Summary of Supplementary Material

This Supplementary document includes literature selection (**Appendix A**), data retraction (**Appendix B**), missing value analysis for case selection (**Appendix C**), selection of participants with chronic depression using Latent Class Growth Analysis (**Appendix D**), results at SNP level (**Appendix E**) and at gene level (**Appendix F**), and comparison with Bosker et al study (**Appendix G**).

Content

Appendix A: Literature selection

Literature search

We conducted a systematic literature search to update genetic case-control association studies on MDD, with those published between Sept.1st 2007, the end search date in Bosker et al. study(1) , and June 10th 2012 using MEDLINE® via PUBMED with the following search terms:

"*(polymorphism, genetic[MeSH Terms] OR gene[Text Word] OR genes[Text Word] OR polymorphism[Text Word] OR polymorphisms[Text Word] OR chromosome[Text Word] OR allele[Text word]) AND (depressive disorder[MeSH Terms] OR major depressive disorder[Text Word] OR major depression[Text Word] OR unipolar depression[Text Word]), Limits: Humans[MeSH terms]"*. This search yielded 1145 articles.

Study selection

From the 1145 articles, we selected studies that fulfilled the following criteria: 1) the patients had a primary diagnosis of major depressive disorder; 2) the study examined the association between a candidate gene (a SNP, a microsatellite marker or a haplotype) and MDD; 3) the study was a case-control association study; 4) the sample of the study included at least 30 patients and 30 healthy controls. We included studies focusing on subgroups within MDD, such as MDD in women or men, or recurrent MDD. In addition, to be as inclusive as possible we included candidate SNPs that deviated from Hardy-Weinberg equilibrium or had low allele frequencies. We initially included all studies that fulfilled these criteria, including those reporting null-findings, so that the number and the outcomes of studies published between 2007 and 2012 were known.

Two independent raters (XL and NS) selected studies based on the abstracts,

and then read full-texts of each potential study to verify eligibility. In case of disagreement on study selection, consensus was reached with the help of a third investigator (CAH).

Exclusion criteria

We excluded studies that: 1) only used questionnaires to assess MDD, however we included studies that used the Hamilton Rating Scale for Depression (HRSD-17(2)) since it is a diagnostic scale administered by trained professionals; 2) did not specify the "depressed" patients as patients suffering from major depression, major depressive disorder, or unipolar depression; 3) focused on patients with a depressive episode in the course of a bipolar disorder or a seasonal affective disorder, or patients with a secondary depression and a primary diagnosis of physical disease or other mental disorders; 4) focused on clinical populations suffering from both MDD and a specific co-morbid disorder or condition (e.g. diabetes, alcoholism); 5) were linkage studies or included participants biologically related to each other; 6) did not examine genetic associations with MDD but with other phenotypes such as personality features, brain structure, or treatment response; 7) were post-mortem studies; 8) were not published in English; 9) used data from NESDA and/or NTR cohorts.

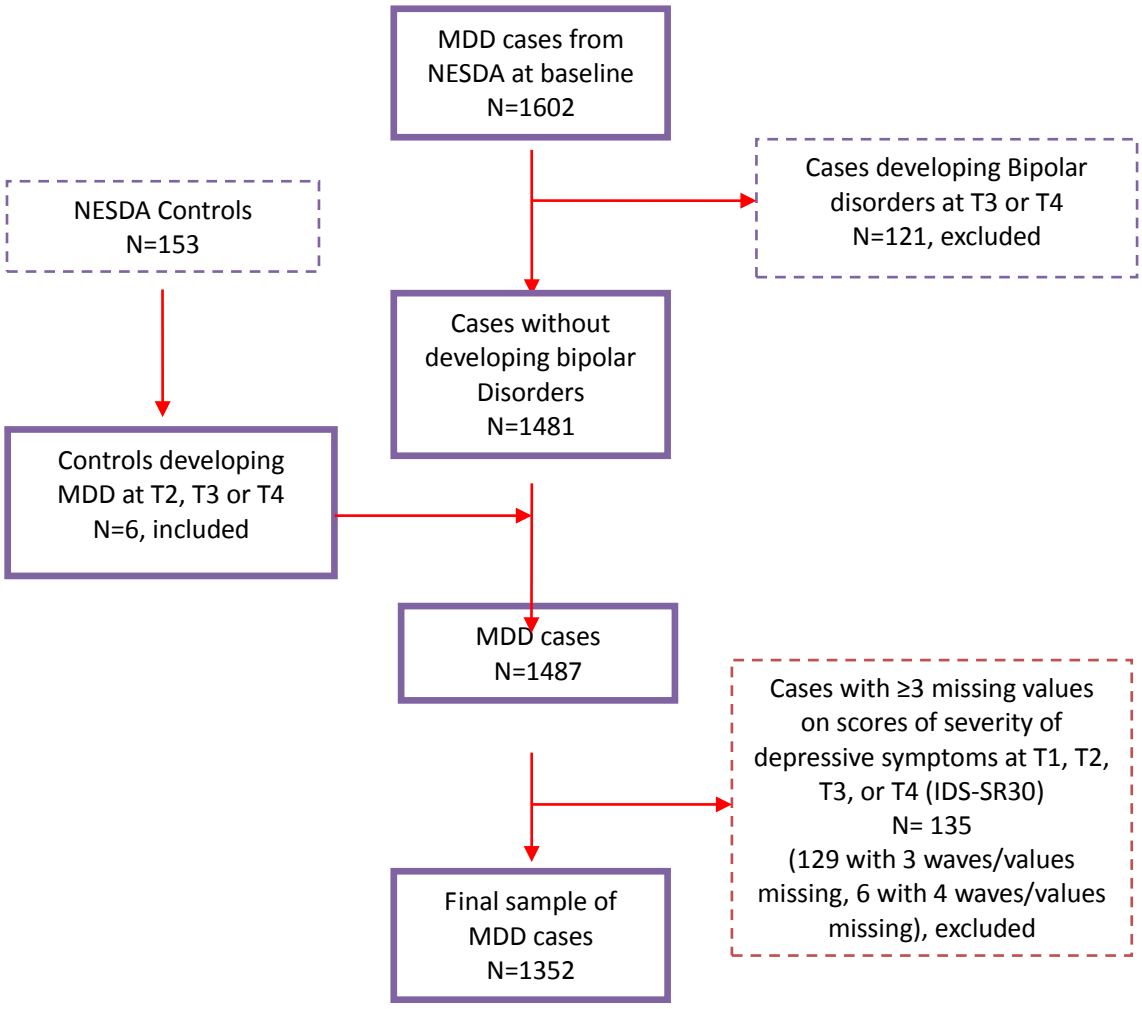

Figure S1. Flowchart for the selection of cases with MDD

Appendix B: Data extraction

The following information was extracted from each selected study: author(s), year of publication, sample sizes for cases and controls, study design, genes, SNPs/haplotypes. If associations between SNPs and MDD were significant, we extracted raw p-values and odds ratios (ORs) for genotypes and/or allele frequencies and the corrected results if the study had applied corrections for multiple testing. Additionally, we extracted p-values and ORs from secondary subgroup analyses only when these fulfilled our inclusion criteria and the results in the primary analysis were not significant. We did not exclude SNPs/haplotypes that did not remain statistically significant after multiple testing correction. Only information from the MDD sample and the healthy control sample was retrieved if several psychiatric disorders were investigated within a single study.

When the reference SNP identification number (rs-id) was not reported, we used PubMed and the SNP database of the National Center for Biotechnology information (NCBI) (http://www.ncbi.nlm.nih.gov/SNP/) to identify the corresponding rs-ids.

Appendix C Mann-Whitney tests for cases excluded for the LCGA due to missing values

Mann-Whitney tests were performed to investigate whether there was a difference in baseline depressive symptoms between the full MDD sample (n=1,352) and the excluded cases (n=135), and between the most severe cases from the chronic subsample (n=225) and the excluded cases (n=135).

The results from the Mann-Whitney tests showed that the groups that were excluded because of too many missing values had higher baseline depressive symptoms (Mean=29.9, SD=13.5) compared to the total sample (Mean=24.8, SD=13.2; $p<0.001$, Cohen's d=0.38; a small effect), but had lower baseline depressive symptoms compared to the selected subsample of chronic, severe MDD (Mean=41.1, SD=8.7; $p<0.001$; Cohen's d=0.99; a large effect). This indicates that despite the exclusion of participants with relatively severe baseline depressive symptoms, the chronic subsample was clearly more severely depressed than those who were lost at follow up.

Appendix D Latent Class Growth Analysis

Methods

We used Latent Class Growth Analysis (LCGA) to identify the subgroup of MDD patients with a chronic and severe course. LCGA is a data-driven method that clusters individuals with similar trajectories, using a repeatedly measured outcome variable. This method was applied to the severity of depressive symptoms assessed repeatedly during the four measurement waves in NESDA using the 30-item inventory of depressive symptomatology, self-report version (IDS-SR30)(5). Items were rated on a four-point Likert scale ranging from zero to three with a total score ranging from 0 to 84 (a summary of 28 of the 30 items). This inventory has been shown to have high concurrent validity with scales such as the Hamilton Rating Scale for Depression (HRSD-17)(7), high internal consistency, and high sensitivity to change.(5) By clustering individuals, LCGA can identify potential subgroups with distinct patterns of depressive symptoms over time. The analysis also yields an index of the likelihood that the individual belongs to each class. For each individual, the highest probability was used to determine class membership. LCGA was conducted using Mplus version 5.1. In order to model the course trajectories of depression, data for at least two measurement waves of depressive symptoms are needed. Thus, all cases with missing values on the IDS-SR30 on more than two waves were excluded. Overall, 135 cases had missed either three or four measurement waves (129 cases and six cases, respectively) and were excluded. This resulted in 1,352 MDD cases for the LCGA analysis and the subsequent genetic association tests.

We modeled the data using a one-class model, and then successively added one class each time. The model fit indices were used to compare between models. We used multiple random starting values for the estimated models (500 initial stage

random sets of starting values, 20 final optimizations and 20 final stage optimizations) to obtain successful convergence and avoid local solutions. The variance and covariance estimates for the growth factors within each class were set to zero, in accordance with the assumption in LCGA models of no variance between individual growth trajectories within one class.(8) To determine the best-fitting model, we compared competing models based on four fit indices: 1) the Bayesian Information Criterion (BIC); Lower BICs indicated better model fit and BIC is recommended as the best of the Information Criteria for LCGA.(9) 2) The Lo-Mendell-Rubin (LMR) likelihood ratio test; The LMR provides a p-value that indicates whether the k–1 class model should be rejected in favor of the k class model. 3) The entropy of the model; High entropy values indicated better certainty in classification. 4) The Bootstrap likelihood ratio test (BLRT); The BLRT also provides a p-value that indicates whether the k class model is significantly different from the k-1 class model. Finally, we also took consideration of our research question and interpretability of the models in the decision making process. We defined the chronic class(es) as the one(s) with a consistently high score trajectory(/ies) of depressive symptoms.

Results

The LCGA results for each model are shown in **Table S1**. Although the BIC kept decreasing until the nine-class model and the p-values of BLRT remained significant until the eleven-class model (data not shown after the seven-class model), the results of the LMR test were not significant for the six-class model relative to the five-class model. The trajectories of the five-class model could be interpreted well, and for parsimony reasons we chose the five-class model as a good approximation of the trajectories in our data. Course trajectories identified from the five-class model are shown in **Figure S2**. The first and the second trajectories (class 1 and class 2) showed

consistently high scores across time. The third class had moderate symptoms while the fourth and the fifth classes had mild symptoms. Individuals categorized in the first and second classes with high chronic scores were selected into the chronic subsample (n=225). They had consistently high depressive symptoms (on average >30 on IDS score) on all measurement waves. They were older, had less years of education, and had more co-morbidity with anxiety disorders compared to the less severe groups (**SI**, **Table S3**).

We additionally compared results from the five-class model with results from the six-class model (the six-class model is shown in **Figure S3**, results shown in **Table S2)**. Apart from the slightly better model fit (according to BIC and BLRT, but not according to the LMR test), the main reason to do so was that the six-class distinguished a class of MDD cases with a sharp decline of symptoms in the follow-up waves from classes of cases having consistent high scores across time, in contrast to all classes from the five-class model which had a stable pattern of depression severity. By comparing these two models, we could determine if individuals in the class with severe symptoms at the beginning and a sharp decline in the six-class model were indeed not categorized in the two chronic and severe groups in the five-class model (which we had selected for study), but rather, in the moderate group. Results confirmed that individuals in the group with a sharp decline of symptoms in the six-class model were mainly categorized in the moderate class of the five-class model (102 out of 117 cases). In fact, the most chronic and severe groups were quite similar in the two models: 219 were consistently categorized into the two most severe groups in the five-class model (219 out of 225: 97%) and in the six-class model (219 out of 229: 96%). In all, these results indicate that the five-class model correctly identified the consistently severe groups and disentangled these from less

chronic and mild cases. These results also show that the moderate group included a substantial number of patients with a decline in depressive symptoms over time, thereby justifying our choice to only include the two most persistently and severely affected classes but not the moderate class in our subsample.

Table S1 Fit indices of the Latent Class Growth Analyses (n=1352)

# of Class	-2Log(likelihood)	# of pars	BIC	Entropy	p LMR	p LMR adjusted	p BLRT	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7
1	-19422.923	6	38889.102	N.A.	N.A.	N.A.	N.A.	1352	-	-	-	-	-	-
2	-18561.796	9	37188.477	0.807	0.0000	0.0000	0.000	475	877	-	-	-	-	-
3	-18264.978	12	36616.467	0.809	0.0000	0.0001	0.000	168	638	546	-	-	-	-
4	-18178.799	15	36465.738	0.781	0.0000	0.0001	0.000	539	60	506	247	-	-	-
5*	**-18154.859**	**18**	**36439.486**	**0.700**	**0.0066**	**0.0080**	**0.000**	**51**	**174**	**379**	**403**	**345**	**-**	**-**
6	-18126.697	21	36404.790	0.684	0.1726	0.1855	0.000	417	335	117	46	183	254	-
7	-18108.018	24	36389.061	0.685	0.1481	0.1552	0.000	300	119	90	118	377	54	294

Note. # = Number, pars = parameters, BIC = Bayesian Information Criterion, p LMR = significance level from the Lo-Mendell-Rubin Likelihood ratio test; p BLRT= significance level from the bootstrap likelihood ratio test. The bolded line with * indicated the selected model for analysis.

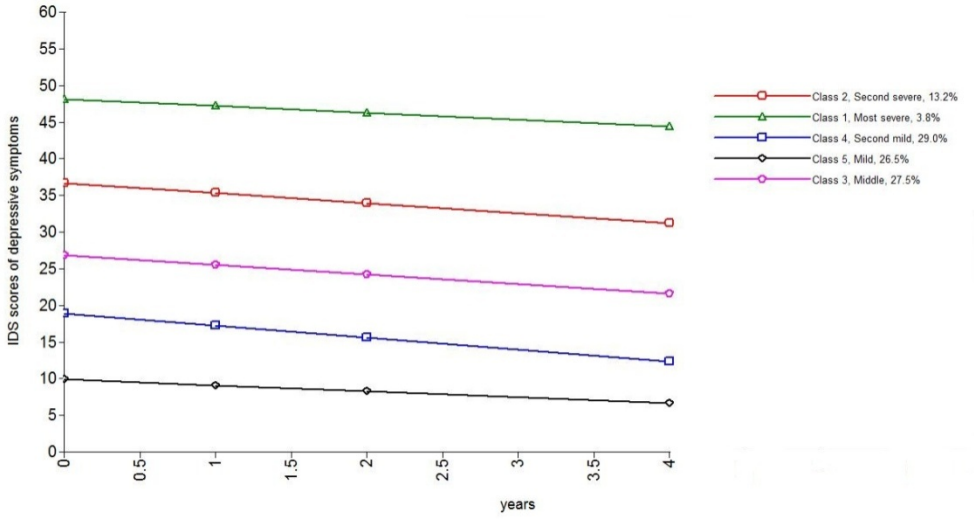

Figure S2. Estimated course trajectories from the five-class model in LCGA

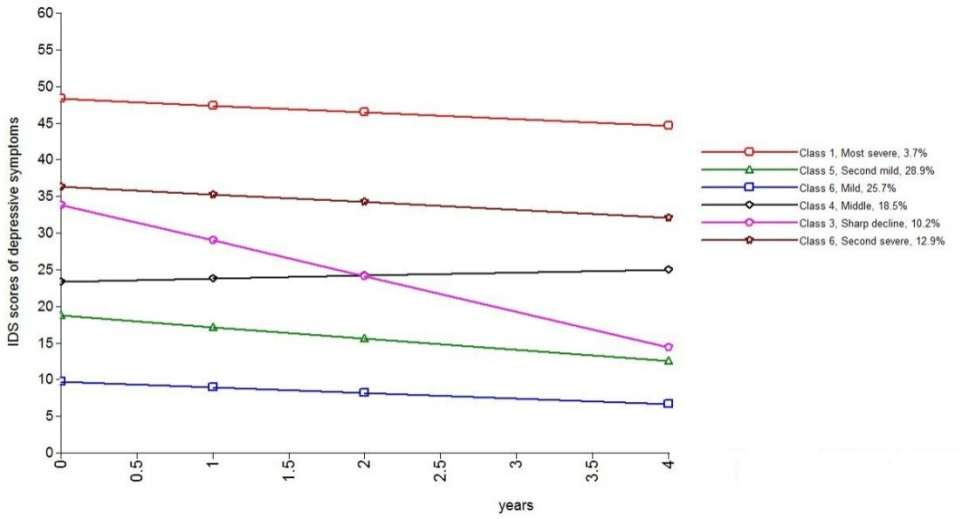

Figure S3. Estimated course trajectories from the six-class model in LCGA

Table S2 Crosstabs of the five-class model versus the six-class model

		Five-class model					
		Severe	**Moderate to severe**	**Moderate**	**Mild to moderate**	**Mild**	**Total**
Six-class model	**Severe**	46	0	0	0	0	46
	Moderate to severe	5	168	10	0	0	183
	Sharp decline	0	6	102	9	0	117
	Moderate	0	0	243	11	0	254
	Mild to moderate	0	0	24	381	12	417
	Mild	0	0	0	2	333	335
	Total	51	174	379	403	345	1352

Table S3 Demographic and clinical characteristics of each group in the five-class model

	Class 1*: Severe	**Class 2*: Moderate to severe**	**Class 3: Moderate**	**Class 4: Mild to moderate**	**Class 5: Mild**	**Total**	**P-value**
Sample size	51	174	379	403	345	1352	
Sex(%female)	60.8	67.8	69.7	73.0	69.0	69.9	.366
Age(SD)	46.6(10.1)	44.3(12.1)	42.9(12.6)	41.6(12.6)	42.6(12.7)	42.7(12.5)	.026
Education years(SD)	10.8(3.2)	11.2(3.2)	11.8(3.3)	12.1(3.2)	13.1(3.0)	12.1(3.2)	<.001
IDS score wave1(SD)	49.0(6.5)	38.8(7.9)	29.9(9.2)	22.4(9.1)	11.1(6.8)	24.8(13.2)	<.001
IDS score wave2(SD)	46.4(9.1)	35.1(6.7)	24.4(7.2)	15.9(5.7)	7.5(4.4)	19.6(12.0)	<.001
IDS score wave3(SD)	47.0(5.5)	33.9(6.2)	23.5(6.4)	13.8(5.1)	6.6(3.7)	18.1(11.7)	<.001
IDS score wave4(SD)	44.7(7.1)	32.3(8.6)	23.2(8.3)	14.1(6.8)	7.2(4.7)	18.1(12.0)	<.001
Co-morbid anxiety(%)	78.4	71.3	72.3	64.8	47.8	63.9	<.001

*= cases with chronic MDD course selected for analysis.

Appendix E Associations with MDD at candidate SNP level

Table S4 Replication results for SNPs in the full MDD sample

Official gene name	SNP(rs-id)	The coded allele	The coded allele in cases	The coded allele in controls	p_all	OR_all	from which study*
AANAT	rs3760138	T	0.49	0.493	0.835	0.99	1
AANAT	rs4238989	G	0.486	0.477	0.484	0.97	1
AANAT	rs8150	C	0.318	0.332	0.243	0.94	1
ABCB1	rs1002205	C	0.049	0.044	0.348	1.11	1
ABCB1	rs1922243	T	0.038	0.038	0.981	1	1
ABCB1	rs2032583	G	0.138	0.129	0.338	1.09	1
ABCB1	rs58898486	T	0.006	0.006	0.818	0.96	1
ACE	rs4291	A	0.375	0.39	0.24	1.07	1, 2
ACE	rs4295	G	0.361	0.378	0.231	1.07	2
ACE	rs4305	G	0.42	0.442	0.09	1.09	2
ACE	rs4309	T	0.473	0.451	0.075	1.09	2
ACE	rs4311	C	0.419	0.437	0.138	1.08	2
ACE	rs4329	G	0.48	0.499	0.113	1.08	2
ACE	rs4333	C	0.451	0.473	0.054	1.09	2
ACE	rs4461142	C	0.504	0.49	0.211	1.06	2
ADA	rs452159	T	0.343	0.336	0.426	1.04	1
ADCYAP1	rs17500692	A	0.139	0.144	0.711	0.96	1
ADK	rs7924176	G	0.436	0.466	**0.016**	0.89	1
ADK	rs946185	G	0.386	0.383	0.81	0.99	1
ADORA1	rs12026765	T	0.105	0.102	0.765	1.03	1
ADORA1	rs17530497	C	0.275	0.289	0.225	0.93	1
ARNTL	rs11022778	G	0.354	0.336	0.195	1.08	1
ARNTL	rs17452383	G	0.131	0.129	0.911	1.01	1
ARNTL	rs2279287	C	0.303	0.294	0.321	0.96	1
ARNTL	rs900144	T	0.439	0.418	0.068	0.92	1
ARNTL	rs969485	A	0.293	0.292	0.965	1	1
ARNTL2	rs10506018	G	0.164	0.164	0.947	1	1
ARNTL2	rs11048994	A	0.202	0.196	0.516	1.03	1
ARNTL2	rs11610949	C	0.106	0.117	0.136	0.9	1
ARNTL2	rs3751222	C	0.131	0.127	0.606	1.04	1
AT1R	rs5186	C	0.3	0.306	0.564	0.97	2
AVPR1B	rs33933482	A	0.138	0.146	0.214	0.94	2
BCR	rs2156921	A	0.442	0.439	0.887	0.99	2
BCR	rs2213172	G	0.444	0.439	0.77	0.98	2
BCR	rs2267012	A	0.055	0.055	0.99	1	2
BCR	rs2267013	G	0.121	0.113	0.42	1.08	2
BCR	rs2267015	T	0.438	0.434	0.815	0.98	2

BCR	rs3761418	G	0.292	0.289	0.832	1.02	2
BDKRB2	rs1046248	T	0.116	0.11	0.478	1.06	1
BDNF	rs11030101	T	0.463	0.456	0.629	1.03	1
BDNF	rs11030103	G	0.01	0.012	0.347	0.83	1
BDNF	rs6265	T	0.196	0.212	0.126	0.9	1, 2
CACNA1C	rs1006737	A	0.325	0.311	0.228	1.07	1
CCL2	rs1024611	G	0.264	0.28	0.172	0.92	2
CDC42SE2	rs798412	A	0.221	0.193	**0.008**	1.18	1
CDC42SE2	rs798416	C	0.221	0.193	**0.008**	1.18	1
CHRM2	rs8191992	A	0.48	0.466	0.295	0.95	2
CLOCK	rs11133379	A	0.369	0.392	0.053	1.1	1
CLOCK	rs3736544	G	0.368	0.392	0.054	1.1	1
CLOCK	rs6850524	G	0.416	0.431	0.212	1.07	1
CNR1	rs1049353	T	0.317	0.294	0.058	1.11	1
CNR2	rs2501432	C	0.455	0.458	0.727	0.99	1
CNTN5	rs6589849	A	0.302	0.3	0.918	1.01	1
CNTNAP2	rs2692359	T	0.233	0.228	0.607	0.97	1
COMT	rs2075507	A	0.465	0.459	0.693	0.98	2
COMT	rs4680	A	0.459	0.46	0.95	1	1, 2
COMT	rs737865	G	0.273	0.277	0.795	0.98	1
CRHBP	rs1053989	A	0.438	0.458	**0.039**	1.08	1
CRHBP	rs1875999	C	0.475	0.491	0.095	1.07	1, 2
CRHBP	rs7718461	G	0.436	0.444	0.444	1.04	1
CRHBP	rs7728378	C	0.422	0.433	0.324	1.04	1, 2
CRHR1	rs242939	T	0.076	0.073	0.601	0.95	2
CRHR2	rs2240403	T	0.092	0.091	0.984	1.01	2
CRHR2	rs2284220	A	0.15	0.147	0.724	0.98	1
CRY1	rs2287161	G	0.47	0.469	0.955	1	1
CRY1	rs4640029	T	0.457	0.457	0.971	1	1
CRY1	rs714359	G	0.213	0.213	0.916	1	1
CSF2RB	rs2284031	C	0.452	0.433	0.158	1.08	1
CSF2RB	rs738149	G	0.298	0.292	0.58	0.97	1
CSF2RB	rs909486	T	0.438	0.421	0.23	1.07	1
CTLA4	rs231779	T	0.379	0.37	0.379	1.04	1
CYP2C9	rs1057910	C	0.073	0.063	0.19	1.17	2
DAOA	rs778336	T	0.234	0.218	0.191	1.1	1
DBP	rs386551	G	0.265	0.257	0.497	1.04	1
DCNP1	rs12520799	A	0.466	0.447	0.14	0.92	2
DIO1	rs11206244	T	0.352	0.361	0.484	0.96	1
DISC1	rs6541281	T	0.314	0.315	0.939	0.99	2
DISC1	rs821616	T	0.28	0.281	0.996	0.99	2
DRD1	rs10063995	T	0.054	0.039	**0.004**	1.39	2
DRD3	rs6280	T	0.312	0.318	0.667	1.03	2
DTNBP1	rs1011313	C	0.093	0.099	0.465	1.07	1
EMP1	rs7315725	A	0.225	0.266	**0**	0.8	1
ESR1	rs2234693	C	0.482	0.484	0.886	0.99	2

ESR1	rs9340799	G	0.351	0.358	0.627	0.97	2
FACL4	rs1324805	G	0.448	0.443	0.614	1.02	2
FKBP5	rs1360780	C	0.288	0.31	**0.045**	1.11	1
FKBP5	rs3800373	A	0.271	0.282	0.27	1.06	1
FKBP5	rs4713916	G	0.294	0.304	0.351	1.05	1
GABRR2	rs3777514	T	0.213	0.197	0.107	1.1	1
GAD2	rs8190646	G	0.093	0.089	0.572	1.06	1
GMIP	rs2043293	A	0.178	0.182	0.686	1.02	2
GMIP	rs2304129	G	0.052	0.051	0.977	1.01	2
GMIP	rs3794996	T	0.045	0.041	0.575	1.08	2
GMIP	rs880090	G	0.256	0.25	0.637	0.97	2
GNB3	rs5443	T	0.307	0.288	0.131	1.09	2
GR	rs10482605	G	0.192	0.188	0.651	1.02	2
GR	rs13340364	A	0.323	0.32	0.714	1.01	2
GR	rs6190	T	0.038	0.04	0.794	0.96	2
GRIN3A	rs10989591	T	0.304	0.301	0.849	1.02	1
GRM3	rs6465084	G	0.238	0.237	0.899	1.01	1
GSK3B	rs6782799	T	0.364	0.375	0.406	0.95	1
HCRTR1	rs2271933	G	0.396	0.417	0.095	1.09	1
HTR1A	rs1800044	A	0.007	0.003	**0.018**	2.41	1
HTR1A	rs6295	G	0.473	0.489	0.188	1.07	1, 2
HTR1A	rs878567	G	0.475	0.491	0.188	1.07	1
HTR2A	rs6311	T	0.395	0.406	0.324	0.96	2
HTR2A	rs6313	A	0.394	0.406	0.297	0.95	2
HTR2C	rs6318	C	0.183	0.173	0.359	1.07	2
HTR3B	rs1176744	C	0.288	0.293	0.679	0.98	2
HTR3B	rs2276305	A	0.006	0.007	0.448	0.8	2
HTR3B	rs2276307	G	0.208	0.206	0.89	1.01	2
HTR3B	rs2276308	G	0.208	0.206	0.891	1.01	2
IKBKE	rs1539243	C	0.155	0.163	0.325	1.06	1
IL10	rs1800896	C	0.481	0.481	0.972	1	1
Intergenic	rs1890866	G	0.054	0.049	0.364	0.91	1
KMO	rs1053230	T	0.225	0.223	0.91	1.01	1
LEPR	rs3806318	G	0.277	0.273	0.764	1.02	1
MAOA	rs1137070	C	0.309	0.301	0.557	0.97	1, 2
MC1R	rs885479	A	0.075	0.077	0.874	0.98	1
MTHFR	rs1801133	A	0.33	0.309	0.08	1.1	2
MYO3A	rs10828902	G	0.103	0.099	0.56	1.05	1
MYT1L	rs3748988	G	0.357	0.351	0.671	1.03	1
MYT1L	rs3748989	T	0.106	0.101	0.571	1.06	1
MYT1L	rs7592630	G	0.372	0.357	0.24	1.07	1
NBEA	rs4941807	C	0.383	0.38	0.838	1.01	1
NEUROD1	rs1801262	C	0.355	0.35	0.765	0.98	1
NGFR	rs2072446	T	0.046	0.041	0.307	1.12	1, 2
NOS2	rs2770248	A	0.334	0.333	0.923	1	1
NOS2	rs3794764	A	0.212	0.213	0.953	0.99	1

NPAS2	rs11123857	G	0.305	0.307	0.835	0.99	1
NPAS2	rs11541353	T	0.189	0.204	0.106	0.91	1
NPAS2	rs13025524	A	0.339	0.319	0.106	1.09	1
NPAS2	rs13394520	G	0.409	0.401	0.472	1.03	1
NPAS2	rs17025005	T	0.16	0.163	0.531	0.98	1
NPAS2	rs17662394	T	0.155	0.167	0.183	0.91	1
NPAS2	rs2117713	A	0.186	0.179	0.464	1.05	1
NPAS2	rs3754674	C	0.39	0.386	0.735	1.02	1
NPR3	rs976576	C	0.257	0.26	0.706	1.02	1
NPY	rs16139	C	0.026	0.04	**0.004**	0.65	2
NPY	rs16147	C	0.469	0.472	0.734	1.01	2
NR1D1	rs2071427	T	0.291	0.27	**0.034**	1.11	1
NR3C1	rs10052957	A	0.319	0.331	0.394	0.95	1
NR3C1	rs1866388	G	0.317	0.33	0.368	0.94	1
NR3C1	rs2918419	C	0.134	0.152	0.068	0.87	1
NR3C1	rs33388	T	0.465	0.46	0.744	1.02	1
NR3C1	rs41423247	C	0.352	0.363	0.35	0.95	1, 2
NR3C1	rs6191	A	0.465	0.46	0.766	0.98	1
NR3C1	rs6198	C	0.183	0.178	0.554	1.03	1
NR3C1	rs852977	G	0.317	0.33	0.387	0.94	1
NR3C1	rs860458	A	0.146	0.157	0.24	0.91	1
NT5E	rs6942065	A	0.139	0.131	0.477	1.07	1
NT5E	rs9450282	G	0.355	0.37	0.205	1.07	1
NTRK2	rs1187323	A	0.22	0.218	0.82	0.98	1
NTRK2	rs1187329	G	0.439	0.449	0.448	1.04	1
NTRK2	rs1545285	T	0.388	0.383	0.634	1.02	1
NTRK2	rs1778929	C	0.499	0.499	0.989	1	1
NTRK2	rs2013566	G	0.082	0.083	0.85	0.98	1
NTRK2	rs7020204	T	0.081	0.083	0.822	0.98	1
OXTR	rs2254298	A	0.111	0.101	0.169	1.11	1
OXTR	rs53576	G	0.349	0.352	0.749	1.01	1
P2RX7	rs208294	C	0.424	0.412	0.342	0.95	1
P2RX7	rs2230912	G	0.139	0.147	0.354	0.93	1, 2
P2RX7	rs591874	A	0.259	0.268	0.435	1.05	1
PAWR	rs8176874	C	0.008	0.008	0.98	0.97	1
PCLO	rs2522833	C	0.479	0.426	**0**	1.24	1
PCNT	rs2073376	G	0.379	0.373	0.555	0.98	1
PCNT	rs2073380	C	0.196	0.201	0.572	0.97	1
PCNT	rs3788265	T	0.191	0.194	0.629	0.98	1
PDE10A	rs220818	A	0.264	0.276	0.329	1.06	2
PDE10A	rs676389	C	0.127	0.128	0.93	0.99	2
PDE10A	rs717602	C	0.373	0.375	1	0.99	2
PDE11A	rs3770018	C	0.117	0.105	0.13	1.13	2
PDE2A	rs370013	A	0.168	0.172	0.59	1.03	2
PDE4B	rs1040716	T	0.438	0.428	0.393	1.04	1
PDE4B	rs2180335	G	0.48	0.496	0.204	1.07	1

PDE4B	rs472952	G	0.404	0.422	0.146	1.08	1
PDE4B	rs910694	T	0.471	0.491	0.103	1.08	1
PDE5A	rs3775845	C	0.308	0.315	0.563	0.97	2
PDE6C	rs650058	A	0.347	0.327	0.11	0.92	2
PDE6C	rs701865	A	0.343	0.348	0.673	0.98	2
PDE9A	rs729861	G	0.494	0.481	0.241	0.95	2
PDLIM5	rs2433320	A	0.436	0.453	0.157	0.93	1
PDYN	rs6136667	C	0.157	0.158	0.96	0.99	1
PER2	rs2304673	G	0.135	0.147	0.172	0.9	1
PER3	rs11121029	A	0.199	0.195	0.67	1.03	1
PLA2G4A	rs10798059	A	0.397	0.403	0.587	0.97	2
PLD1	rs2124147	G	0.481	0.463	0.182	1.07	1
POMC	rs2118404	T	0.24	0.213	**0.012**	1.17	1
PPARGC1A	rs768695	A	0.499	0.494	0.774	1.02	1
PROKR2	rs4815787	A	0.511	0.49	0.102	1.09	1
PSMB4	rs2296840	T	0.004	0.001	**0.044**	2.64	1
PSMB4	rs4603	C	0.188	0.187	0.913	1.01	1
S100A10	rs4845720	A	0.039	0.034	0.288	1.15	1
SERPINE1	rs2227684	A	0.436	0.436	0.963	1	1
SERPINE1	rs7242	G	0.438	0.438	0.931	1	1
SIGMAR1	rs1800866	G	0.152	0.163	0.235	0.91	1
SIRT1	rs10997875	C	0.355	0.327	**0.026**	0.88	1
SLC28A1	rs11853372	G	0.32	0.324	0.626	1.02	1
SLC28A1	rs12910991	G	0.355	0.373	0.104	0.92	1
SLC28A1	rs4271567	T	0.406	0.389	0.14	0.93	1
SLC28A1	rs4980345	T	0.056	0.061	0.362	0.9	1
SLC28A1	rs7182385	A	0.427	0.427	0.969	1	1
SLC29A1	rs324148	C	0.283	0.292	0.438	1.04	1
SLC29A1	rs6905285	T	0.411	0.402	0.443	1.04	1
SLC29A1	rs693955	C	0.216	0.227	0.223	1.07	1
SLC29A2	rs2279861	G	0.328	0.324	0.666	0.98	1
SLC29A2	rs4244813	C	0.331	0.326	0.601	0.98	1
SLC29A3	rs10999776	T	0.347	0.367	0.117	0.92	1
SLC29A3	rs12256138	T	0.458	0.451	0.62	1.03	1
SLC29A3	rs12767108	A	0.129	0.121	0.282	1.08	1
SLC29A3	rs2066210	G	0.141	0.135	0.54	1.05	1
SLC29A3	rs2487067	A	0.403	0.379	**0.043**	0.9	1
SLC29A3	rs780659	A	0.414	0.422	0.561	1.03	1
SLC29A3	rs780662	A	0.122	0.121	0.931	1.01	1
SLC6A2	rs2242446	T	0.272	0.274	0.806	1.01	1, 2
SLC6A3	rs2550936	C	0.27	0.276	0.569	0.97	1
SLC6A3	rs8179029	T	0.189	0.195	0.583	0.97	1
SLC6A4	rs140701	T	0.442	0.437	0.653	1.02	1
SLC6A4	rs2066713	A	0.371	0.38	0.443	0.97	1
SLC6A4	rs3794808	T	0.451	0.445	0.581	1.02	1
SLC6A4	rs3813034	C	0.489	0.487	0.855	1.01	1

SLC6A4	rs6354	T	0.187	0.182	0.594	0.97	1
SLC6A4	rs7224199	T	0.493	0.491	0.846	1.01	1
TACR1	rs13013430	C	0.232	0.254	0.053	0.89	2
TBX21	rs17244587	A	0.088	0.084	0.478	1.06	1
TBX21	rs2325717	C	0.087	0.084	0.537	1.05	1
TBX21	rs41515744	T	0.088	0.084	0.493	1.05	1
TFCP2	rs13463	T	0.049	0.052	0.407	0.93	2
TNF	rs1800629	A	0.192	0.191	0.958	1.01	1, 2
TPH	rs684302	T	0.403	0.382	0.117	1.09	2
TPH1	rs1799913	T	0.395	0.375	0.158	1.09	2
TPH1	rs1800532	T	0.395	0.375	0.159	1.09	1, 2
TPH2	rs1007023	T	0.138	0.135	0.753	0.97	1
TPH2	rs10784941	G	0.496	0.486	0.333	1.04	2
TPH2	rs1386486	G	0.358	0.367	0.391	1.04	2
TPH2	rs1386492	T	0.18	0.186	0.561	1.04	1
TPH2	rs1386494	C	0.173	0.175	0.916	1.01	1, 2
TPH2	rs17110747	A	0.153	0.151	0.814	1.02	1
TPH2	rs1843809	T	0.178	0.176	0.732	0.99	1, 2
TPH2	rs2171363	G	0.508	0.489	0.05	1.08	1, 2
TPH2	rs4570625	T	0.225	0.244	0.055	0.9	1
TPH2	rs6582078	T	0.431	0.438	0.372	1.03	1
TPH2	rs7300641	G	0.161	0.159	0.794	0.98	1
TPH2	rs7305115	G	0.441	0.45	0.314	1.04	1
TSNAX	rs766288	T	0.353	0.36	0.518	0.97	1
VEGFA	rs699947	C	0.489	0.475	0.291	1.06	1
VIPR2	rs12670064	C	0.244	0.24	0.82	1.03	1
VIPR2	rs2540352	T	0.472	0.46	0.347	1.05	1
WFS1	rs1046316	G	0.341	0.343	0.915	1.01	2
WFS1	rs1801206	T	0.409	0.421	0.327	1.05	2
WFS1	rs56072215	T	0.06	0.072	**0.05**	0.83	2

*****1= the SNP was reported in the literature reviewed in the current study, 2= the SNP was reported in the literature reviewed in the Bosker et al. study (2011).

Note. The bolded number indicates $p<0.05$.

Table S5 Replication results for SNPs in the chronic, severe MDD subsample

Official gene name	SNP(rs-id)	The coded allele	MAF in cases	MAF in controls	p_severe	OR_severe	from which study*
AANAT	rs3760138	T	0.49	0.493	0.931	0.99	1
AANAT	rs4238989	G	0.483	0.477	0.807	0.98	1
AANAT	rs8150	C	0.329	0.332	0.912	0.99	1
ABCB1	rs1002205	C	0.063	0.044	0.052	1.44	1
ABCB1	rs1922243	T	0.042	0.038	0.696	1.11	1
ABCB1	rs2032583	G	0.14	0.129	0.526	1.1	1
ABCB1	rs58898486	T	0.004	0.006	0.521	0.63	1
ACE	rs4291	A	0.378	0.39	0.618	1.05	1, 2
ACE	rs4295	G	0.362	0.378	0.538	1.07	2
ACE	rs4305	G	0.422	0.442	0.406	1.08	2
ACE	rs4309	T	0.461	0.451	0.683	1.04	2
ACE	rs4311	C	0.431	0.437	0.791	1.03	2
ACE	rs4329	G	0.49	0.499	0.709	1.03	2
ACE	rs4333	C	0.454	0.473	0.393	1.08	2
ACE	rs4461142	C	0.501	0.49	0.597	1.05	2
ADA	rs452159	T	0.36	0.336	0.209	1.11	1
ADCYAP1	rs17500692	A	0.119	0.144	0.157	0.8	1
ADK	rs7924176	G	0.401	0.466	**0.006**	0.77	1
ADK	rs946185	G	0.402	0.383	0.417	0.93	1
ADORA1	rs12026765	T	0.102	0.102	0.989	1.01	1
ADORA1	rs17530497	C	0.296	0.289	0.768	1.03	1
ARNTL	rs11022778	G	0.351	0.336	0.546	1.07	1
ARNTL	rs17452383	G	0.131	0.129	0.904	1.01	1
ARNTL	rs2279287	C	0.29	0.294	0.918	1.02	1
ARNTL	rs900144	T	0.435	0.418	0.438	0.93	1
ARNTL	rs969485	A	0.308	0.292	0.457	0.93	1
ARNTL2	rs10506018	G	0.191	0.164	0.145	1.2	1
ARNTL2	rs11048994	A	0.227	0.196	0.122	1.2	1
ARNTL2	rs11610949	C	0.098	0.117	0.226	0.82	1
ARNTL2	rs3751222	C	0.107	0.127	0.247	0.83	1
AT1R	rs5186	C	0.298	0.306	0.703	0.96	2
AVPR1B	rs33933482	A	0.149	0.146	0.843	1.02	2
BCR	rs2156921	A	0.464	0.439	0.331	0.91	2
BCR	rs2213172	G	0.462	0.439	0.342	0.91	2
BCR	rs2267012	A	0.059	0.055	0.723	1.07	2
BCR	rs2267013	G	0.139	0.113	0.107	1.27	2
BCR	rs2267015	T	0.455	0.434	0.401	0.92	2
BCR	rs3761418	G	0.313	0.289	0.301	1.12	2
BDKRB2	rs1046248	T	0.138	0.11	0.085	1.3	1
BDNF	rs11030101	T	0.478	0.456	0.4	1.09	1

BDNF	rs11030103	G	0.008	0.012	0.45	0.72	1
BDNF	rs6265	T	0.198	0.212	0.494	0.92	1, 2
CACNA1C	rs1006737	A	0.323	0.311	0.6	1.06	1
CCL2	rs1024611	G	0.26	0.28	0.364	0.9	2
CDC42SE2	rs798412	A	0.213	0.193	0.3	1.13	1
CDC42SE2	rs798416	C	0.213	0.193	0.301	1.13	1
CHRM2	rs8191992	A	0.461	0.466	0.838	1.02	2
CLOCK	rs11133379	A	0.364	0.392	0.236	1.13	1
CLOCK	rs3736544	G	0.364	0.392	0.246	1.12	1
CLOCK	rs6850524	G	0.416	0.431	0.519	1.07	1
CNR1	rs1049353	T	0.32	0.294	0.257	1.13	1
CNR2	rs2501432	C	0.426	0.458	0.139	0.88	1
CNTN5	rs6589849	A	0.317	0.3	0.399	1.08	1
CNTNAP2	rs2692359	T	0.23	0.228	0.901	0.99	1
COMT	rs2075507	A	0.48	0.459	0.415	0.92	2
COMT	rs4680	A	0.433	0.46	0.294	1.11	1, 2
COMT	rs737865	G	0.261	0.277	0.498	0.92	1
CRHBP	rs1053989	A	0.446	0.458	0.528	1.05	1
CRHBP	rs1875999	C	0.49	0.491	0.975	1	1, 2
CRHBP	rs7718461	G	0.44	0.444	0.817	1.02	1
CRHBP	rs7728378	C	0.425	0.433	0.713	1.03	1, 2
CRHR1	rs242939	T	0.076	0.073	0.825	0.96	2
CRHR2	rs2240403	T	0.109	0.091	0.221	1.22	2
CRHR2	rs2284220	A	0.153	0.147	0.71	0.95	1
CRY1	rs2287161	G	0.46	0.469	0.701	1.04	1
CRY1	rs4640029	T	0.447	0.457	0.679	0.96	1
CRY1	rs714359	G	0.204	0.213	0.71	1.05	1
CSF2RB	rs2284031	C	0.466	0.433	0.173	1.14	1
CSF2RB	rs738149	G	0.264	0.292	0.218	1.15	1
CSF2RB	rs909486	T	0.449	0.421	0.265	1.12	1
CTLA4	rs231779	T	0.376	0.37	0.785	1.03	1
CYP2C9	rs1057910	C	0.067	0.063	0.819	1.06	2
DAOA	rs778336	T	0.244	0.218	0.226	1.16	1
DBP	rs386551	G	0.247	0.257	0.62	0.95	1
DCNP1	rs12520799	A	0.464	0.447	0.479	0.93	2
DIO1	rs11206244	T	0.38	0.361	0.422	1.08	1
DISC1	rs6541281	T	0.304	0.315	0.582	0.95	2
DISC1	rs821616	T	0.267	0.281	0.519	0.93	2
DRD1	rs10063995	T	0.042	0.039	0.76	1.07	2
DRD3	rs6280	T	0.3	0.318	0.459	1.09	2
DTNBP1	rs1011313	C	0.075	0.099	0.105	1.35	1
EMP1	rs7315725	A	0.24	0.266	0.247	0.88	1
ESR1	rs2234693	C	0.447	0.484	0.147	0.86	2
ESR1	rs9340799	G	0.335	0.358	0.367	0.91	2
FACL4	rs1324805	G	0.458	0.443	0.515	1.06	2

FKBP5	rs1360780	C	0.298	0.31	0.584	1.06	1
FKBP5	rs3800373	A	0.284	0.282	0.96	0.99	1
FKBP5	rs4713916	G	0.296	0.304	0.708	1.04	1
GABRR2	rs3777514	T	0.229	0.197	0.101	1.21	1
GAD2	rs8190646	G	0.109	0.089	0.154	1.26	1
GMIP	rs2043293	A	0.179	0.182	0.876	1.02	2
GMIP	rs2304129	G	0.044	0.051	0.461	0.85	2
GMIP	rs3794996	T	0.035	0.041	0.498	0.84	2
GMIP	rs880090	G	0.249	0.25	0.93	1.01	2
GNB3	rs5443	T	0.304	0.288	0.486	1.08	2
GR	rs10482605	G	0.198	0.188	0.587	1.07	2
GR	rs13340364	A	0.322	0.32	0.887	1.01	2
GR	rs6190	T	0.051	0.04	0.224	1.31	2
GRIN3A	rs10989591	T	0.279	0.301	0.319	0.9	1
GRM3	rs6465084	G	0.237	0.237	0.992	1	1
GSK3B	rs6782799	T	0.358	0.375	0.49	0.93	1
HCRTR1	rs2271933	G	0.4	0.417	0.484	1.07	1
HTR1A	rs1800044	A	0.009	0.003	**0.022**	3.33	1
HTR1A	rs6295	G	0.489	0.489	0.98	1	1, 2
HTR1A	rs878567	G	0.491	0.491	0.994	1	1
HTR2A	rs6311	T	0.412	0.406	0.872	1.02	2
HTR2A	rs6313	A	0.409	0.406	0.957	1.01	2
HTR2C	rs6318	C	0.164	0.173	0.727	0.94	2
HTR3B	rs1176744	C	0.24	0.293	**0.023**	0.76	2
HTR3B	rs2276305	A	0.008	0.007	0.89	1.1	2
HTR3B	rs2276307	G	0.158	0.206	**0.019**	0.72	2
HTR3B	rs2276308	G	0.158	0.206	**0.019**	0.72	2
IKBKE	rs1539243	C	0.147	0.163	0.359	1.13	1
IL10	rs1800896	C	0.492	0.481	0.642	0.95	1
Intergenic	rs1890866	G	0.05	0.049	0.922	0.98	1
KMO	rs1053230	T	0.236	0.223	0.572	1.07	1
LEPR	rs3806318	G	0.251	0.273	0.313	0.89	1
MAOA	rs1137070	C	0.313	0.301	0.646	0.95	1, 2
MC1R	rs885479	A	0.08	0.077	0.765	1.05	1
MTHFR	rs1801133	A	0.342	0.309	0.153	1.16	2
MYO3A	rs10828902	G	0.124	0.099	0.098	1.29	1
MYT1L	rs3748988	G	0.383	0.351	0.183	1.15	1
MYT1L	rs3748989	T	0.124	0.101	0.132	1.27	1
MYT1L	rs7592630	G	0.42	0.357	**0.01**	1.3	1
NBEA	rs4941807	C	0.382	0.38	0.946	1.01	1
NEUROD1	rs1801262	C	0.378	0.35	0.265	0.89	1
NGFR	rs2072446	T	0.047	0.041	0.505	1.15	1, 2
NOS2	rs2770248	A	0.323	0.333	0.661	0.95	1
NOS2	rs3794764	A	0.178	0.213	0.095	0.8	1
NPAS2	rs11123857	G	0.318	0.307	0.664	1.05	1

NPAS2	rs11541353	T	0.208	0.204	0.838	1.02	1
NPAS2	rs13025524	A	0.304	0.319	0.511	0.93	1
NPAS2	rs13394520	G	0.416	0.401	0.552	1.06	1
NPAS2	rs17025005	T	0.149	0.163	0.311	0.9	1
NPAS2	rs17662394	T	0.153	0.167	0.445	0.9	1
NPAS2	rs2117713	A	0.218	0.179	0.045	1.28	1
NPAS2	rs3754674	C	0.358	0.386	0.235	0.89	1
NPR3	rs976576	C	0.252	0.26	0.697	1.04	1
NPY	rs16139	C	0.029	0.04	0.251	0.71	2
NPY	rs16147	C	0.461	0.472	0.607	1.05	2
NR1D1	rs2071427	T	0.297	0.27	0.136	1.14	1
NR3C1	rs10052957	A	0.332	0.331	0.928	1	1
NR3C1	rs1866388	G	0.327	0.33	0.959	0.99	1
NR3C1	rs2918419	C	0.143	0.152	0.644	0.93	1
NR3C1	rs33388	T	0.464	0.46	0.888	1.02	1
NR3C1	rs41423247	C	0.352	0.363	0.627	0.95	1, 2
NR3C1	rs6191	A	0.466	0.46	0.827	0.98	1
NR3C1	rs6198	C	0.184	0.178	0.711	1.04	1
NR3C1	rs852977	G	0.329	0.33	0.966	1	1
NR3C1	rs860458	A	0.15	0.157	0.745	0.95	1
NT5E	rs6942065	A	0.142	0.131	0.578	1.09	1
NT5E	rs9450282	G	0.341	0.37	0.23	1.13	1
NTRK2	rs1187323	A	0.214	0.218	0.841	1.02	1
NTRK2	rs1187329	G	0.444	0.449	0.856	1.02	1
NTRK2	rs1545285	T	0.407	0.383	0.332	1.1	1
NTRK2	rs1778929	C	0.493	0.499	0.827	0.98	1
NTRK2	rs2013566	G	0.084	0.083	0.918	1.02	1
NTRK2	rs7020204	T	0.084	0.083	0.899	1.02	1
OXTR	rs2254298	A	0.104	0.101	0.829	1.04	1
OXTR	rs53576	G	0.365	0.352	0.572	0.94	1
P2RX7	rs208294	C	0.413	0.412	0.942	0.99	1
P2RX7	rs2230912	G	0.116	0.147	0.081	0.76	1, 2
P2RX7	rs591874	A	0.23	0.268	0.084	1.22	1
PAWR	rs8176874	C	0.004	0.008	0.313	0.5	1
PCLO	rs2522833	C	0.451	0.426	0.316	1.11	1
PCNT	rs2073376	G	0.363	0.373	0.664	1.05	1
PCNT	rs2073380	C	0.192	0.201	0.62	0.94	1
PCNT	rs3788265	T	0.185	0.194	0.607	0.94	1
PDE10A	rs220818	A	0.279	0.276	0.886	0.99	2
PDE10A	rs676389	C	0.134	0.128	0.7	1.05	2
PDE10A	rs717602	C	0.373	0.375	0.951	0.99	2
PDE11A	rs3770018	C	0.132	0.105	0.067	1.3	2
PDE2A	rs370013	A	0.166	0.172	0.689	1.05	2
PDE4B	rs1040716	T	0.489	0.428	**0.012**	1.28	1
PDE4B	rs2180335	G	0.442	0.496	0.034	1.24	1

PDE4B	rs472952	G	0.362	0.422	**0.016**	1.29	1
PDE4B	rs910694	T	0.435	0.491	0.025	1.25	1
PDE5A	rs3775845	C	0.321	0.315	0.779	1.03	2
PDE6C	rs650058	A	0.362	0.327	0.147	0.86	2
PDE6C	rs701865	A	0.336	0.348	0.568	0.94	2
PDE9A	rs729861	G	0.489	0.481	0.708	0.97	2
PDLIM5	rs2433320	A	0.437	0.453	0.519	0.94	1
PDYN	rs6136667	C	0.156	0.158	0.879	0.98	1
PER2	rs2304673	G	0.127	0.147	0.241	0.84	1
PER3	rs11121029	A	0.193	0.195	0.966	0.99	1
PLA2G4A	rs10798059	A	0.387	0.403	0.502	0.94	2
PLD1	rs2124147	G	0.5	0.463	0.143	1.16	1
POMC	rs2118404	T	0.264	0.213	**0.013**	1.32	1
PPARGC1A	rs768695	A	0.499	0.494	0.868	1.02	1
PROKR2	rs4815787	A	0.531	0.49	0.088	1.18	1
PSMB4	rs2296840	T	0.01	0.001	**0**	7.2	1
PSMB4	rs4603	C	0.187	0.187	0.993	1	1
S100A10	rs4845720	A	0.047	0.034	0.148	1.4	1
SERPINE1	rs2227684	A	0.419	0.436	0.509	0.94	1
SERPINE1	rs7242	G	0.417	0.438	0.383	0.92	1
SIGMAR1	rs1800866	G	0.151	0.163	0.509	0.91	1
SIRT1	rs10997875	C	0.34	0.327	0.601	0.95	1
SLC28A1	rs11853372	G	0.34	0.324	0.513	0.93	1
SLC28A1	rs12910991	G	0.384	0.373	0.675	1.05	1
SLC28A1	rs4271567	T	0.409	0.389	0.384	0.92	1
SLC28A1	rs4980345	T	0.061	0.061	0.968	0.99	1
SLC28A1	rs7182385	A	0.434	0.427	0.774	1.03	1
SLC29A1	rs324148	C	0.307	0.292	0.536	0.93	1
SLC29A1	rs6905285	T	0.396	0.402	0.818	0.98	1
SLC29A1	rs693955	C	0.244	0.227	0.399	0.91	1
SLC29A2	rs2279861	G	0.334	0.324	0.621	0.95	1
SLC29A2	rs4244813	C	0.341	0.326	0.475	0.93	1
SLC29A3	rs10999776	T	0.344	0.367	0.336	0.9	1
SLC29A3	rs12256138	T	0.44	0.451	0.641	0.95	1
SLC29A3	rs12767108	A	0.111	0.121	0.565	0.91	1
SLC29A3	rs2066210	G	0.123	0.135	0.47	0.9	1
SLC29A3	rs2487067	A	0.379	0.379	0.985	1	1
SLC29A3	rs780659	A	0.439	0.422	0.475	0.93	1
SLC29A3	rs780662	A	0.115	0.121	0.686	0.94	1
SLC6A2	rs2242446	T	0.25	0.274	0.27	1.13	1, 2
SLC6A3	rs2550936	C	0.249	0.276	0.204	0.87	1
SLC6A3	rs8179029	T	0.176	0.195	0.329	0.88	1
SLC6A4	rs140701	T	0.459	0.437	0.368	1.09	1
SLC6A4	rs2066713	A	0.37	0.38	0.67	0.96	1
SLC6A4	rs3794808	T	0.481	0.445	0.143	1.15	1

SLC6A4	rs3813034	C	0.519	0.487	0.19	1.14	1
SLC6A4	rs6354	T	0.172	0.182	0.631	1.07	1
SLC6A4	rs7224199	T	0.519	0.491	0.236	1.12	1
TACR1	rs13013430	C	0.216	0.254	0.076	0.81	2
TBX21	rs17244587	A	0.091	0.084	0.596	1.09	1
TBX21	rs2325717	C	0.086	0.084	0.856	1.03	1
TBX21	rs41515744	T	0.091	0.084	0.603	1.09	1
TFCP2	rs13463	T	0.042	0.052	0.23	0.8	2
TNF	rs1800629	A	0.232	0.191	0.048	1.28	1, 2
TPH	rs684302	T	0.393	0.382	0.651	1.05	2
TPH1	rs1799913	T	0.386	0.375	0.691	1.05	2
TPH1	rs1800532	T	0.386	0.375	0.692	1.05	1, 2
TPH2	rs1007023	T	0.153	0.135	0.291	0.86	1
TPH2	rs10784941	G	0.483	0.486	0.962	0.99	2
TPH2	rs1386486	G	0.347	0.367	0.369	1.09	2
TPH2	rs1386492	T	0.198	0.186	0.443	0.93	1
TPH2	rs1386494	C	0.178	0.175	0.819	0.98	1, 2
TPH2	rs17110747	A	0.113	0.151	0.033	0.72	1
TPH2	rs1843809	T	0.189	0.176	0.352	0.92	1, 2
TPH2	rs2171363	G	0.49	0.489	0.938	1	1, 2
TPH2	rs4570625	T	0.208	0.244	0.08	0.81	1
TPH2	rs6582078	T	0.432	0.438	0.691	1.03	1
TPH2	rs7300641	G	0.178	0.159	0.323	0.87	1
TPH2	rs7305115	G	0.445	0.45	0.754	1.02	1
TSNAX	rs766288	T	0.382	0.36	0.367	1.1	1
VEGFA	rs699947	C	0.463	0.475	0.623	0.95	1
VIPR2	rs12670064	C	0.251	0.24	0.62	1.06	1
VIPR2	rs2540352	T	0.462	0.46	0.947	1.01	1
WFS1	rs1046316	G	0.355	0.343	0.582	0.95	2
WFS1	rs1801206	T	0.419	0.421	0.949	1.01	2
WFS1	rs56072215	T	0.055	0.072	0.143	0.75	2

*****1= the SNP was reported in the literature reviewed in the current study, 2= the SNP was reported in the literature reviewed in the Bosker et al. study (2011).

Note. The bolded number indicates $p<0.05$.

Appendix F Associations with MDD at candidate gene level

Table S6 Significant SNPs or in/dels at gene-wide level in the full MDD sample

Gene	SNP	SNP p-value	Gene-wide p-value
ARNTL	rs7315725	0.00023	0.039
CREB1	rs184608248	7.2E-05	0.0057
HTR2C	rs141891742	0.00024	0.014
NR1D1	chr17:38252582:I	0.0018	0.049
PCLO	rs2247523	1.4E-05	0.0053
PCLO	rs2522832	1.6E-05	0.0056
PCLO	chr7:82457498:I	1.6E-05	0.0056
PCLO	rs2371214	1.5E-05	0.0056
PCLO	rs2522831	1.6E-05	0.0057
PCLO	rs2522835	1.7E-05	0.0060
PCLO	rs2715153	1.7E-05	0.0061
PCLO	rs2715151	1.7E-05	0.0061
PCLO	rs2715154	1.7E-05	0.0063
PCLO	rs2715157	1.8E-05	0.0066
PCLO	rs2715161	1.8E-05	0.0067
PCLO	rs2715148	1.9E-05	0.0078
PCLO	rs2715147	2.0E-05	0.0079
PCLO	rs2522836	2.0E-05	0.0085
PCLO	rs2371215	2.2E-05	0.0089
PCLO	rs2371362	2.4E-05	0.0098
PCLO	rs2888019	3.3E-05	0.014
PCLO	rs1986742	3.4E-05	0.014
PCLO	rs6965423	3.7E-05	0.015
PCLO	rs10250881	4.9E-05	0.021
PCLO	chr7:82464271:D	5.8E-05	0.024
PCLO	rs2522833	8.2E-05	0.035
PCLO	rs1044639	8.5E-05	0.036
PCLO	rs2715150	8.5E-05	0.036
PCLO	rs2715156	8.9E-05	0.038
PCLO	rs2715155	9.2E-05	0.039
PCLO	chr7:82475316:I	9.4E-05	0.040
PCLO	rs2257207	9.5E-05	0.040
PCLO	rs2715152	9.6E-05	0.040
PCLO	rs2715159	0.00010	0.043
PCLO	rs2715158	0.00010	0.044
PCLO	rs2522837	0.00011	0.045
PCLO	rs2522838	0.00011	0.045
PCLO	rs2522842	0.00011	0.045
PCLO	chr7:82463042:D	0.00011	0.046
PCLO	rs2522841	0.00011	0.046
PCLO	rs2522843	0.00011	0.046
PCLO	rs2522844	0.00011	0.046

PCLO	rs2107069	0.00011	0.046
PCLO	chr7:82455084:I	0.00012	0.047
PCLO	rs73157791	0.00012	0.048
PCLO	chr7:82475786:D	0.00012	0.049
PCLO	rs2522845	0.00012	0.050
PDE2A	rs142786372	3.90E-05	0.0072
SLC6A2	rs146042716	0.00039	0.037
TSNAX	rs183938582	0.00068	0.035

Table S7 Genes with more significant SNPs or in/dels than expected by chance in the full MDD sample

Gene	Nr of nominal significant variants / total nr of variants	p-value
PCLO	443 / 1741	0.0023
NPR3	91 / 431	0.010
CNR1	26 / 158	0.014
CHRFAM7A	7 / 38	0.015
CDC42SE2	97 / 530	0.020
CREB1	71 / 277	0.022
SLC6A2	43 / 309	0.032
PROKR2	81 / 222	0.037
POMC	11 / 70	0.037
SLC29A3	51 / 331	0.042
DAOA	62 / 248	0.043
HCRTR1	20 / 66	0.043
SIRT1	40 / 165	0.046

Table S8 Significant SNPs or in/dels at gene-wide level in the chronic and severe MDD subsample

Gene	SNP	SNP p-value	Gene-wide p-value
ARNTL2	rs145473801	1.06E-20	0.012
AVPR1B	rs34847455	1.35E-06	0.041
BCR	rs181674519	3.58E-13	0.033
COMT	rs116969180	2.86E-20	0.0021
CTLA4	rs78739751	5.11E-07	0.020
KCNK2	rs184373731	1.22E-14	0.039
MAOA	rs191501890	3.26E-08	0.028
PDE5A	rs146338796	5.26E-12	0.027
PLD1	rs190040430	1.86E-14	0.020
*POMC**	rs185055657	3.25E-07	0.046
POMC	chr2:25384092	3.51E-07	0.046
*PSMB4**	rs2296840	1.80E-07	0.010
PSMB4	rs6704126	1.74E-07	0.010

* The two SNPs in PSMB4 are in complete LD r^2 =1; the two SNPs in POMC are in strong LD r^2=0.998, too.

Table S9 Genes with more significant SNPs or in/dels than expected by chance in the chronic and severe MDD subsample

Gene	Number of nominal significant variants / total number of variants	p-value
POMC	19 / 66	0.0019
MYT1L	472 / 3105	0.0049
PDE11A	552 / 2679	0.0091
MTHFR	63 / 205	0.015
PDE4B	324 / 2417	0.018
MYO3A	469 / 1833	0.023
ADK	301 / 1171	0.033

Appendix G Comparing replication results with the Bosker et al. study

At candidate SNP level

Since the current study used a more homogeneous sample (e.g., the exclusion of those who developed a bipolar disorder) and a larger and better reference set for imputation(11), we reanalyzed the candidate SNPs selected in the Bosker et al. study(1) to determine if this improved the replication rate of candidate SNPs (**Appendix F, Table S4 & S5**). Out of 93 SNPs that were identified in Bosker et al.'s paper, 82 SNPs were in our dataset in contrast to the 65 previously in the Bosker et al.'s study. Three of these 82 were significantly associated with MDD (rs16139 in *NPY*: p=0.0036 [previously also associated]; rs10063995 in *DRD1*: p=0.0037 [previously not tested]; rs56072215 in *TNF*: p=0.05 [previously not tested]). One SNP that was found to be associated with MDD by Bosker et al. could not be replicated in the present study (rs12520799 in C5orf20, p=0.14).

Thus, 1) earlier SNPs that were not significant in the Bosker et al. paper were not significant in our paper either; 2) one of the two SNPs that were significant in the Bosker et al. paper [rs16139 in NPY] was also significant in our paper; while 3) the remaining SNP significant in the Bosker et al. paper was not [rs12520799 in C5orf20; currently p=0.14 in the full sample). This may be due to the more homogeneous sample (e.g., exclusion of those developing bipolar disorders) or from the reduced statistical power associated with this, as well as with the additional loss of cases due to attrition at follow up. In addition , 4) two SNPs that were significant in the current re-analysis (rs10063995 in DRD1 and rs56072215 in TNF) were not genotyped or imputed in the Bosker et al. study, although they were identified in the literature review of that study. Overall, then, the results are highly similar across studies, as the

SNPs that were significant in the current study were either significant in the former study, or not genotyped or imputed then.

At candidate gene level

We additionally compared replication rates of genes in our full sample with those in the Bosker et al. study. Specifically, we examined replication rates in the Bosker et al. study for all genes and in our study separately for genes that were 1) from the Bosker et al. study but not included in our new literature search, 2) from the Bosker et al. study and also identified in our literature search, and 3) new, i.e., only included in our study but not in the Bosker et al. study. because reported since 2007 but not before.

For the Bosker et al. study, two genes out of 55 genes were significantly associated with MDD in either of the two gene-wide tests (i.e., TNF and SLC6A2). Thus, the replication rate in that study was 4% (p=0.91, based on the binomial distribution).

Of the 55 genes that were examined in the Bosker et al. study, 38 were not identified in the current literature search (i.e. there were no replication studies on MDD with these genes between 2007 and 2012). Among these 38, three genes were significant in our current sample (i.e.,CHRFAM7A, HTR2C and PDE2A) resulting in a replication rate of 8% (p=0.51) for the 38 genes.

Seventeen genes from the Bosker et al. study were also identified in our current literature search. One of these (i.e., SLC6A2) was significantly associated with MDD, resulting in a replication rate of 6% (p=0.50).

Seventy two genes included in our literature search were not examined in the Bosker et al. study, among which 14 genes were significant in either of the two gene-wide tests. Thus, the replication rate for these new genes was 19% (p=0.004).

Thus, overall, the replication rate in our full sample (14%) was substantially higher than it is in the Bosker et al. study (4%), and the replication rate was highest for genes reported only since 2007 and had therefore not been tested in the Bosker et al. study. These results can give us clues about the reason for the higher replication rates in our study. Possible reasons are improved imputation, the newer set of candidate genes and the more homogenous sample. Improved imputation and/or improved homogeneity of the sample contributed, as the replication rate improved somewhat when comparing genes that were only included in the previous literature search but were reexamined in our study. However, the results suggest that it was primarily the newer set of candidate genes that increased the replication rate. The replication rates increased substantially for genes that were only identified in studies since 2007. These studies are likely to be of higher methodological quality, including improved phenotyping and larger sample sizes.

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