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Does Refining the Phenotype Improve Replication Rates? A Review and Replication of Candidate Gene Studies on Major Depressive Disorder and Chronic Major Depressive Disorder

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Replication has been poor for previously reported candidate genes involved in Major Depressive Disorder (MDD). One possible reason is phenotypic and genetic heterogeneity. The present study replicated genetic associations with MDD as defined in DSM-IV and with a more narrowly defined MDD subtype with a chronic and severe course. We first conducted a systematic review of genetic association studies on MDD published between September 2007 and June 2012 to identify all reported candidate genes. Genetic associations were then tested for all identified single nucleotide polymorphisms (SNPs) and the entire genes using data from the GAIN genome-wide association study (MDD: n = 1,352; chronic MDD subsample: n = 225; controls: n = 1,649). The 1,000 Genomes database was used as reference for imputation. From 157 studies identified in the literature, 81 studies reported significant associations with MDD, involving 245 polymorphisms in 97 candidate genes, from which we were able to investigate 185 SNPs in 89 genes. We replicated nine candidate SNPs in eight genes for MDD and six in five genes for chronic MDD. However, these were not more than expected by chance. At gene level, we replicated 18 genes for MDD and 17 genes for chronic MDD, both significantly more than expected by chance. We showed that replication rates were improved for MDD compared to a previous, highly similar, replication study based on studies published before 2007. Effect sizes of the SNPs and replication rates of the candidate genes were improved in the chronic subsample compared to the full sample. Nonetheless, replication rates were still poor.

Key words: major depressive disorder; candidate genes; genome-wide association study; chronic depression; severe depression; replication

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INTRODUCTION

Major depressive disorder (MDD) is one of the leading causes of disability [Vos et al., 2013]. Key characteristics are a persistently depressed mood or an inability to experience pleasure [American

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Psychiatric Association, 1994]. Genetic factors substantially contribute to MDD. A meta-analysis of twin studies showed that the heritability of MDD averages 37% [Sullivan et al., 2000]. However, results from linkage studies have been inconsistent [Holmans et al., 2004; McGuffin et al., 2007] and almost all large-scale genome-wide association studies (GWAS) for MDD failed to detect genes at genome-wide significance level [Lewis et al., 2010; Muglia et al., 2010; Rietschel et al., 2010; Shi et al., 2011]. Moreover, candidate gene studies have been only marginally successful. A large-sample replication study by Bosker et al. [2011] based on studies published before September 2007 replicated only a small fraction of previously reported candidate genes for MDD (7% of genes; 3–4% of single nucleotide polymorphisms (SNPs)). Based on the same samples (i.e., the Netherlands Study of Depression and Anxiety (NESDA) and the Netherlands Twin Registry (NTR)) [Boomsma et al., 2008], the current study extends the replication study of Bosker et al. in several ways. First, we aimed to identify and test candidate genes reported to be associated with MDD since September 1st, 2007, which was the end date of the literature search in Bosker et al. [2011]. Candidate genes that have emerged in the 5 years since then would likely provide additional insights on genes and SNPs involved in MDD and need to be replicated in an independent sample. Second, by using the 1,000 Genomes data as reference datasets for imputation [Marchini et al., 2007; 1000 Genomes Project Consortium, 2010], we expected to be able to test more candidate SNPs than before. Bosker et al. was unable to test one third of the 93 polymorphisms that had been reported to be associated with MDD because the information was not available for these polymorphisms from the genotyping chip or HapMap CEU data used for imputation [Bosker et al., 2011].

Besides incorporating additional candidate genes of MDD and enlarging the SNP dataset using the 1,000 Genome reference set, our aim was to not only study genetic associations with MDD as defined in DSM-IV, but also with a more narrowly defined MDD phenotype based on a chronic and severe course. Poor replication rates reported in the literature [Bosker et al., 2011] may partly be due to the imprecision and subjectivity inherent to the MDD diagnosis. This yields measurement error diluting the relationship between genotype and phenotype [Kendler et al., 1993]. The use of repeated assessments of MDD has been shown to reduce measurement error in the phenotype, resulting in higher heritability estimates compared to single diagnosis [Foley et al., 1998]. But, when retrospectively reporting on previous MDD episodes, recall bias and mood-congruence effects may add to measurement error [Bromet et al., 1986]. Therefore, the chronic MDD phenotype in the present study was defined on the basis of the longitudinal course of MDD symptoms that have been repeatedly rather than retrospectively assessed. Another reason for the inconsistent findings on genes for MDD is the heterogeneity of MDD itself [Cohen-Woods et al., 2013]. For example, the diverging estimates on the heritability of MDD from twin studies [ranging from 17% to 80%; Foley et al., 1998; Sullivan et al., 2000] may be partly due to diversity of MDD patients across studies. Hence, focusing on more phenotypically homogeneous subtypes may help identify genes that contribute consistently to MDD [Flint and Kendler, 2014]. One such subtype could be recurrent or chronic MDD, which is suggested to be more heritable [Sullivan et al., 2000; Kendler et al., 2007]. Refining the MDD phenotype according to chronicity reduces phenotypic and most likely also genetic heterogeneity, and will increase chances to replicate the underlying genes. Therefore, in this study we expected stronger associations and a higher replication rate of candidate genes with chronic MDD than with DSM-IV defined MDD.

MATERIALS AND METHODS

Literature Selection

We conducted a systematic literature search to update genetic case-control association studies on MDD, with those published between September 1st, 2007, the end search date in Bosker et al. [2011], and June 10th, 2012 using MEDLINE® via PUBMED. Search terms, study inclusion and exclusion criteria, and information regarding how studies were rated can be found in the Supplementary Information (SI), Appendix A. Briefly, we selected studies that fulfilled the following criteria: (i) the patients had a primary diagnosis of major depressive disorder; (ii) the study examined the association between a candidate gene (a SNP, a microsatellite marker, or a haplotype) and MDD; (iii) the study was a case-control association study; (iv) the sample of the study included at least 30 patients and 30 healthy controls. 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). Figure 1 shows how studies were selected. A description of the data extracted from these studies is provided in the SI, Appendix B. Briefly, we extracted information for author(s), year of publication, sample sizes for cases and controls, study design, genes, SNPs/haplotypes, 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.

Sample

Cases. Cases were selected if they: (i) had a lifetime MDD according to DSM-IV criteria (Diagnostic and Statistical Manual, Fourth Edition [American Psychiatric Association, 1994]; (ii) assessed with the Composite International Diagnostic Interview (CIDI), assessed at baseline (T1) [Kessler and Ustun, 2004]; (iii) were between 18 and 65 years old, and; (iv) were of western European ancestry. Individuals who were not fluent in Dutch or did not have a primary diagnosis of MDD were excluded. There were 1,738 cases fulfilling the criteria after the genotyping quality check (for additional information, see quality control section below and Bosker et al. [2011]). Unlike the Bosker et al. [2011], participants with an MDD diagnosis from NTR ($n = 136$) were excluded as depressive symptoms were not studied longitudinally in NTR, leaving 1,602 MDD patients from NESDA included. Participants from NESDA filled in the IDS-SR (Inventory of Depressive Symptomatology, self-report version) [Rush et al., 1996]) at four measurement waves (i.e., baseline (T1), 1-year follow-up (T2), 2-year follow-up (T3), and 4-year follow-up (T4)) and received diagnostic interviews at waves 1, 3, and 4. From these 1,602 patients, 121 developed a bipolar disorder (104

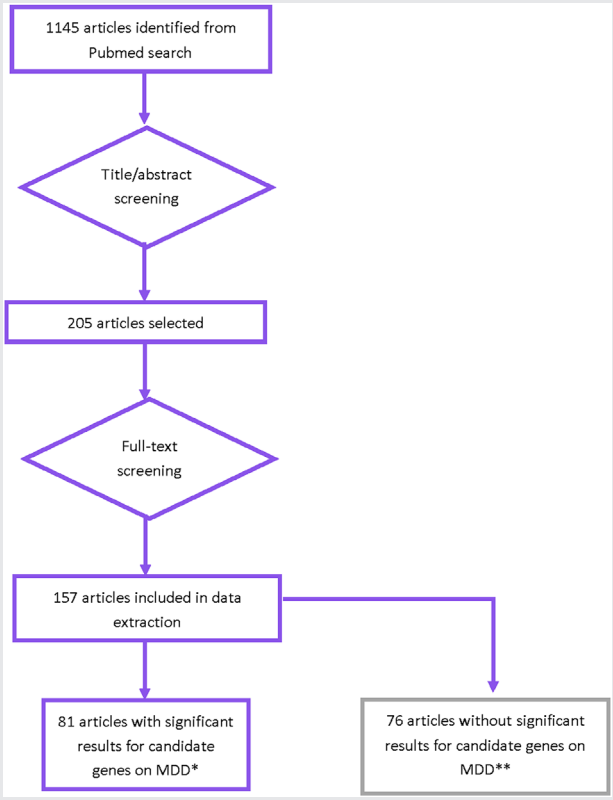

FIG. 1. Flowchart showing how the studies were selected from the literature search. *Seventy papers reported significant genetic associations with MDD in primary analysis; the other 11 papers did not find significant associations in their primary analyses but in their subgroup analyses. **The 76 articles included seven GWAS studies, none of which had genome-wide significant results ($P < 5 \times 10\text{-}8$). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].

diagnosed at wave 3 (T3); 17 at wave 4 (T4)) and were excluded. In addition, six controls from the NESDA cohort developed at least one major depressive episode in the follow-up period and thus, were included in the final MDD sample, leaving a total of 1,487 cases. Finally, 135 cases were excluded because they had missing values on the IDS-SR on three or four measurement waves, leaving a sample of 1,352 cases for this study (see SI Appendix C for missing value analysis for case selection). See the flowchart depicted in SI, Figure S1 for an overview.

Identification of cases with chronic and severe depression. We used Latent Class Growth Analysis (LCGA) to identify the subgroup of MDD patients with a chronic and severe course. LCGA was applied to the scores on the IDS-SR from four measurement waves to cluster individuals with similar trajectories of MDD severity over time. The results indicated that five trajectories best summarized the variation in course of depressive symptoms over time (Details on the methodology and results are in SI, Appendix D). Individuals in the first and the second trajectories with consistently high scores across time (on average a score >30 on the IDS at all waves) were selected as the chronic, MDD subsample (n = 225). Selected individuals were older, had less years of education, and had more comorbidity with anxiety disorders compared to the less severe groups (SI, Appendix D, Table S3).

Controls. In brief, the NTR included assessments of depressive symptoms (with multiple instruments such as the Beck Depression Inventory [Beck et al., 1961]), anxiety symptoms and neuroticism. Inclusion criteria for controls were further: (i) participants did not report a history of MDD or were not diagnosed with MDD in any measurement wave; (ii) participants had never scored high (≥1 s.d.) on a repeatedly measured combined score of neuroticism, anxiety, and depressive symptoms; (iii) participants and their parents were born in the Netherlands or Western Europe. Only one control participant per family was selected. After quality control check, 1,802 controls were included initially in the sample. However, unlike the Bosker et al. [2011], we excluded controls from NESDA (n = 153). They were not screened for low neuroticism as was done in NTR, and a small percentage of NESDA controls came from a high risk cohort, from which six people developed MDD during the follow-up and were included as cases. Therefore, the control group in the subsequent genetic analyses consisted of 1,649 individuals.

Genetic Analyses

Genotyping and quality control. Genotyping was performed according to strict standard operating procedures by Perlegen Science. DNA samples from cases and controls were randomly assigned to plates, shipped to Perlegen and identified only by barcode. High-density oligonucleotide arrays were used yielding 599,164 SNPs, from which 435,291 passed all quality control tests. Further details have been described elsewhere [Boomsma et al., 2008]. Briefly, in terms of quality control for subjects, genotypes were delivered for 3,761 samples of the 3,820 Dutch samples sent to Perlegen (excluding the 20 HapMap internal control samples). A total of 59 samples did not have GWAS data: 39 samples with uncertain linkage between genotype and phenotype records, seven samples with evidence of contamination, six samples that failed genotyping, and seven miscellaneous failures (two of these were excluded as chrX and chrY genotyping data were consistent with the presence of XO and XXY sex chromosome status). After further analysis, eight subjects were removed for excessive missing genotype data (>25%), one case for high genome-wide homozygosity (~75%), 38 subjects whose genome-wide IBS estimates were consistent with first- or second-degree relationships and 57 additional subjects whose ancestry diverged from the remainder of the sample. After these exclusions (n = 104) and removing duplicated, and trio quality control samples, there were 3,540 subjects in the analysis data set including 1,738 cases and 1,802 controls (from which we further excluded cases and controls for reasons described above).

In terms of quality control for SNPs, the unfiltered data set obtained from dbGaP contained 599,156 unique SNPs. The Perlegen genotyping algorithm yielded a quality score for each individual genotype, and a more stringent quality score cutoff (≥10) than that used by Perlegen was applied. The SNP quality control process is described in detail elsewhere [Bosker et al., 2011]. Briefly, to be included in the final analysis data set, SNPs were required not

to have any of the following features: gross mapping problem, ≥2 genotype disagreements in 40 duplicated samples, ≥2 Mendelian inheritance errors in 38 complete trio samples, minor allele frequency <0.01 or >0.05 missing genotypes in either cases or controls. A Hardy–Weinberg filter was not used as lack of fit to Hardy–Weinberg expectations can occur for valid reasons (for example, a true association) and given that 95.6% (= 51,592/53,994) of SNPs with $P < 0.00001$ from an exact test of Hardy–Weinberg equilibrium in controls were already flagged for exclusion. A total of 435,291 SNPs met these criteria and were included in the final analysis data set. A total of 13 controls were genotyped in a different study using the Illumina 317 K platform and, of the 82,636 SNPs common to both platforms, the genotype agreement was 99.94%.

Imputation. The genotype data were imputed using data from the 1,000 Genomes database (March 2012 release, global population; http://www.1000genomes.org/) as the reference [1000 Genomes Project Consortium, 2010]. Imputations were performed by IMPUTE version 2.1.2 [Howie et al., 2009]. In this way, we extended the genome-wide SNP data set to about 30 M SNPs or insertion–deletion polymorphisms (in/dels). We selected all variants located within 5 kb of the selected MDD genes (n = 120,815) and excluded those with a low imputation quality (n = 35,019) (proper_info <0.5), leaving 86,421 variants for the analysis.

Statistical analysis. We conducted two association studies, in the full and the severe sample, adjusting for sex and the uncertainty of the genotypes that were imputed. We set a significance level of 0.05 for the full sample, given hypothesis driven testing derived from findings in the literature. However, the chronic and severe MDD cases are a subset of the full MDD sample and hence, it could be that the association with MDD extends to either this subset or the complementary subsample of the less severe or less chronic cases. Therefore, the significance for the subset needs to be corrected for two tests. For the chronic and severe subsample, a significance level of 0.025 (= 0.05/2) was chosen to adjust for multiple testing due to subsampling. This was done both at candidate SNP and candidate gene level. Associations between MDD and the SNPs or in/dels were tested using a frequentist case–control test assuming an additive model provided in the software package SNPTEST version 2.2.0 [Marchini et al., 2007]. For the two-marker haplotypes of the SNPs rs4251417 and rs2020934 that tag the 5HTTLPR polymorphism [Wray et al., 2009] we applied an Expectation Maximization algorithm to estimate the number of CA haplotypes in MDD cases, severe and chronic cases, and controls. These numbers were next compared using a chi-square test to determine association of the CA haplotype and hence, the short allele of 5HTTLPR with MDD in general and chronic and severe MDD.

At candidate SNP level, we examined the original SNPs derived from the literature without correcting for multiple testing as these tests can be seen as hypothesis driven. However, we additionally tested if the number of replicated associations were larger than expected by chance to examine if replicated SNPs are likely to be false positives.

At the candidate gene level, we tested all SNPs or in/dels located within and <5 kb from the boundaries of the gene and used a permutation procedure to determine significance in order to correct for multiple testing. We calculated three *P*-values by permutation following the procedures in Bosker et al.: (i) a gene-wide significance in which the significance of a SNP or in/dels is corrected for all SNPs and in/dels in the gene; (ii) an overall significance corrected for all SNPs and in/dels in all selected genes; and (iii) the significance of the number of nominal significant SNPs or in/dels ($P < 0.05$) within a candidate gene. In the permutation procedure, case and control statuses were randomly assigned to each of the individuals leaving the dependency structure between the SNPs or in/dels intact and hence, the resulting three *P*-values are corrected for linkage disequilibrium (LD) between SNPs or in/dels. The former two significances were computed as the fraction of permutations in which any SNP or in/del within the gene or any of the SNPs or in/del, respectively, was more significant than the SNP in the original (unpermuted) dataset. For the latter significance, the fraction of permutations with a higher number of nominal significant SNPs or in/dels than originally observed determined the significance of the number of significant SNPs of that candidate gene. The number of permutations was 10,000. For more details see Bosker et al. Finally, in addition to these permutation tests, we determined if the total number of replicated genes identified at the candidate gene level were larger than expected by chance.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the significant candidate SNPs comparing allele frequencies using counted numbers of genotyped or imputed SNPs, respectively. In the latter case allele frequencies determined from expected genotype counts are used, meaning that genotype probabilities, which account for uncertainties due to imputation, are summed across all individuals in the sample. Note that the difference in procedure to calculate the OR (using allele frequencies) as compared to the additive model used for determining significance may cause the CI of the OR to contain 1, even though SNPTEST assigned a significant *P*-value to the SNP. Finally, to establish true replication, we additionally checked whether the effect was found for the same allele and in the same direction as reported in the literature.

RESULTS

Literature Search

Our systematic search yielded 157 articles investigating candidate gene associations with MDD, from which 81 articles reported nominal significant associations ($P < .05$). These 81 articles reported significant results for 245 polymorphisms, including 201 SNPs, 37 haplotypes, and 7 microsatellite markers, in 97 candidate genes (Table I). Among these, one single SNP and four SNPs in five haplotypes could not be mapped. For the 5HTTLPR polymorphism, the two-marker haplotype CA of the SNPs rs4251417 and rs2020934 tag the short allele ($r^2 = 0.72$; Wray et al. [2009]). For the remaining six microsatellite markers, no information on LD with SNPs could be found. Hence, these polymorphisms were not analyzed.

Replication of Candidate SNPs Reported in the Literature

For the SNPs that could be mapped, 185 SNPs in 89 genes were present on the chip or could be imputed. We examined whether the associations with MDD for these SNPs were replicated based on our

TABLE I. Candidate Genes and Polymorphisms for MDD From the Literature Search

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
AANAT	AANAT	17q25	16.8		rs3760138	Soria et al. [2010a]	257	440	0.0021		0.0006	1.92 (1.39–2.64)			1	
AANAT	AANAT	17q25	16.8		rs4238989	Soria et al. [2010a]	257	440	0.0135		0.005	1.61 (1.16–2.27)			1	
AANAT	AANAT	17q25	16.8		rs3760138-rs4238989-rs8150	Soria et al. [2010a]	257	440					<0.001			
AANAT	AANAT	17q25	16.8		rs8150	Soria et al. [2010a]	257	440	0.0282							
ABCB1	ABCB1	7q21.12	209.5		rs2032583	Dong et al. [2009]	272	264	0.04	1.64 (1.04–2.59)					1	
ABCB1	ABCB1	7q21.12	209.5		rs4728697	Dong et al. [2009]	272	264	0.01	2.24 (1.18–4.28)	0.02				1	
ABCB1	ABCB1	7q21.12	209.5		rs58898486	Dong et al. [2009]	272	264	0.02	8.40 (1.05–67.39)	0.02				1	
ABCB1	ABCB1	7q21.12	209.5		rs1002205	Wong et al. [2008]	278	281	0.03	1.45 (1.05–2.02)						1
ABCB1	ABCB1	7q21.12	209.5		rs1922243	Wong et al. [2008]	278	281	0.03	1.45 (1.04–1.99)						1
ACE	ACE	17q23.3	20.8	-240A/T	rs4291	Angunsri et al. [2009]	187	207	0.040	0.70 (0.50–0.97)	0.036					
ACE	ACE	17q23.3	20.8		rs4291-rs4292	Angunsri et al. [2009]	187	207					0.002			
ADA	ADA	20q13.12	32.2		rs452159	Gass et al. [2010]	103	409	0.0165	0.63 (0.43–0.93)					2	0
ADA	ADA	20q13.12	32.2		rs6031682	Gass et al. [2010]	258	557	0.0398	0.74 (0.55–0.98)					2	0
ADCYAP1	ADCYAP1	18p11	7.2		rs17500692	Soria et al. [2010b]	335	440	0.038		0.021	0.67 (0.47–0.94)				0
PACAP	ADCYAP1	18p11	7.2		rs1893154	Hashimoto et al. [2010]	637	967	0.031	0.78 (0.62–0.97)						
ADK	ADK	10q11-q24	558.1		rs7924176	Gass et al. [2010]	194	449	0.0402	0.77 (0.60–0.99)					2	0
ADK	ADK	10q11-q24	558.1		rs946185	Gass et al. [2010]	125	483	0.0296	0.72 (0.53–0.96)					2	0
ADORA1	ADORA1	1q32.1	39.7		rs12026765	Gass et al. [2010]	194	449	0.046	0.64 (0.42–0.99)					2	0
ADORA1	ADORA1	1q32.1	39.7		rs17530497	Gass et al. [2010]	194	449	0.0464	1.30 (1.01–1.67)					2	0
APOE	APOE	19q13.2	3.5	e2	N.A.[a]	Lin et al. [2009a]	253	411			<0.001	0.05 (0.01–0.21)				
ARNTL	ARNTL	11p15	109.5		rs11022778	Soria et al. [2010b]	335	440			0.022	1.67 (1.08–2.58)				0
ARNTL	ARNTL	11p15	109.5		rs17452383	Soria et al. [2010b]	335	440			0.035	3.00 (1.03–8.77)				0
ARNTL	ARNTL	11p15	109.5		rs2279287	Soria et al. [2010b]	335	440			0.022	0.71 (0.53–0.95)				0
ARNTL	ARNTL	11p15	109.5		rs900144	Soria et al. [2010b]	335	440			0.023	0.69 (0.50–0.95)				0
ARNTL	ARNTL	11p15	109.5		rs969485	Soria et al. [2010b]	335	440			0.041	0.75 (0.55–1.02)				0
ARNTL2	ARNTL2	12p12.2-p11.2	93.0		rs10506018	Soria et al. [2010b]	335	440			0.009	0.63 (0.44–0.88)				0
ARNTL2	ARNTL2	12p12.2-p11.2	93.0		rs11048994	Soria et al. [2010b]	335	440			0.014	0.65 (0.47–0.90)				0

(*Continued*)

TABLE I. (*Continued*)

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
ARNTL2	ARNTL2	12p12.2-p11.2	93.0		rs11610949	Soria et al. [2010b]	335	440	0.043		0.018	0.65 (0.46–0.94)				0
ARNTL2	ARNTL2	12p12.2-p11.2	93.0		rs3751222	Soria et al. [2010b]	335	440			0.011	0.54 (0.33–0.87)				0
BDKRB2	BDKRB2	14q32.1-q32.2	39.5	hcv7565899	rs1046248	Gratacos et al. [2009]	422	615	0.0123	1.60 (1.16–2.20)						0
BDNF	BDNF	11p13	67.2	rs57083135-NT_009237.17_rs26469156-rs11030103-rs12273539	N.A.	Licinio et al. [2009]	272	264					<0.001		1	
BDNF	BDNF	11p13	67.2		rs11030101	Licinio et al. [2009]	272	264	0.02	1.37 (1.05–1.78)	0.04				1	
BDNF	BDNF	11p13	67.2		rs11030103	Licinio et al. [2009]	272	264	0.008	1.80 (1.18–2.74)	0.03				1	
BDNF	BDNF	11p13	67.2		rs12273539	Licinio et al. [2009]	272	264	<0.001	1.75 (1.32–2.31)	<0.001				1	
BDNF	BDNF	11p13	67.2		rs28722151	Licinio et al. [2009]	272	264	0.01	1.48 (1.10–1.99)	0.009				1	
BDNF	BDNF	11p13	67.2		rs41282918	Licinio et al. [2009]	272	264	0.01	2.13 (1.18–3.86)	0.02				1	
BDNF	BDNF	11p13	67.2		rs56820186-rs6265-	rs11030101-rs28722151-rs11030102		Licinio	et al.	[2009]	272	264				
<0.001		1														
BDNF	BDNF	11p13	67.2		rs6265	Licinio et al. [2009]	272	264	0.009	1.66 (1.14–2.41)	0.08				1	
BDNF	BDNF	11p13	67.2	val66met	rs6265	Lin et al. [2009b]	155	195	0.0277		0.0031					1
BDNF	BDNF	11p13	67.2	val66met	rs6265	Suchanek et al. [2011]	116	218			<0.05	1.72 (1.06–2.79)				
BDNF	BDNF	11p13	67.2	Val66met	rs6265	Taylor et al. [2007]	245	94	0.024	1.92 (1.09–3.38)						
BDNF	BDNF	11p13	67.2			val66met-C-281A rs28383487			rs6265-	Suchanek et al. [2011]	116	218				
0.012	0.63 (0.30–0.86)															
BDNF	BDNF	11p13	67.2	270C/T-196A/G-11757G/C	N.A.	You et al. [2010]	144	110					0.049			
BDNF	BDNF	11p13	67.2	-712G/A–270C/T	N.A.	You et al. [2010]	144	110					0.049			
BDNF	BDNF	11p13	67.2	-712G/A–270C/T–196A/G–11757G/C	N.A.	You et al. [2010]	144	110					<0.001			
BDNF	BDNF	11p13	67.2	G-712A	N.A.	Sun et al. [2011]	202	346	0.0007	2.28 (1.40–3.71)	0.0005					1
CACNA1C	CACNA1C	12p13.3	644.7		rs1006737	Green et al. [2010]	1165	1019		1.15 (1.02–1.31)	0.013					
KAT III	CCBL2	1p22.2	57.2		rs12729558-rs17130657-rs1325924-rs2038905-rs7556189-rs7517036	Claes et al. [2011]	266	310					<0.001			1

(*Continued*)

TABLE I. (*Continued*)

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
CDC42SE2	CDC42SE2	5q31.1	130.7		rs798412	Wong et al. [2008]	278	281	0.005	1.43 (1.11–1.83)						1
CDC42SE2	CDC42SE2	5q31.1	130.7		rs798416	Wong et al. [2008]	278	281	0.008	1.40 (1.09–1.79)						1
CLOCK	CLOCK	4q12	119.0		rs11133379	Soria et al. [2010b]	335	440			0.046	1.53 (1.01–2.32)				0
CLOCK	CLOCK	4q12	119.0		rs3736544	Kishi et al. [2011]	139	889			0.0174	2.23 (1.11–4.20)				0
CLOCK	CLOCK	4q12	119.0		rs6850524	Soria et al. [2010b]	335	440			0.015	1.30 (1.05–1.61)				0
CNR1	CNR1	6q14-q15	26.2	1359G/A	rs1049353	Monteleone et al. [2010]	83	117	0.001	2.46 (1.46–4.137)	0.01					
CB2	CNR2	1p36.11	39.4	Q63R	rs2501432	Onaivi et al. [2008]	166	487	0.0067	1.42 (1.09–1.83)	0.01	1.95 (1.11–3.44)				
CNTN5	CNTN5	11q22.1	1337.9		rs6589849	Gratacos et al. [2009]	422	615	0.0035	0.70 (0.56–0.86)						0
CNTNAP2	CNTNAP2	7q35	2304.6		rs2692359	Gratacos et al. [2009]	422	615	0.049	2.14 (1.07–4.29)						0
COMT	COMT	22q11.21	28.2		rs737865	Massat et al. [2011]	152	293	0.04		0.03				2	
COMT	COMT	22q11.21	28.2	G/A	rs4680	Massat et al. [2011]	462	295			0.03					
COMT	COMT	22q11.21	28.2		rs4680	Kocabas et al. [2010]	396	295			0.0397					0
COMT	COMT	22q11.21	28.2		rs6269-rs4633-rs4818-rs4680	Kocabas et al. [2010]	396	295					0.0001			1
CREB1	CREB1	2q34	75.7		rs3732076	Dong et al. [2009]	272	264	0.004	11.45 (1.46–89.77)	0.003				1	
CRF-BP	CRHBP	5q11.2-q13.3	16.6	CRF-BPs12	rs1053989	Van Den Eede et al. [2007]	81	333	0.038		0.036					0
CRF-BP	CRHBP	5q11.2-q13.3	16.6	CRF-BPs11	rs1875999	Van Den Eede et al. [2007]	81	333	0.043							0
CRF-BP	CRHBP	5q11.2-q13.3	16.6	CRF-BPs2	rs7728378	Van Den Eede et al. [2007]	81	333	0.017		0.01					0
CRHBP	CRHBP	5q11.2-q13.3	16.6		rs1875999	Gratacos et al. [2009]	422	615	0.022	0.78 (0.65–0.94)						0
CRHBP	CRHBP	5q11.2-q13.3	16.6		rs7718461	Gratacos et al. [2009]	422	335	0.043	0.81 (0.66–0.99)						0
CRHR2	CRHR2	7p14.3	48.2		rs2284220	Gratacos et al. [2009]	422	615	0.011	0.64 (0.48–0.87)						0
CRY1	CRY1	12q23-q24.1	102.5		rs2287161	Soria et al. [2010b]	335	440			8×10^{-5}	0.66 (0.53–0.81)				1
CRY1	CRY1	12q23-q24.1	102.5		rs4640029	Soria et al. [2010b]	335	440			0.048	1.40 (1.00–1.95)				0
CRY1	CRY1	12q23-q24.1	102.5		rs714359	Soria et al. [2010b]	335	440	0.032		0.022	0.70 (0.51–0.95)				0
CSF2RB	CSF2RB	22q13.1	26.8	C/T	rs2284031	Chen et al. [2011]	1139	1140	0.006	0.80						1
CSF2RB	CSF2RB	22q13.1	26.8		rs2284031-rs909486-rs738149	Chen et al. [2011]	1139	1140					0.0004	0.8		1
CSF2RB	CSF2RB	22q13.1	26.8	A/G	rs738149	Chen et al. [2011]	1139	1140	0.001	1.32						1
CSF2RB	CSF2RB	22q13.1	26.8	C/T	rs909486	Chen et al. [2011]	1139	1140	0.026	1.17						1
CTLA-4	CTLA4	2q33	6.2		rs231779	Liu et al. [2011]	1140	1140	0.0006		0.0026					1
DAOA	DAOA	13q34	25.2		rs778336	Soronen et al. [2011]	272	1322	0.0406							

(*Continued*)

TABLE I. (*Continued*)

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
G72	DAOA	13q34	25.2	M23-M24	rs3918342-rs1421292	Rietschel et al. [2008]	500	1030					0.04	1.18 (1.01–1.38)		
DBH	DBH	9q34	23.0	a 19 bp insertion/deletion polymorphism	N.A.	Togsverd et al. [2008]	67	1304	0.04		0.03					
DBP	DBP	19q13.3	6.8		rs386551	Soria et al. [2010b]	335	440			0.011	2.15 (1.18–3.93)				
DIO1	DIO1	1p33-p32	16.9	3'UTR	rs11206244	Philibert et al. [2011]	-[b]	-			<0.004				2	
DISC1	DISC1	1q42.1	414.5		rs7546310-rs821597	Schosser et al. [2010]	1469	1376					0.034			
DTNBP1	DTNBP1	6p22.3	140.3	A/C	rs1011313	Kim et al. [2008]	188	350			0.025					
DTNBP1	DTNBP1	6p22.3	140.3	C/T	rs3213207-rs1011313-rs760761-rs2619522	Kim et al. [2008]	188	350					0.0007			
EMP1	EMP1	12p12.3	20.1		rs4763327	Nakataki et al. [2011]	76	147	0.028		0.008				2	
EMP1	EMP1	12p12.3	20.1		rs7315725	Nakataki et al. [2011]	76	147	0.012		0.031				2	
FKBP5	FKBP5	6p21.31	155.0		rs1360780	Lekman et al. [2008]	1256	634			0.0038				2	
FKBP5	FKBP5	6p21.31	155.0		rs4713916	Lekman et al. [2008]	1256	634			0.046				2	
FKBP5	FKBP5	6p21.31	155.0		rs1360780	Zobel et al. [2010]	268	284	0.0356							
FKBP5	FKBP5	6p21.31	155.0		rs3800373	Zobel et al. [2010]	268	284	0.014		0.049					
FKBP5	FKBP5	6p21.31	155.0		rs4713916	Zobel et al. [2010]	268	284	0.013		0.008					
GABRR2	GABRR2	6q15	58.2		rs3777514	Gratacos et al. [2009]	422	615	0.0123	0.72 (0.58–0.90)						0
GAD2	GAD2	10p11.23	88.3		rs8190646	Unschuld et al. [2009]	541	541	0.0004		0.0005	1.65				1
GRIN3A	GRIN3A	9q31.1	169.2		rs10989591	Gratacos et al. [2009]	422	615	0.0026	1.99 (1.33–2.98)						0
GRM3	GRM3	7q21.1-q21.2	221.0		rs6465084	Tsunoka et al. [2009]	325	802	0.0093		0.0344					
GSK3B	GSK3B	3q13.3	272.5		rs6782799	Zhang et al. [2010]	447	432	0.022	1.25 (1.03–1.52)						0
HCRTR1	HCRTR1	1p33	9.6	G/A	rs2271933	Rainero et al. [2011]	130[c]	259	0.002		0.0006					
HTR1A	HTR1A	5q11.2-q13	2.2	R219L	rs1800044	Haenisch et al. [2009]	426	643			0.024	3.8 (1.2–12.3)				
HTR1A	HTR1A	5q11.2-q13	2.2	C-1019G	rs6295	Wu et al. [2008]	400	400	0.001		0.004					
HTR1A	HTR1A	5q11.2-q13	2.2		rs878567	Kishi et al. [2009b]	331	804	0.045							0
IKBKE	IKBKE	1q32.1	26.6		rs1539243	Koido et al. [2010]	312	356	0.01		0.02					0
IL-10	IL10	1q31-q32	4.9	-1082G/A	rs1800896	Clerici et al. [2009]	32	363			<0.01					
KCNK2	KCNK2	1q41	231.6		rs668529[d]	Liou et al. [2009]	449	421			5.2×10^{-5}	1.58 (1.17–2.12)				1
KMO	KMO	1q42-q44	63.5		rs1053230	Claes et al. [2011]	266	310	0.044							0
LEPR	LEPR	1p31	216.8		rs3806318	Gratacos et al. [2009]	422	615	0.017	0.49 (0.28–0.85)						0
MAOA	MAOA	Xp11.3	91.9	uVNTR	N.A.	Huang et al. [2009]	122	111			0.041				2	
MAOA	MAOA	Xp11.3	91.9	uVNTR	N.A.	Lung et al. [2011]	146	182	0.041						2	
MAOA	MAOA	Xp11.3	91.9	EcoRV	rs1137070	Huang et al. [2009]	122	111			0.017				2	
MAOA	MAOA	Xp11.3	91.9	high-activity long alleles of promoter	N.A.	Lin et al. [2009a]	253	411			0.039	1.51 (1.07– 2.12)				

(*Continued*)

TABLE I. (*Continued*)

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
MAOA	MAOA	Xp11.3	91.9	uVNTR	NA	Rivera et al. [2009]	243	980			0.0014	1.91 (1.26–2.91)				
MC1R	MC1R	16q24.3	3.1	R163q	rs885479	Wu et al. [2011]	181	185			0.04				1	
MYO3A	MYO3A	10p11.1	278.5		rs10828902	Unschuld et al. [2009]	541	541			0.029					0
MYT1L	MYT1L	2p25.3	542.2		rs1617213-rs6759709	Wang et al. [2010]	1139	1140					0.0007			1
MYT1L	MYT1L	2p25.3	542.2		rs3748988	Wang et al. [2010]	1139	1140	0.024		0.005					1
MYT1L	MYT1L	2p25.3	542.2		rs3748989	Wang et al. [2010]	1139	1140	0.0008		0.0034					1
MYT1L	MYT1L	2p25.3	542.2		rs7592630	Wang et al. [2010]	1139	1140			0.0369					0
NBEA	NBEA	13q13	730.5		rs4941807	Gratacos et al. [2009]	422	615	0.019	0.78 (0.65–0.93)						0
NEUROD1	NEUROD1	2q32	4.6		rs1801262	Gratacos et al. [2009]	422	615	0.0093	1.49 (1.14–1.94)						0
p75NTR	NGFR	17q21-q22	19.7	Ser205Leu	rs2072446	Fujii et al. [2011]	668	1130	0.037	0.78 (0.61–0.99)	0.021	0.74 (0.58–0.96)				
NOS2A	NOS2	17q11.2-q12	43.8		rs2297518-rs8072199-rs2779248	Schosser et al. [2011]	2170[e]	1810	0.001				0.017			1
NOS2A	NOS2	17q11.2-q12	43.8		rs2770248	Schosser et al. [2011]	2170	1810	0.001		0.006					1
NOS2A	NOS2	17q11.2-q12	43.8		rs3794764	Schosser et al. [2011]	2170	1810	0.007		0.022					0
NPAS2	NPAS2	2q11.2	176.7		rs11123857	Soria et al. [2010b]	335	440	2×10^{-4}		7.4×10^{-4}	1.51 (1.19–1.92)				0
NPAS2	NPAS2	2q11.2	176.7		rs11541353	Soria et al. [2010b]	335	440	0.009		0.028	1.35 (1.03–1.76)				0
NPAS2	NPAS2	2q11.2	176.7		rs13025524	Soria et al. [2010b]	335	440	0.017		0.004	0.52 (0.33–0.83)				0
NPAS2	NPAS2	2q11.2	176.7		rs13394520	Soria et al. [2010b]	335	440			0.036	1.59 (1.03–2.44)				0
NPAS2	NPAS2	2q11.2	176.7		rs17025005	Soria et al. [2010b]	335	440	0.092		0.039	0.72 (0.53–0.98)				0
NPAS2	NPAS2	2q11.2	176.7		rs17662394	Soria et al. [2010b]	335	440	0.014		0.022	1.43 (1.05–1.95)				0
NPAS2	NPAS2	2q11.2	176.7		rs2117713	Soria et al. [2010b]	335	440	0.01		0.006	1.51 (1.13–2.01)				0
NPAS2	NPAS2	2q11.2	176.7		rs3754674	Soria et al. [2010b]	335	440			0.016	0.62 (0.41–0.92)				0
NPR3	NPR3	5p14-p13	81.1		rs976576	Gratacos et al. [2009]	422	615	0.0248	1.30 (1.07–1.59)						0
NPY	NPY	7p15.1	7.7		haplotype	combinations of rs3037354, rs17149106, rs16147, rs16139,rs5573, rs5574		Mickey	et al.	[2011]	39	113			0.04	
NR1D1	NR1D1	17q11.2	7.9		rs2071427	Soria et al. [2010b]	335	440			0.039	1.80 (1.03–3.16)				0
NR3C1	NR3C1	5q31.3	157.6		rs10052957	Zobel et al. [2008]	322	298	0.0052	0.71	0.02					1
NR3C1	NR3C1	5q31.3	157.6		rs1866388	Zobel et al. [2008]	322	298	0.0042	0.71	0.017					1
NR3C1	NR3C1	5q31.3	157.6		rs2918419	Zobel et al. [2008]	322	298	0.025		0.028					0
NR3C1	NR3C1	5q31.3	157.6		rs33388	Szczepankiewicz et al. [2011]	193	732	0.018	0.76 (0.61–0.95)						
NR3C1	NR3C1	5q31.3	157.6	BclI	rs41423247	Zobel et al. [2008]	322	298	0.012		0.021					0

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TABLE I. (*Continued*)

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
NR3C1	NR3C1	5q31.3	157.6		rs6191	Szczepankiewicz et al. [2011]	193	732	0.015	1.34 (1.06–1.69)	0.049					
NR3C1	NR3C1	5q31.3	157.6		rs6198	Szczepankiewicz et al. [2011]	193	732		0.95	0.018					
NR3C1	NR3C1	5q31.3	157.6		rs6198-rs6191-rs6196-rs258813-rs33388	Szczepankiewicz et al. [2011]	193	732					0.038			0
NR3C1	NR3C1	5q31.3	157.6		rs852977	Wong et al. [2008]	278	281	0.007	1.61 (1.13–2.27)						1
NR3C1	NR3C1	5q31.3	157.6		rs860458	Zobel et al. [2008]	322	298	0.011		0.014					0
NT5E	NT5E	6q14-q21	46.2		rs6942065	Gass et al. [2010]	109	554	0.0185	1.67 (1.10–2.53)					2	0
NT5E	NT5E	6q14-q21	46.2		rs9450282	Gass et al. [2010]	109	554	0.0404	0.72 (0.53–0.98)					2	0
NTRK2	NTRK2	9q22.1	355.0		rs2013566	Dong et al. [2009]	272	264	0.04	1.47 (1.02–2.10)					1	
NTRK2	NTRK2	9q22.1	355.0		rs7020204	Dong et al. [2009]	272	264	0.02	1.57 (1.07–2.32)	0.05				1	
NTRK2	NTRK2	9q22.1	355.0		rs1187323	Lin et al. [2009b]	155	195	0.0042		0.002					1
NTRK2	NTRK2	9q22.1	355.0		rs1187323-rs1187329	Lin et al. [2009b]	155	195	0.0042				0.003			1
NTRK2	NTRK2	9q22.1	355.0		rs1187329	Lin et al. [2009b]	155	195	0.0089		0.0223					0
NTRK2	NTRK2	9q22.1	355.0		rs1545285	Lin et al. [2009b]	155	195	0.0343							0
NTRK2	NTRK2	9q22.1	355.0		rs1778929	Lin et al. [2009b]	155	195	0.0102		0.0014					1
OXTR	OXTR	3p25	19.2	9073G>A	rs2254298	Costa et al. [2009]	93	192			0.04	0.55 (0.31–0.98)				
OXTR	OXTR	3p25	19.2	6930G>A	rs53576	Costa et al. [2009]	93	192			0.02	0.56 (0.34–0.93)				
P2RX7	P2RX7	12q24	53.7		rs208294	Soronen et al. [2011]	272	1322	0.007	1.29						
P2RX7	P2RX7	12q24	53.7		rs2230912	Soronen et al. [2011]	272	1322	0.0217	1.34						
P2RX7	P2RX7	12q24	53.7		rs591874	Soronen et al. [2011]	272	1322	0.0053							
PAWR	PAWR	12q21	99.0		rs7305141-	rs2307223[f]-	Liou		et al.	[2011]	602	543				
0.043																
PAWR	PAWR	12q21	99.0		rs8176874	Liou et al. [2011]	602	543	0.0015		0.005	1.70 (1.21–2.39)				1
PCLO	PCLO	7q11.23-q21.3	408.9		rs2522833	Hek et al. [2010]	178	912	0.0025	1.42 (1.13–1.79)						
PCNT	PCNT	21q22.3	121.6		rs2073376	Numata et al. [2009a]	173	348	0.005							1
PCNT	PCNT	21q22.3	121.6		rs2073380	Numata et al. [2009a]	173	348	0.021							0
PCNT	PCNT	21q22.3	121.6		rs3788265	Numata et al. [2009a]	173	348	0.006							1
PCNT	PCNT	21q22.3	121.6		rs3788265-rs2073376	Numata et al. [2009a]	173	348					0.015			1
PDE4B	PDE4B	1p31	582.1		rs1040716	Numata et al. [2009b]	174	348	0.012		0.021					
PDE4B	PDE4B	1p31	582.1		rs2180335	Numata et al. [2009b]	174	348	0.009		0.029					
PDE4B	PDE4B	1p31	582.1		rs2180335-rs910694	Numata et al. [2009b]	174	348					0.017			

(*Continued*)

TABLE I. (*Continued*)

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
PDE4B	PDE4B	1p31	582.1		rs472952	Numata et al. [2009b]	174	348	0.002		0.007					
PDE4B	PDE4B	1p31	582.1		rs910694	Numata et al. [2009b]	174	348	0.004		0.013					
PDLIM5	PDLIM5	4q22	216.4		rs2433320	Liu et al. [2008]	181	186	0.007	1.75 (1.17–2.60)	0.007					
PDYN	PDYN	20p13	15.5		rs6136667	Gratacos et al. [2009]	422	615	0.026	0.21 (0.05–0.93)						0
PER2	PER2	2q37.3	44.5		rs2304673	Soria et al. [2010b]	335	440			0.049	1.39 (1.00–1.94)				0
PER3	PER3	1p36.23	60.5		rs11121029	Soria et al. [2010b]	335	440			0.047	0.43 (0.18–1.04)				0
PLD1	PLD1	3q26	210.1	hcv15882560	rs2124147	Gratacos et al. [2009]	422	615	0.0403	1.25 (1.04–1.50)						0
POMC	POMC	2p23.3	7.8		rs2118404	Wong et al. [2008]	278	281	0.02	1.35 (1.06–1.73)						1
PPARGC1A	PPARGC1A	4p15.1	98.1		rs768695	Schosser et al. [2011]	2170	1810	0.033		0.018					1
PPARGC1A	PPARGC1A	4p15.1	98.1		rs768695-rs3755863	Schosser et al. [2011]	2170	1810	0.033				0.024			1
PROKR2	PROKR2	20p12.3	12.3	G>A	rs17721321-rs6085086-rs3746684-rs3746682-rs4815787	Kishi et al. [2009a]	319	340					0.00069			
PROKR2	PROKR2	20p12.3	12.3	G>A	rs4815787	Kishi et al. [2009a]	319	340	0.00068		0.0042					1
PSMB4	PSMB4	1q21	2.4	T/C	rs2296840	Wong et al. [2008]	278	281		1.65 (1.28, 2.12)	0.007					1
PSMB4	PSMB4	1q21	2.4		rs4603	Wong et al. [2008]	278	281	0.01	1.38 (1.07–1.78)						1
p11	S100A10	1q21	11.3		rs4845720	Verma et al. [2007]	176	176	0.03						1	
SERPINE1	SERPINE1	7q22.1	12.2		rs2227631-rs1799889	Tsai et al. [2008]	188	346					0.035			0
SERPINE1	SERPINE1	7q22.1	12.2		rs2227684	Tsai et al. [2008]	188	346	0.01		0.019	2.06 (1.21–3.49)				
SERPINE1	SERPINE1	7q22.1	12.2		rs6090-rs2227684-rs7242	Tsai et al. [2008]	188	346					0.0011			
SERPINE1	SERPINE1	7q22.1	12.2		rs7242	Tsai et al. [2008]	188	346	0.01		0.017	2.07 (1.21–3.49)				
SIGMAR1	SIGMAR1	9p13.3	3.0		rs1800866	Kishi et al. [2010b]	466	516			0.0202	0.56 (0.35–0.91)				
SIRT1	SIRT1	10q21.3	33.7	T>C	rs10997875	Kishi et al. [2010a]	450	766	0.00038		0.0004					1
SLC28A1	SLC28A1	15q25.3	61.1		rs11853372	Gass et al. [2010]	125	483	0.013	1.42 (1.07–1.88)					2	0
SLC28A1	SLC28A1	15q25.3	61.1		rs12910991	Gass et al. [2010]	125	483	0.0465	1.34 (1.01–1.79)					2	0
SLC28A1	SLC28A1	15q25.3	61.1		rs4271567	Gass et al. [2010]	61	483	0.0441	0.62 (0.41–0.96)					2	0
SLC28A1	SLC28A1	15q25.3	61.1		rs4980345	Gass et al. [2010]	103	409	0.0468	0.35 (0.12–0.99)					2	0
SLC28A1	SLC28A1	15q25.3	61.1		rs7182385	Gass et al. [2010]	61	483	0.016	1.61 (1.10–2.35)					2	0
SLC29A1	SLC29A1	6p21.1	14.6		rs324148	Gass et al. [2010]	109	554	0.04	0.66 (0.44–0.98)					2	0
SLC29A1	SLC29A1	6p21.1	14.6		rs6905285	Gass et al. [2010]	258	557	0.0117	1.31 (1.06–1.62)					2	0

(*Continued*)

TABLE I. (*Continued*)

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
SLC29A1	SLC29A1	6p21.1	14.6		rs693955	Gass et al. [2010]	109	554	0.0167	0.47 (0.26–0.87)					2	0
SLC29A2	SLC29A2	11q13	9.3		rs2279861	Gass et al. [2010]	103	409	0.0323	0.66 (0.46–0.95)					2	0
SLC29A2	SLC29A2	11q13	9.3		rs4244813	Gass et al. [2010]	125	483	0.0293	0.69 (0.49–0.96)					2	0
SLC29A3	SLC29A3	10q22.1	44.1		rs10999776	Gass et al. [2010]	109	554	0.034	0.71 (0.52–0.97)					2	0
SLC29A3	SLC29A3	10q22.1	44.1		rs12256138	Gass et al. [2010]	258	557	0.0004	0.68 (0.55–0.84)					2	1
SLC29A3	SLC29A3	10q22.1	44.1		rs12767108	Gass et al. [2010]	258	557	0.0405	1.46 (1.02–2.07)					1	0
SLC29A3	SLC29A3	10q22.1	44.1		rs2066210	Gass et al. [2010]	194	449	0.0301	0.62 (0.41–0.94)					1	0
SLC29A3	SLC29A3	10q22.1	44.1		rs2487067	Gass et al. [2010]	258	557	0.0212	1.29 (1.04–1.60)					1	0
SLC29A3	SLC29A3	10q22.1	44.1		rs780659	Gass et al. [2010]	258	557	0.0327	1.25 (1.01–1.54)					1	0
SLC29A3	SLC29A3	10q22.1	44.1		rs780662	Gass et al. [2010]	258	557	0.0109	1.52 (1.10–2.08)					1	0
SLC29A3	SLC29A3	10q22.1	44.1		rs12256138-rs780659	Gass et al. [2010]	258	557					0.0006	0.68		
SLC29A3	SLC29A3	10q22.1	44.1		rs12256138-rs780659-rs780662	Gass et al. [2010]	258	557					0.0006	0.69		
SLC29A3 0.0005	SLC29A3 1.47	10q22.1	44.1		rs2066210-	rs12256138	Gass		et al.	[2010]	258	557				
SLC29A3	SLC29A3	10q22.1	44.1		rs780659-rs780662	Gass et al. [2010]	258	557					0.0003	0.67		
SLC6A2	SLC6A2	16q12.2	50.6	F528C	rs5558	Haenisch et al. [2009]	426	643			0.017	4.6 (1.2–17.1)				1
SLC6A2	SLC6A2	16q12.2	50.6	T-182C	rs2242446	Sun et al. [2008]	388	388	0.011	1.33 (1.07–1.65)	0.034					1
SLC6A3	SLC6A3	5p15.3	52.6		rs2550936	Dong et al. [2009]	272	264			0.004				1	
SLC6A3	SLC6A3	5p15.3	52.6		rs8179029	Dong et al. [2009]	272	264	0.02	1.71 (1.12–2.58)	0.02				1	
SLC6A4	SLC6A4	17q11.2	39.6		rs140701	Dong et al. [2009]	272	264	0.09	1.25 (0.97–1.61)	0.01				1	
SLC6A4	SLC6A4	17q11.2	39.6		rs2066713	Dong et al. [2009]	272	264	0.03	1.37 (1.04–1.80)	0.004				1	
SLC6A4	SLC6A4	17q11.2	39.6		rs28914831	Dong et al. [2009]	272	264	0.02	8.37 (1.20–∞)	0.01				1	
SLC6A4	SLC6A4	17q11.2	39.6		rs3813034	Dong et al. [2009]	272	264	0.08	1.25 (0.98–1.60)	0.04				1	
SLC6A4	SLC6A4	17q11.2	39.6		rs56355214	Dong et al. [2009]	272	264	0.01	8.47 (1.22–∞)	0.01				1	
SLC6A4	SLC6A4	17q11.2	39.6		rs6354	Wray et al. [2009]	880	1045	<0.05	1.17 (1.01–1.26)					1	
SLC6A4	SLC6A4	17q11.2	39.6		rs7212502	Dong et al. [2009]	272	264	0.01	8.56 (1.23–∞)	0.01				1	
SLC6A4	SLC6A4	17q11.2	39.6		rs7224199	Dong et al. [2009]	272	264			0.004				1	
SLC6A4	SLC6A4	17q11.2	39.6	NT_010799.14_3288789	N.A.	Dong et al. [2009]	272	264	0.01	8.63 (1.24–∞)	0.01				1	
SLC6A4	SLC6A4	17q11.2	39.6	5-HTTLPR+Stin 2 VNTR	5-HTTLPR / + rs57098334	Gelabert et al. [2012]	122	115					0.049	3.81 (1–14.48)		
SLC6A4	SLC6A4	17q11.2	39.6	5-HTTLPR+rs25531	5-HTTLPR+rs25531	Bonvicini et al. [2010]	310	284					0.01	0.64 (0.45–0.91)		

(*Continued*)

TABLE I. (*Continued*)

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
SLC6A4	SLC6A4	17q11.2	39.6	5HTTLPR	NA	Soronen et al. [2011]	272	1322	0.0006	1.39						
SLC6A4	SLC6A4	17q11.2	39.6	5-HTTLPR(L/S)	NA	Bonvicini et al. [2010]	310	284	0.04		0.1	/				
SLC6A4	SLC6A4	17q11.2	39.6	STin 2	NA	Sarosi et al. [2008]	71	99			<0.05					
SLC6A4	SLC6A4	17q11.2	39.6	5-HTTLPR	NA	Frodl et al. [2008]	77	77	0.001		0.002					
SLC6A4	SLC6A4	17q11.2	39.6	vntr2i	NA	Soronen et al. [2011]	272	1322	0.0017							
SLC6A4	SLC6A4	17q11.2	39.6		rs3794808	Soronen et al. [2011]	272	1322	0.0046							
TBX21	TBX21	17q21.32	12.9		rs17244587	Wong et al. [2008]	278	281		1.97 (1.41–2.74)	0.007					1
TBX21	TBX21	17q21.32	12.9		rs2325717	Wong et al. [2008]	278	281	0.0004	1.84 (1.31–2.56)						1
TBX21	TBX21	17q21.32	12.9		rs41515744	Wong et al. [2008]	278	281	0.0004	1.80 (1.30–2.50)						1
TNF-a	TNF	6p21.3	2.8	-308G/A	rs1800629	Cerri et al. [2010]	50	240	0.05		0.007	2.43 (1.09–5.43)				
TPH1	TPH1	11p15.3-p14	20.3	218A/C	rs1800532	Viikki et al. [2010a]	217	395			0.008					
TPH1	TPH1	11p15.3-p14	20.3	218A/C	rs1800532	Wang et al. [2011]	115	105	0.025	0.507						
TPH2	TPH2	12q21.1	93.6		rs4290270-rs7305115	Shen et al. [2011]	278	189					0.001	1.65 (1.23–2.22)	1	1
TPH2	TPH2	12q21.1	93.6	-703G/T	rs4570625	Yoon and Kim [2009]	181	176	0.002		0.009	1.97 (1.21–3.21)			1	
TPH2	TPH2	12q21.1	93.6		rs7305115	Shen et al. [2011]	90	182			0.047				1	0
TPH2	TPH2	12q21.1	93.6		rs1007023	Kloiber et al. [2010]	300	300			0.0359					0
TPH2	TPH2	12q21.1	93.6		rs1386492	Kloiber et al. [2010]	300	300			0.0134					0
TPH2	TPH2	12q21.1	93.6		rs1386494	Kloiber et al. [2010]	300	300			0.0359					0
TPH2	TPH2	12q21.1	93.6	-G	rs17110747	Tsai et al. [2009]	508	463	0.001		0.002	1.75				
TPH2	TPH2	12q21.1	93.6		rs1843809	Kloiber et al. [2010]	300	300			0.0365					0
TPH2	TPH2	12q21.1	93.6		rs2171363	Kloiber et al. [2010]	300	300			0.0489					0
TPH2	TPH2	12q21.1	93.6		rs6582078	Kloiber et al. [2010]	300	300			0.0224					0
TPH2	TPH2	12q21.1	93.6		rs7300641	Kloiber et al. [2010]	300	300			0.0216					0
TPH2	TPH2	12q21.1	93.6		rs7305115	Kloiber et al. [2010]	300	300			0.0436					0
TSNAX	TSNAX	1q42.1	37.9		rs1630250-rs766288-rs6662926	Okuda et al. [2010]	159	459	0.0059				0.0481		1	1
TSNAX	TSNAX	1q42.1	37.9		rs766288	Okuda et al. [2010]	159	459	0.0059		0.0066				1	1
USP46	USP46	4q12	68.4		rs12646800-rs2244291-1	Fukuo et al. [2011]	432	792								
		9.9×10^{-5}														
USP46	USP46	4q12	68.4		rs2244291-1	rs10034164-rs346005 Fukuo et al. [2011]	432	792								
		2.2×10^{-5}														
VEGF	VEGFA	6p12	16.3	-2578C/A	rs699947	Viikki et al. [2010b]	119	391				0.014			1	
VIPR2	VIPR2	7q36.3	116.8		rs12670064	Soria et al. [2010b]	335	440			0.044	0.73 (0.53–0.99)				0
VIPR2	VIPR2	7q36.3	116.8		rs2540352	Soria et al. [2010b]	335	440	0.035		0.023	0.67 (0.48–0.95)				0

(*Continued*)

TABLE I. (*Continued*)

Gene name	Official name	Chromosome position	Gene size (kb)	Variant	rs-id	Author info	N case	N control	p allele	OR allele	p geno	OR geno	p-multi-marker	OR multi-marker	Study type	Correction
VIPR2	VIPR2	7q36.3	116.8		rs885861	Soria et al. [2010b]	335	440	0.009		0.004	1.71 (1.18–2.46)				0
Intergenic[g]					rs1890866	Koido et al. [2010]	312	356	0.05		0.05					0

Gene name, the name of investigated gene from the study; official name, the official HUGO name of the gene; author info, the reference of the study; P-allele/P-geno/P-multi-marker, raw *P*-values of allelic/genotypic/haplotype frequency; OR-allele/OR-geno/OR-multimarker, raw odds ratios of investigated allele/genotype/haplotype; study type indicates special types of study: 1 indicates a fine-mapping study, 2 indicates that results come from a subgroup analysis; correction, 1 (or 0) indicates that the study applied a multiple testing correction and that the result remained significant (or not significant); the absence of a number (either 0 or 1) indicates no report of multiple testing correction.

[a]N.A. indicates that there was no rs-id in the paper and it could not be determined from other resources.

[b]The sample sizes of cases and controls [i.e., sample sizes for a subgroup analysis] could not be found from the paper and the authors did not respond to email requests.

[c]The sample size of cases was not given directly but relevant information could be used to calculate sample size.

[d]This SNP has been merged with rs351138.

[e]We extracted the results from a combined sample in this study.

[f]This SNP has been merged to rs78187003.

[g]This is an intergenic SNP.

data. For complete results see SI, Appendix E; see also Appendix G for current re-analysis of SNPs identified in the Bosker et al. [2011].

In the full sample, 13 SNPs in 12 genes showed significant associations with MDD (Table II). Associations of three SNPs were in the opposite direction than in the original studies. In addition, the direction for one SNP could not be determined from the original study. Hence, we replicated nine candidate SNPs in eight genes (*PSMB4*, *ADK*, *POMC*, *HTR1A*, *PCLO*, *CDC42SE2*, *SIRT1*, *SLC29A3*) in the full sample. In the subsample, seven SNPs in six genes were significantly associated with severe and chronic MDD. The direction of effects for one SNP in the chronic sample was inconsistent with the literature. Therefore, we replicated six SNPs in five genes (*PSMB4*, *ADK*, *POMC*, *HTR1A*, *PDE4B*) in the subsample. Four SNPs (rs2296840 in *PSMB4*, rs7924176 in *ADK*, rs1800044 in *HTR1A*, and rs2118404 in *POMC*) overlapped for the full sample and the subsample. The two-marker haplotype that tagged the 5HTTLPR polymorphism showed no association with either MDD in the full sample or chronic and severe MDD.

We next examined if the number of replicated candidate SNPs was higher than expected by chance (i.e., at $\alpha = 5\%$ for the full sample and $\alpha = 2.5\%$ for the chronic sample). According to the binomial distribution, neither the number of SNPs replicated in the full sample [9/179; $P = 0.41$] nor the number in the chronic subsample [6/179; $P = 0.16$] was more than expected by chance (The total number of SNPs tested was 185-6 = 179, because the direction of effect for six SNPs could not be retrieved from the literature).

Comparing Replications of Candidate SNPs in the Full Sample With Replications in the Chronic Subsample

We compared the effects of all 185 SNPs in the full sample with their effects in the chronic sub-dataset by plotting the odds ratios of SNPs in both samples (Fig. 2). Overall, the effects in the chronic subsample were larger than those in the full sample (slope >1). In addition, we also applied a binomial sign test to compare the overall effects of SNPs in the full sample versus the overall effects in the subsample. This test can be used to determine if the number of SNPs with a larger effect in the subsample was significantly higher than the number of SNPs with a larger effect in the full sample. For 111 of the 185 SNPs, the effect sizes were larger in the subsample, whereas for 57 SNPs the effect sizes were larger in the full sample. For the remaining 17 SNPs, the directions of the effects were inconsistent between the full sample and the subsample (effects of five SNPs in the full sample were consistent with the literature, whereas effects of six SNPs in the chronic sample were consistent with the literature), or could not retrieved from the literature (for six SNPs). Therefore, in total, for 117 (111 + 6) SNPs, the effect sizes were larger in the subsample than in the full sample, whereas for 62 (57 + 5) SNPs the effect sizes were larger in the full sample. The result of the binomial sign test indicated that, under the null hypothesis of no differences between the two samples, the probability that 117 SNPs out of 179 SNPs had a larger effect in the expected direction in the subsample than in the full sample is associated with a *P*-value <0.00005 (one sided). Thus, effect sizes

TABLE II. Candidate SNPs That are Significantly Associated With MDD and With Chronic MDD[a]

Gene	SNP (rs-id)	Coding allele	P_all[b]	OR_all	95%CI	P_severe	OR_severe	95%CI
PSMB4	rs2296840	T	0.044*	2.64	(0.89–7.81)	1.80E-07*	7.20	(2.00–25.88)
ADK	rs7924176	G	0.016*	0.89	(0.80–0.98)	0.0061*	0.77	(0.63–0.94)
POMC	rs2118404	T	0.012*	1.17	(1.03–1.32)	0.013*	1.32	(1.06–1.66)
HTR1A	rs1800044	A	0.018*	2.41	(1.09–5.34)	0.022*	3.33	(1.05–10.68)
PCLO	rs2522833	C	8.19E-05*	1.24	(1.12–1.37)	0.32	1.11	(0.91–1.35)
EMP1**	rs7315725	A	0.00023*	0.80	(0.71–0.90)	0.25	0.88	(0.70–1.10)
CDC42SE2	rs798412	A	0.0079*	1.18	(1.04–1.34)	0.30	1.13	(0.89–1.44)
CDC42SE2	rs798416	C	0.0079*	1.18	(1.04–1.34)	0.30	1.13	(0.89–1.44)
SIRT1	rs10997875	C	0.026*	0.88	(0.79–0.98)	0.60	0.95	(0.77–1.16)
NR1D1***	rs2071427	T	0.034*	1.11	(0.99–1.24)[c]	0.14	1.14	(0.92–1.42)
CRHBP**	rs1053989	A	0.039*	1.08	(0.98–1.20)	0.53	1.05	(0.86–1.28)
SLC29A3	rs2487067	A	0.043*	0.90	(0.81–1.00)	0.99	1.00	(0.82–1.22)
FKBP5**	rs1360780	C	0.045*	1.11	(0.99–1.24)	0.58	1.06	(0.85–1.31)
MYT1L**	rs7592630	G	0.24	1.07	(0.96–1.19)	0.010*	1.30	(1.06–1.59)
PDE4B	rs1040716	T	0.39	1.04	(0.94–1.16)	0.012*	1.28	(1.05–1.56)
PDE4B	rs472952	G	0.15	1.08	(0.97–1.19)	0.016*	1.29	(1.05–1.58)

[a]This table shows results for SNPs that are from the current literature search and are significantly associated with MDD or with chronic MDD in our replication.
[b]*P*all and *P*severe: *P*-values of the MDD association in the full sample and in the chronic and severe subsample comparing allele frequencies under an additive model. OR_all and OR_severe: odds ratios of alleles for MDD and for severe and chronic MDD, respectively based on expected genotype frequencies (i.e., the sum of genotype probabilities).
[c]Some confidence intervals of odds ratios of significantly associated SNPs contain 1, because of differences of model used for calculating *P*-values (additive model, i.e., using genotype frequencies) and odds ratios (allele B versus allele A using allele frequencies).
*Indicates $P < 0.05$ for the full sample, or $P < 0.025$ for the chronic subset.
**Indicates that the directions of effects for these SNPs were not consistent with directions reported in the literature.
***Indicates that the direction of effects for this SNP could not be determined from the original literature.

for candidate SNPs were generally larger in the chronic subsample than in the full sample.

Replication of Candidate Genes Reported in the Literature at Gene-Wide Level

In the full sample, 50 SNPs or in/dels in eight genes were significant from a total of 86,421 SNPs in 127 genes (89 from the current study, 38 genes from Bosker et al. [2011]) when corrected at gene-wide level. Forty three SNPs or in/dels were located in the *PCLO* gene (all in high LD) and the remaining seven SNPs or in/dels were from seven other genes, i.e., *ARNTL*, *CREB1*, *HTR2C*, *NR1D1*, *PDE2A*, *SLC6A2*, and *TSNAX* (results summarized in Table III; details see SI, Appendix F, Table S6). Thirteen genes had significantly higher numbers of significant SNPs or in/dels than expected by chance (SI, Table S7). Thus, 18 genes in total were significantly associated with MDD at gene level using these two approaches (three genes overlapped). The replication rate for the full sample was 14% (18/127). Note that when we corrected for all SNPs or in/dels in all genes that were tested, none of the 50 SNPs significant at gene-wide level remained significant.

In the chronic MDD subsample, 13 SNPs or in/dels in 11 genes were significant at gene-wide level. Two SNPs were located in *PSMB4* (in high LD), two in *POMC* (also in high LD), whereas the remaining nine SNPs came from nine genes, i.e., *ARNTL2*, *AVPR1B*, *BCR*, *COMT*, *CTLA4*, *KCNK2*, *MAOA*, *PDE5A*, and *PLD1* (results summarized in Table III; details see SI, Table S8). Seven genes, *POMC*, *MYT1L*, *PDE11A*, *MTHFR*, *PDE4B*, *MY03A*, and *ADK*, had significantly higher numbers of significant SNPs than expected by chance in the chronic and severe MDD subsample (SI, Table S9). Thus, 17 genes in total were significantly associated with chronic and severe MDD (one gene overlapped) resulting in a replication rate of 13% (17/127). None of the 13 SNPs significant at gene-wide level were significant after correction for multiple testing for all SNPs and in/dels in all genes.

We examined if the number of replicated genes was higher than expected by chance. As we replicated genes using two tests at gene-based level, a gene can be significant by chance at $\alpha = 0.05$ with a probability of $0.05 + 0.95 \times 0.05 = 0.0975$ ($0.025 + 0.975 \times 0.025 = 0.0494$ for the chronic subsample), which means that we expect almost 10% of genes in the full sample (about 5% in the subsample) to be significant for either gene-based test by chance. According to the binomial distribution, the number of genes replicated were significantly more than expected both in the full sample ($P = 0.04$) and in the chronic subsample ($P < 0.0001$).

Comparing Our Replication Results With the Previous Replication Study

We compared replication rates in our full sample with those reported by Bosker et al. to explore whether replication rates have increased in our study from last large replication study (detailed analyses comparing the two studies see SI, Appendix G). We could do so also because our study extended the Bosker et al. [2011] based on a similar sample and included their set of genes at gene level analyses, yet used a different reference for imputation (i.e., 1,000 Genomes rather than HapMap CEU data). In brief, the replication rates were higher in our study, especially for genes examined only in our study (i.e., genes

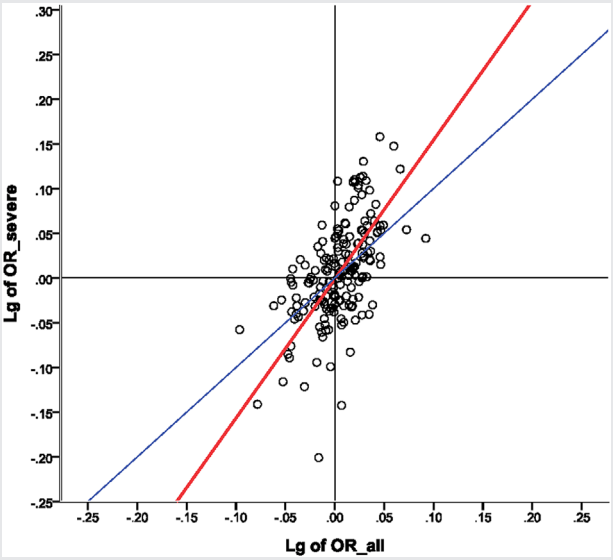

FIG. 2. Relationships between the effects of SNPs in general MDD and chronic MDD. #Note: Figure 2 described the relationships between the odds ratios (ORs) of SNPs in the full sample and the ORs of the same SNPs in the subsample for chronic MDD. The X-axis is the Log transformation of ORs of each SNP in the full sample, the Y-axis is the Log transformation of ORs of each SNP in the chronic, severe subsample. To visualize the effects we applied log transformation of the odds ratios, we plotted the ORs for the 185 SNPs that were reported having associations with MDD in the literature. Some extreme ORs were not shown in this graph (i.e., OR >2). The blue line is a reference line with slope = 1, indicating the same effects in the full sample and in the chronic subsample; the red line is the best-fitting line based on the data (slope = 1.55); This suggests that the effects of SNPs in the chronic subsample were larger than those in the full sample. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].

originally reported after 2007). Specifically, the replication rate at gene level was 4% (2/55) in the previous Bosker et al. study, whereas in the present study it was 8% (3/38) for genes that were only reported in the previous study, 6% (1/17) for genes that were reported in both studies (combined 7% ((3 + 1)/(38 + 17) = 4/55) for all genes studied by Bosker et al. [2011]), and 19% (14/72) for genes that were examined only in our study.

DISCUSSION

The present study provided a comprehensive review on candidate genes for MDD reported from 2007 to 2012, and replicated identified candidate SNPs and genes for DSM-IV defined MDD as well as for chronic and severe MDD. At candidate SNP level, the numbers of original SNPs successfully replicated in both samples were not more than expected. However, the overall effects of all original SNPs were larger with chronic and severe MDD than with the broad MDD phenotype. At candidate gene level, we replicated significant associations for 18 genes for DSM-IV defined MDD and 17 genes for chronic and severe MDD (four overlapped), both of which were significantly more than expected by chance. The replication rate with DSM-IV defined MDD at gene-wide level was also higher in the present study (14%) than in the previous replication study (4%, Bosker et al., 2011).

At least three reasons may account for these higher replication rates in our sample than in the previous Bosker et al. study. First, we improved diagnostic accuracy, in particular that by using longitudinal diagnostic data we were able to identify and remove those who developed a bipolar disorder. Second, we used an improved imputation procedure so that more SNPs were imputed and examined within a gene. Third, we included recent studies since 2007 which in general were better conducted compared to all genetic studies on MDD published before 2007 (e.g., improved phenotyping of MDD; larger samples). Importantly, our post hoc analysis suggested that the last reason contributed substantially (a replication rate of 19% for genes identified only in our current literature search compared to 7% for genes already retrieved in the Bosker et al. study), while improved imputation and/or sample selection contributed as well (for genes selected in the previous study, the replication rate in our study was currently 7% compared to 4% before). It follows that while the methodology of the replication study (e.g., homogeneous sample, imputation) matters to the success of replication rates, the most crucial factor remains that the original results come from high quality studies (e.g., large sample sizes, good phenotyping) in general.

The present study also showed that refining the broad MDD phenotype into chronic and severe MDD improved replication rates. Our study is, to our knowledge, the first genetic study that used longitudinal measures of depressive symptoms to identify a more narrowly defined and therefore, less heterogeneous MDD phenotype. At candidate SNP level, effect sizes were overall larger in this chronic subsample than in the full sample. In addition to the larger effect sizes at candidate SNP level in the chronic subsample, at gene level, the replication rates in this subsample was almost the same as in the full sample (13% vs. 14%), despite the stricter significance level and the much smaller sample size. Due to the stricter significance level, the replication rate in the subsample was much more significant ($P < 0.0001$) than that in the full sample ($P = 0.04$). With the larger effect sizes and reduced statistical power in mind, our approach of reducing the heterogeneity by a refined phenotype seems promising in enhancing the replication rate.

Nevertheless, even though the replication rate was improved, 28% (35/127, the total number of genes significant in any test divided by the total number of genes tested) is still a small part of the candidate genes reported in the literature. Poor replication is common in the genetic literature of MDD [Cohen-Woods et al., 2013], likely due to, first and foremost, false-positives. Although genetic studies seemed to have improved their methodology in some aspects as we mentioned above, the issues of false-positives seem still prevalent. Specifically, studies did not consistently correct for multiple testing (correction for multiple testing was reported for 56% of the results in our literature review: 19% of results remained significant whereas 37% were no longer significant after corrections; 44% of the results were not corrected). False-positives also increase in the absence of strong a priori hypotheses on how candidate genes relate to MDD. Retrieved papers often

TABLE III. Candidate Genes Replicated at Gene Level[a]

Type of test	Genes replicated in the full sample	*P* value at gene level in the full sample	Genes replicated in the subsample	*P* value at gene level in the subsample
Gene-wide test[b]				
	ARNTL	0.039	ARNTL2	0.012
	CREB1	0.0057	AVPR1B[c]	0.041
	HTR2C[c]	0.014	BCR[c]	0.033
	NR1D1	0.049	COMT	0.0021
	PCLO	0.0053	CTLA4	0.020
	PDE2A[c]	0.0072	KCNK2	0.039
	SLC6A2	0.037	MAOA	0.028
	TSNAX	0.035	PDE5A[c]	0.027
	–	–	PLD1	0.020
	–	–	POMC	0.046
	–	–	PSMB4	0.010
Significant numbers of nominal significant SNPs within a gene[d]				
	CDC42SE2	0.020	ADK	0.033
	CHRFAM7A[c]	0.015	MTHFR[c]	0.015
	CNR1[c]	0.014	MYO3A	0.023
	CREB1	0.022	MYT1L	0.0049
	DAOA	0.043	PDE11A[c]	0.0091
	HCRTR1	0.043	PDE4B	0.018
	NPR3	0.010	POMC	0.0019
	PCLO	0.0023	–	–
	POMC	0.037	–	–
	PROKR2	0.037	–	–
	SIRT1	0.046	–	–
	SLC6A2	0.032	–	–
	SLC29A3	0.042	–	–

[a]This table summarized *P* values at gene level for each candidate gene replicated through either of two methods: the gene-wide test and the test for the significant number of nominal significant SNPs. See SI Table S6–S9 for more detailed information of results.
[b]*P*-value for the gene-wide test is the *P*-value of the most significant SNP or in/del corrected at gene-wide level.
[c]These candidate genes were only identified from the literature search in the Bosker et al. study and were not identified in the new literature search after 2007. They were not listed in Table I, but the references for these genes can be found in the Bosker et al. study.
[d]*P*-value for the significant number of nominal significant SNPs within a gene was determined using permutation.

provide no or very weak hypotheses on presumed biological pathways [Tabor et al., 2002]. In addition, publication bias increases the false-positive associations in the literature. Indeed, effect sizes of candidate gene polymorphisms investigated previously were likely to be overestimated as is illustrated by their much smaller estimated effect sizes in the GWAS results [Lewis et al., 2010; Muglia et al., 2010; Rietschel et al., 2010; Shi et al., 2011]. Finally, ethnicity may influence replication rates. Here, we studied individuals of Western European ancestry, whereas some of the candidate genes were firstly investigated in other populations such as Mexican-Americans or Asians [e.g., Wong et al., 2008; Dong et al., 2009; Kishi et al., 2009b]. Some of these genetic effects may not be consistent across different populations and this may have added to the non-replication rate in our sample.

Our results should be interpreted with some caution due to several limitations present. First, our study was powered for detecting medium effects sizes (80% power for candidate SNPs with an allele frequency >10% (or >1%) and OR >1.23(1.76) in the full sample or OR >1.47(2.60) in the chronic and severe subsample). Some studies have suggested either relatively small effects for common candidate SNPs for MDD or reasonable effects for rare candidate SNPs [Cohen-Woods et al., 2013], which our subsample of chronic and severe MDD was not able to detect. Furthermore because of the moderate size of the chronic and severe sample, our estimates of the effect sizes are less stable and larger studies are needed to confirm these. Second, we were unable to examine 15 SNPs because they were neither present on the genotype chip nor imputed with the 1,000 Genomes database [1000 Genomes Project Consortium, 2010]. Third, in our analyses we excluded individuals of non-Caucasian ancestry to avoid bias in the results due to population stratification. However, more subtle genetic differences between Caucasian individuals from different geographic areas from the Netherlands may exist, but our result were not corrected for this by for instance including genetic principal components. As a consequence it could be that our results are still somewhat inflated. Lastly, we posited that no multiple testing correction is required for testing the associations of candidate SNPs with MDD because these were taken directly from the literature and therefore, our study is hypothesis driven. However, one could also argue that since the majority of these candidate SNPs may themselves be false positives, correction is still required. Exploring the implication of this view was revealing: at a

significance level of 0.05 for the broad MDD phenotype (0.025 for chronic and severe MDD), it is expected that nine ($\approx 179 \times 0.05$) for broad MDD, respectively five ($\approx 179 \times 0.025$) for chronic MDD, SNPs are significant by chance which correspond exactly to the numbers currently found. Nevertheless, at gene level, we applied permutation to correct for testing multiple SNPs or in/dels within a gene and still replicated significantly more genes than the number of genes that would be significant by chance in both the full sample and the chronic subsample. This finding suggests that the genes rather than the specific SNPs that were identified in prior research are of relevance. However, since MDD is likely a polygenic disease, the null hypothesis of no association with MDD of none of the selected genes is not realistic. It is plausible that for instance 10–15% of all genes in the genome are involved in MDD and in that regard the percentages of associated genes that we observe are not larger than would be found in any random set of genes. Furthermore, none of the genes survived multiple testing correction when correcting for all SNPs or in/dels in all genes tested. Therefore, the involvement of these genes in MDD remains debatable.

In conclusion, due to inclusion of candidate SNPs and genes from recent literature and a larger and better reference set for imputation, replication of associations with MDD improved compared to a previous similar replication study by Bosker et al. [2011], but was still poor overall. Refining the MDD phenotype to the chronic and severe MDD subtype increased the overall effect sizes of candidate SNPs and the replication rates of the candidate genes. This provides modest support for our hypothesis that reduction in phenotypic heterogeneity enhances the replication of genetic findings.

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