P = 0.021$, $n = 129$, odds ratio = 3.1; Figure 2). The SNP is in strong LD with a number of other SNPs in introns 2, 3 and 4 (Figure 2). The patients, both European- and African-Americans, carrying the rare variant were more likely to continue with quetiapine treatment than those without (TT: 33/38 discontinued; CT: 36/62 discontinued; CC 13/29 discontinued). To confirm that the association was not caused by stratification beyond that accounted for by the first PCA axis, we repeated the analysis with 10 significant axes of ancestry included as covariates. Again, the resulting raw *P*-value was still strongly significant at $P = 0.00027$, but when corrected by permutation for all SNPs, this becomes 0.31. This SNP was not associated with discontinuation of any of the other drugs.

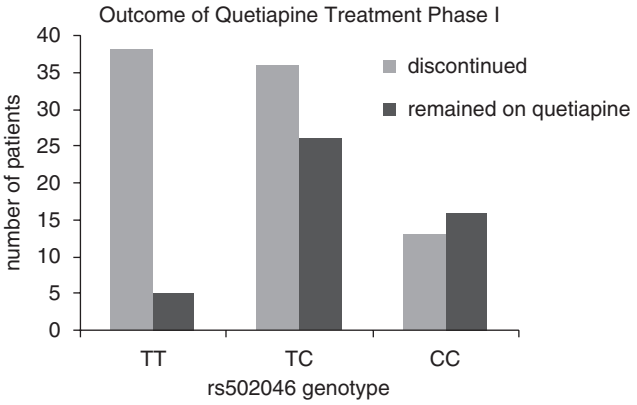

Figure 2 Association of *RIMS1* SNP rs502046 with quetiapine discontinuation ($n = 129$; uncorrected $P = 0.00009$). The patients carrying the rarer variant were much less likely to discontinue than those without.

Top hits All significant hits (uncorrected $P < 0.05$), along with their genic position, are shown in Supplementary Table S3. None of the strongest hits for discontinuation from a drug due to inefficacy made any strong biological sense. The top hit for discontinuation from olanzapine ($n = 141$) was an intronic SNP in *GRM7* that was associated with various other intronic SNPs within the gene, none of which had any obvious function (proximity to an exon, association with gene expression, location in known regulatory region). The top hit for discontinuation from perphenazine ($n = 106$), the single typical antipsychotic tested in CATIE, was rs2756271, located 1.5 kb upstream of the start of the prion protein gene *PRNP*, and again the SNP showed no obvious function, nor was it associated with any SNPs closer to the gene. The top hit for discontinuation from risperidone ($n = 136$) was rs10495449, an SNP just downstream from the muscarinic acetylcholine receptor gene *CHRM3*. The SNP shows no association with any other SNP within the gene and has no obvious function. Finally, the top hit for ziprasidone ($n = 60$) was rs7614915, a synonymous coding SNP in exon 8 of the *GRM7* metabotropic glutamate receptor gene.

Weight gain No weight-gain association stood up to correction for multiple testing. All *P*-values described are uncorrected.

Top hits The strongest association with maximum weight gain during phase I was an intronic SNP, rs7164043, in the α7-nicotinic acetylcholine receptor

subunit gene *CHRNA7* that was associated with quantitative weight gain $P=0.0001$. The SNP was also associated with change in PANSS total ($P=0.006$), positive ($P=0.01$), negative ($P=0.03$) and general (0.04) scores, change in visuospatial working memory ($P=0.01$) and change in verbal memory score (0.03). This SNP, however, is only present in African-American populations, with the exception of one patient self-described as 'White alone' and identified as of European ancestry by Eigenstrat analysis. Restricting the association of weight to African-Americans increases the significance of the association, such that those carrying the rare variant ($n=20$) gained an average of 7.02% of their baseline weight, whereas those without the variant allele ($n=176$) gained, on average, only 0.17% of their baseline weight.

The strongest hit for the weight-gain case–control association test was an intronic SNP in the serotonin receptor gene *HTR2A*, rs1928042 ($P=0.001$). This SNP was not associated with the quantitative measure of weight gain, so it is possible that the effect is a false positive. All significant hits (uncorrected $P<0.05$) for weight gain are displayed in Supplementary Table S4, and the top hits plus others that are of interest due to their genic position are displayed in Table 6.

Genotype imputation analysis Using tagging SNPs, we found strongly suggestive associations with different SNPs in the *GRM7* and *GRM8* genes with neurocognitive, PANSS and discontinuation phenotypes, and a strongly suggestive association of an *RIMS1* SNP with quetiapine discontinuation. As not all common variants in these genes have been genotyped, it is possible that there are ungenotyped SNPs that are more strongly associated with these phenotypes. We therefore imputed genotypes for all the HapMap SNPs for *GRM7*, *GRM8* and *RIMS1* using MaCH (Supplementary Methods). We first checked to see if there was a stronger association with discontinuation from quetiapine for any *RIMS1* SNP. We found that the genotyped SNP, rs502046, was the lowest associated SNP in this gene, even after examining associations with all permuted genotypes.

As *GRM7* and *GRM8* were associated particularly strongly with many phenotypes, we looked to see if imputed SNPs had stronger associations with any phenotype. For most phenotypes, the lowest *P*-value for an imputed SNP was of the same order of magnitude as that of the most strongly associated genotyped SNP. However, some phenotypes showed much stronger association with an imputed SNP; these are documented in Supplementary Table S1. None of the strongest associated phenotype detailed for *GRM7* and *GRM8* (above) improved when imputed SNPs were examined.

Previous findings Where possible, we also checked to see if we were able to replicate other findings of SNPs determining antipsychotic response in schizophrenia. In many cases, this was not possible, as previously associated polymorphisms have been non-SNP variants, such as VNTRs or in/dels. In addition, some important SNPs failed genotyping quality control (see Supplementary Information). Previously associated SNPs that we successfully genotyped here include *COMT* val108/158met (rs4680), *DRD2* -241-A/G (rs1799978), *DRD3* Ser9Gly (rs6280) and *HTR2A* 102-T/C(rs6313). The *COMT* SNP has been associated with antipsychotic-related

Table 6 Top associations with weight gain ($n=616$), tested either as a quantitative trait or as a case–control phenotype

Test	*SNP*	P-*value*	*Gene*	*Gene product*	*Type*
Quantitative	rs7164043	0.0001	CHRNA7	Neuronal nicotinic receptor A7	Intronic
Quantitative	rs2079731	0.0003	ADCY9	Adenylate cyclase 9	Intronic
Quantitative	rs1934124	0.0004	RIMS1	RAB3A-interacting molecule 1	Intronic
Case–control	rs1928042	0.0010	HTR2A	Serotonin receptor 2A	Intronic
Case–control	rs2770292	0.0017	HTR2A	Serotonin receptor 2A	Intronic
Quantitative	rs632994	0.0017	HRH2	Histamine receptor H2	7.6 kb downstream
Case–control	rs10505778	0.0019	GRIN2B	NMDA receptor 2b	Intronic
Case–control	rs480409	0.0019	GRM7	Metabotropic glutamate receptor 7	Intronic
Case–control	rs5320	0.006	DBH	Dopamine β-hydroxylase	Non-synonymous
Case–control	rs8192591	0.006	NOTCH4	NOTCH 4 (drosophila homolog)	Non-synonymous
Case–control	rs1390939	0.007	SLC18A1	Vesicular monoamine transporter 1	5′-UTR
Quantitative	rs1805482	0.009	GRIN2B	NMDA receptor 2B	Synonymous
Quantitative	rs11575553	0.014	DDC	DOPA decarboxylase	3′-UTR
Quantitative	rs1805522	0.02	GRIN2B	NMDA receptor 2B	Synonymous
Case–control	rs1948	0.02	CHRNB4	Neuronal nicotinic receptor B4	3′-UTR
Case–control	rs11575553	0.02	DDC	DOPA decarboxylase	3′-UTR
Quantitative	rs326175	0.03	ADCY2	Adenylate cyclase 2	3′-UTR
Case–control	rs130003	0.03	CREBBP	CREB-binding protein	Synonymous
Case–control	rs8178990	0.03	CHAT	Choline acetyltransferase	Non-synonymous
Case–control	rs660652	0.03	CHRNA3	Neuronal nicotinic receptor, A3	3′-UTR
Quantitative	rs3746295	0.04	SLC1A6	Excitatory amino-acid transporter 4	Synonymous
Quantitative	rs3749380	0.05	GRM7	Metabotropic glutamate receptor 7	Synonymous
Case–control	rs2270641	0.05	SLC18A1	Vesicular monoamine transporter 1	Non-synonymous

All drugs included in a single analysis.

improvement in working memory and negative symptoms[21,22] and better treatment response[23] (as well as other phenotypes not captured here). We found no significant associations of *COMT* val108/158met with any phenotype evaluated in this study. The *DRD2* SNP −241-A/G has been associated of a faster response to antipsychotic treatment,[24] but again we saw no association with any treatment response measures at the time points measured (PANSS scores: 12 weeks; neurocognitive change: 8 weeks). The *DRD3* Ser9Gly SNP has earlier been associated with a better response to risperidone treatment in Chinese (carriers of ser allele better response[25]), worse response to atypical antipsychotic treatment in Caucasians (ser/ser worse than other genotypes[26]) and improvement in positive symptoms while on olanzapine.[27] In this study, the SNP was associated with change in verbal memory at 8 weeks (uncorrected $P=0.008$), change in visuospatial memory at 8 weeks (uncorrected $P=0.03$) and discontinuation from risperidone due to inefficacy (uncorrected $P=0.02$, gly/gly less likely to discontinue due to inefficacy). Finally, the *HTR2A* 102-T/C SNP has been associated with better response to risperidone in Chinese (CC better response[28]) and with non-response to antipsychotic treatment in Caucasians (CC overrepresented in non-responders[29]). In this study, we saw only a very borderline association with change in verbal fluency (uncorrected $P=0.05$). In summary, although previously associated SNPs and related phenotypes were tested here, we could not provide strong support for the previous associations.

Discussion

This study has identified suggestive associations that if confirmed could be of considerable clinical significance. Notable among these findings is a polymorphism that is strongly associated with discontinuation of quetiapine (rs502046, in *RIMS1*). When randomized onto quetiapine in phase 1 of the CATIE trial, a minority of patients stayed on the drug (35%) but most discontinued. We have shown that those patients who continued on the drug, presumably responding well, carried a rare variant at the associated locus, and for those patients homozygous for the rare allele, the continuation rate was 55%. If this association is confirmed, quetiapine would likely emerge as a first-line choice for the 22% of patients who carry the favorable genotype. Attempted replication therefore of this association is a priority.

The second study-wide significant association was between a *GRM8* variant (rs7778604) and improvement in verbal memory over 8 weeks of antipsychotic treatment. No measure of cognitive improvement, including verbal memory, differed between the medications used in this trial,[30] nor did the genetic association with rs7778604 differ significantly between treatment groups. This variant, therefore, appears to convey a general increased responsiveness to the cognitive benefits of antipsychotic treatment. An improved understanding of the mechanisms of this effect could be useful in developing adjunctive medications for improving cognitive response to antipsychotic drugs in schizophrenia. This may have great relevance to the study of cognitive deficits in schizophrenia. Numerous pharmaceutical industry drug-development programs and government efforts, such as the NIH-sponsored project Measurement and Treatment Research to Improve Cognition in Schizophrenia,[31] are currently devoted to finding pharmacologic compounds or behavioral strategies that may improve cognitive impairment in schizophrenia.

On balance, these results, like most findings in psychiatric genetics, remain equivocal. There was no single association that stood up to correction for all SNPs and all phenotypes analyzed. However, given the study size and the number of pharmacogenetic questions addressed, there is clearly potential for type II error. This could have been reduced in part by matching particular candidate genes up to the phenotypes that they could most plausibly affect, rather than testing all genes against all phenotypes. However, with the current state of knowledge, we felt that such matching would have to be based at least in part on guesswork and consequently opted for the broader approach presented here. For these reasons, we felt that it was important to make available all associations with uncorrected *P*-values <0.05, for potential targeted replication by other interested researchers. It should also be noted that as this study was limited to common SNPs there could be unrepresented polymorphisms in these genes with stronger effects on the pharmacogenetic phenotypes than we have found here such as rare SNPs, large structural variants recently implicated in schizophrenia,[32,33] in-dels or VNTRs.

In addition, it is important to appreciate that the CATIE study was not designed with genetic hypotheses in mind, and it is not well powered to test many of the most pressing pharmacogenetic questions. Clinical studies such as CATIE could be an invaluable resource for conducting genetic studies that have direct relevant to patient populations. However, for these studies to be effective, it is an absolute requirement that the genetic component is considered *a priori* and a set of genetic hypotheses established in advance to ensure sufficient power to explore the relevant questions and reduce the potential for data mining. All study patients should be encouraged to take part in the genetic analyses both to maximize power for the genetic hypotheses and so that the genetic component accurately reflects the overall sample composition. In addition, it is important that psychiatric practitioners facilitate complementary collections in the regular care setting that allow the same hypotheses to be tested and replication analyses to be performed. This is the only way to realize the potential of these trials for advancing personalized medicine.

By contemporary standards for association genetics, nothing in psychiatric genetics has yet qualified as a

definitive association.[34] A key question for the field is what to do with its results that do not pass contemporary standards. Although we agree that suggestive results need to be widely available, it is difficult to see any advantage in the continued publication of only slightly suggestive results individually, polymorphism by polymorphism and phenotype by phenotype. In many cases, the quality of a gene as a candidate for the condition has made up for very modest *P*-values to motivate separate publication.[14,35–39] Large-scale genotyping being carried out here and elsewhere, however, makes clear such an approach is untenable. In our study, there are at least 856 and 368 genetic associations with raw *P*-values superior to the 0.049 and 0.015 reported for *RGS4* SNPs rs2661319 and rs2842030 published in a recent paper[35] (see Supplementary Information Tables, noting that the figures 856 and 368 for nominal genetic associations include only the strongest associated SNP per gene to prevent inflation of estimates by LD). Each of these is in genes that can be argued to be plausibly involved (as they were selected as candidate genes). Clearly, it would be both unnecessary and misleading to publish these associations one by one in individual research papers. These considerations demonstrate that the earlier practice in psychiatric genetics of individual reports for suggestive candidate genes is no longer appropriate given the scale of genetic data being generated, including for large numbers of suggestive candidate genes.

The alternative we propose is to report all associations resulting from large-scale screens that both explicitly and implicitly convey the magnitude of testing actually taking place in the community and allow ready interpretation and comparison of the results. To facilitate this effort, we have included as Supplementary Information all raw *P*-values (<0.05) in a file format that contains the phenotype, SNP and *P*-value. These results can therefore be easily interrogated by any software tool for comparison with other data sets. With the increase in larger scale genetic studies, and in particular, the increasing prevalence of whole-genome analyses, the risk of producing type II errors when correcting for thousands of SNPs increases exponentially. Many SNPs with real effects will not stand up to correction for study-wide significance. This mandates the use of software programs such as WGAviewer[19] to allow the examination and interpretation of results in their genomic context, and necessitates data sharing between studies so that replications of SNPs that may not come out in the top *P*-values can be detected and followed up.

Acknowledgements

We thank Kevin Shianna and team for genotype data, Jeff Dawson for management of the phenotype database and Mike Weale for tagging. We are indebted to the patients and families who took part in this study. We also thank Sonia Davies for her help in providing and interpreting the CATIE phenotype data. The CATIE project was supported by NIMH contract N01 MH90001.

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