Genome-wide Association for Major Depression Through Age at Onset Stratification

Supplemental Information

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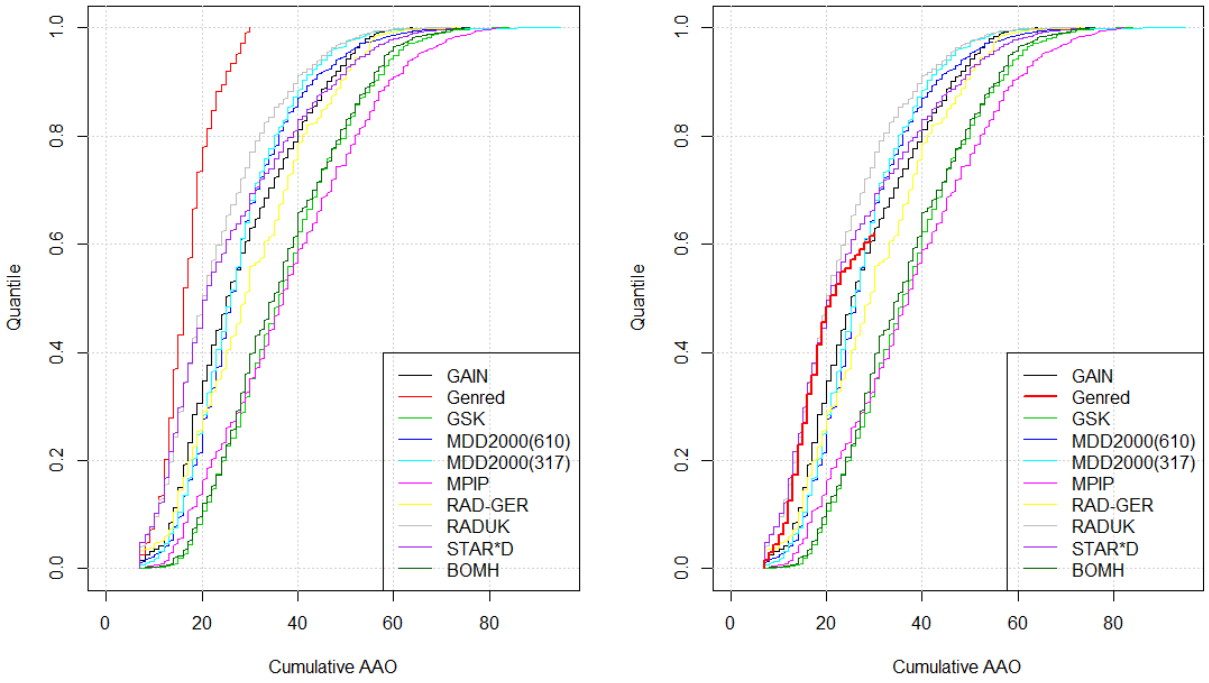

Figure S1. Cumulative distribution of AAO in discovery studies, showing how GenRED distribution (red line) was scaled due to ascertainment on age at onset of 30 or less.

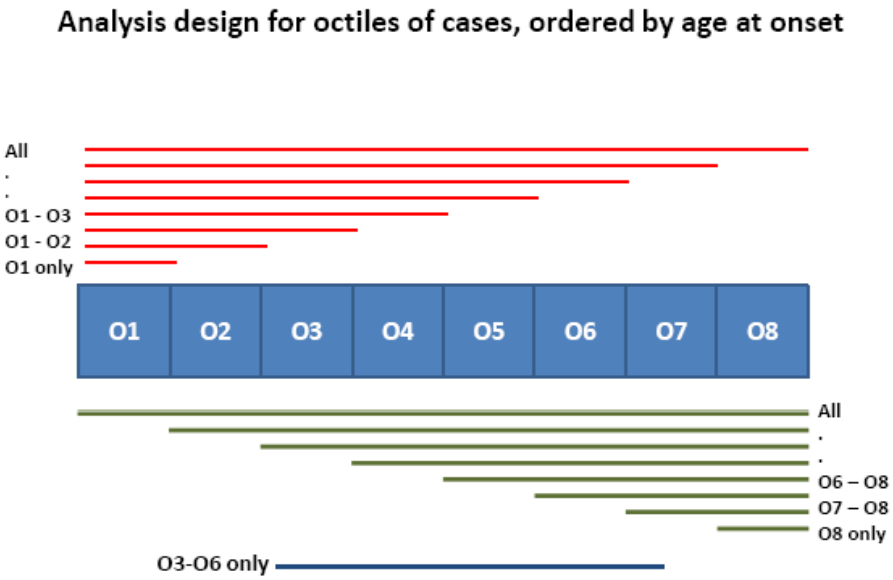

Figure S2. Analysis strategy of MDD cases by overlapping subsets of AAO.

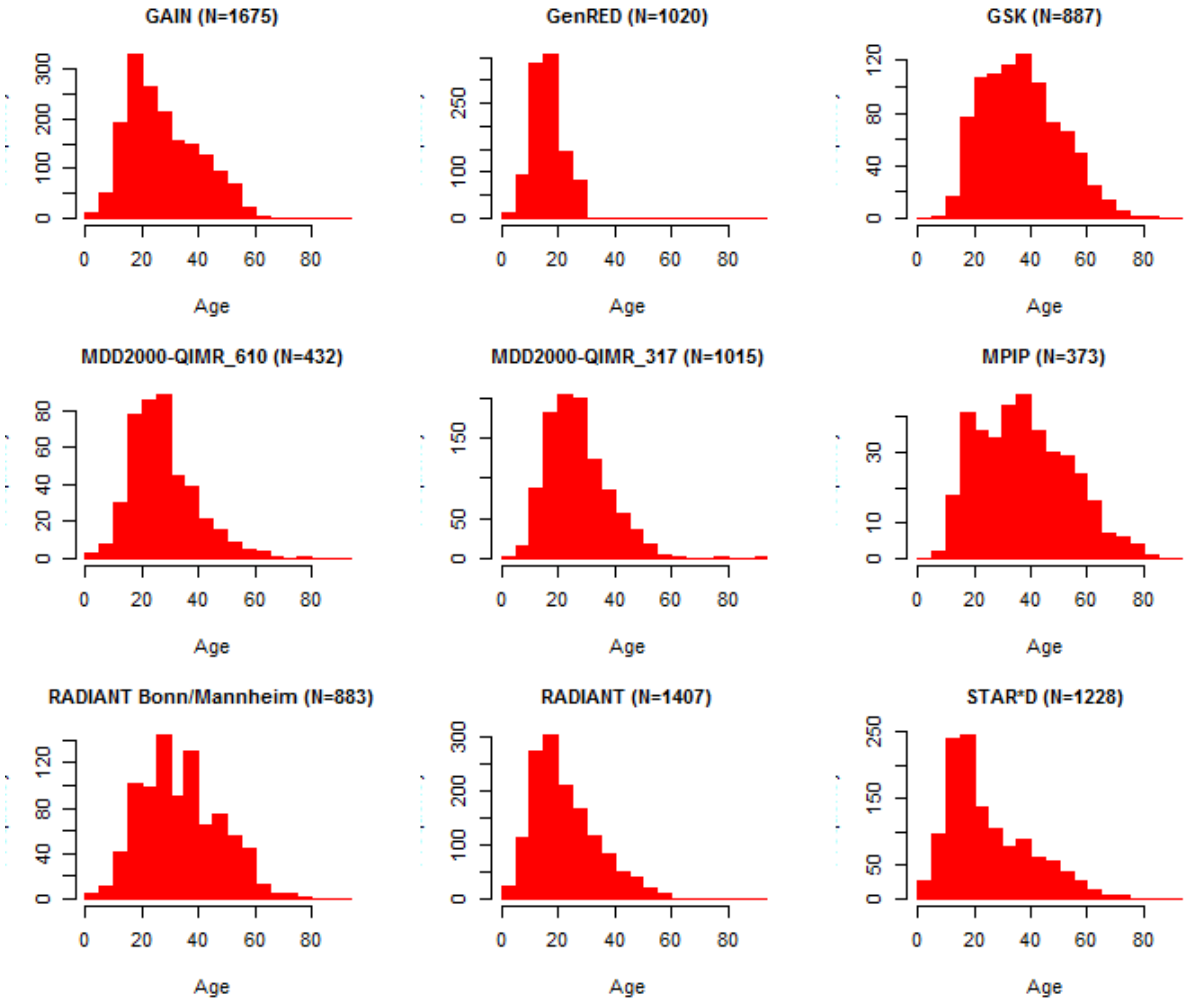

Figure S3. Distribution of age at onset in discovery samples.

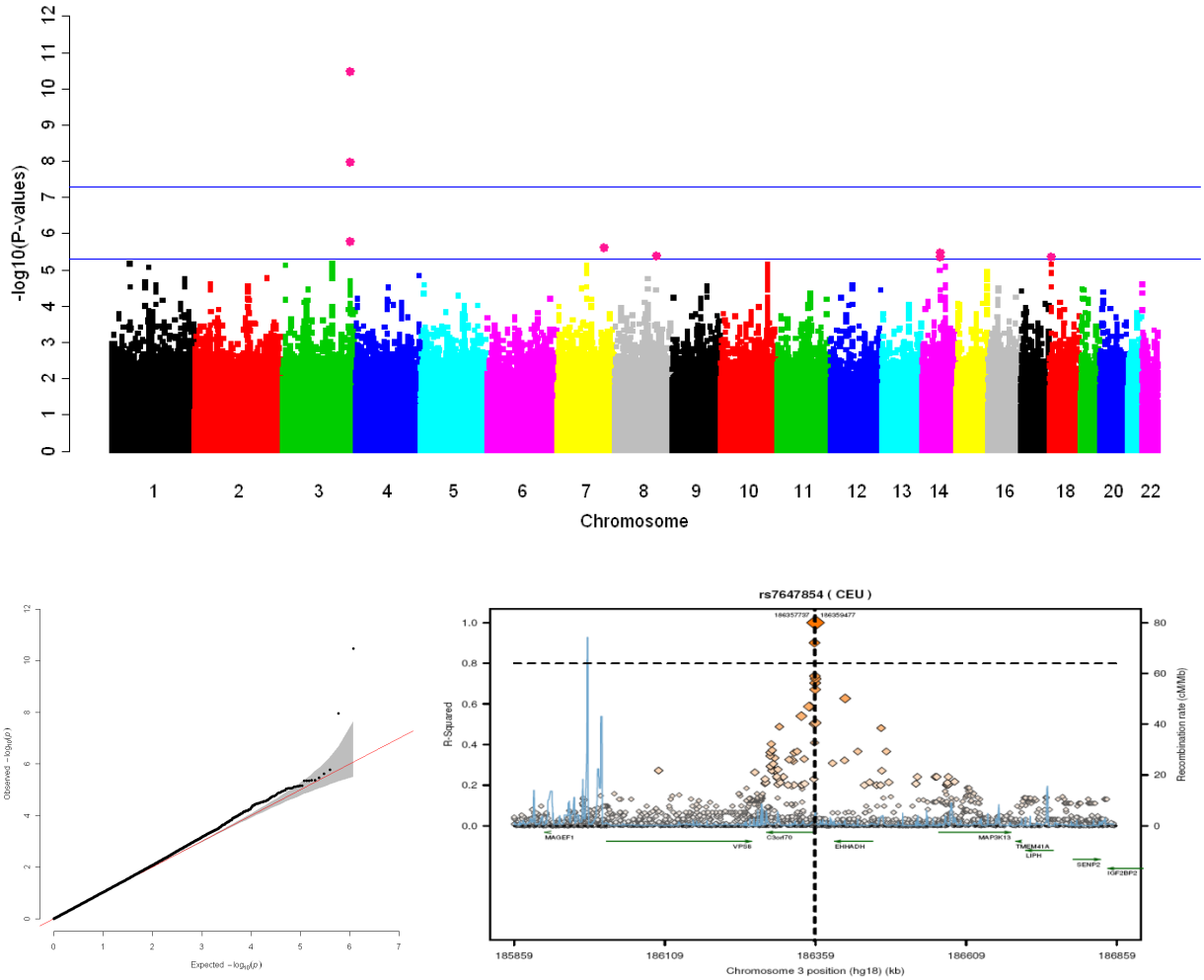

Figure S4. Manhattan, QQ, and SNAP plots for rs7647854 in O5-8 of the discovery samples.

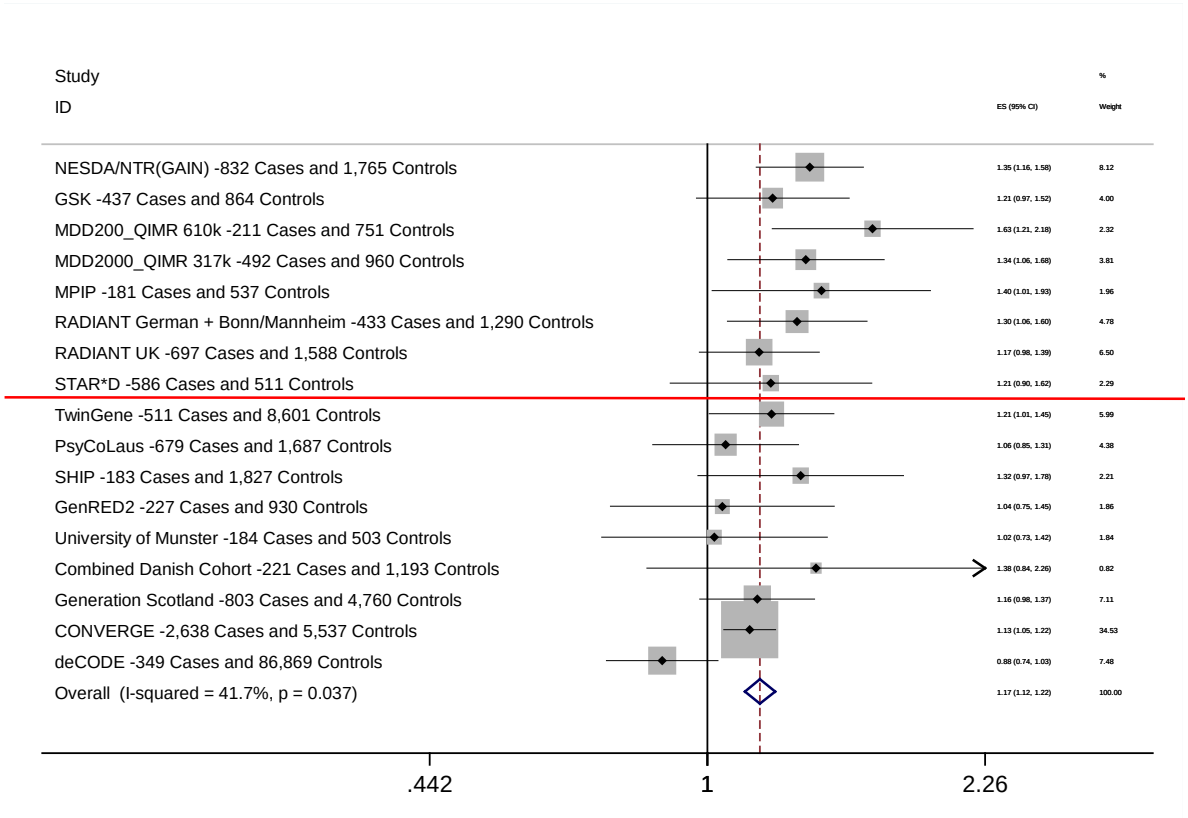

Figure S5. Forest plot of effect sizes (odds ratios) for rs7647854 in 50% latest-onset cases against controls across eight discovery studies (above horizontal line; GenRED not included) and nine replication studies (below line).

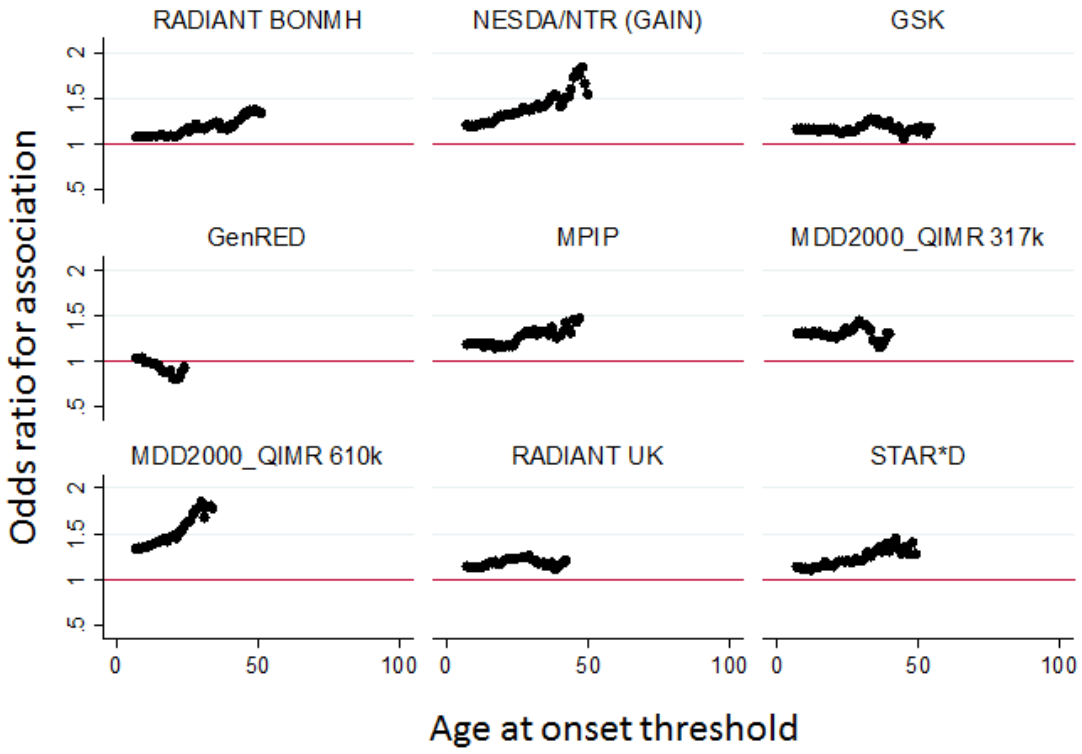

Figure S6. By-study association analysis of rs7647854, following the one-year sequential addition method of Macgregor *et al.* (1)**.** For each discovery study, the figure shows the odds ratio for association in a case control study, where only cases onset above the AAO indicated on the x-axis are included in the analysis. Analysis was terminated when fewer than 100 cases remained. Analysis shows consistency of effect across studies, with the OR increasing when only older-onset cases are included.

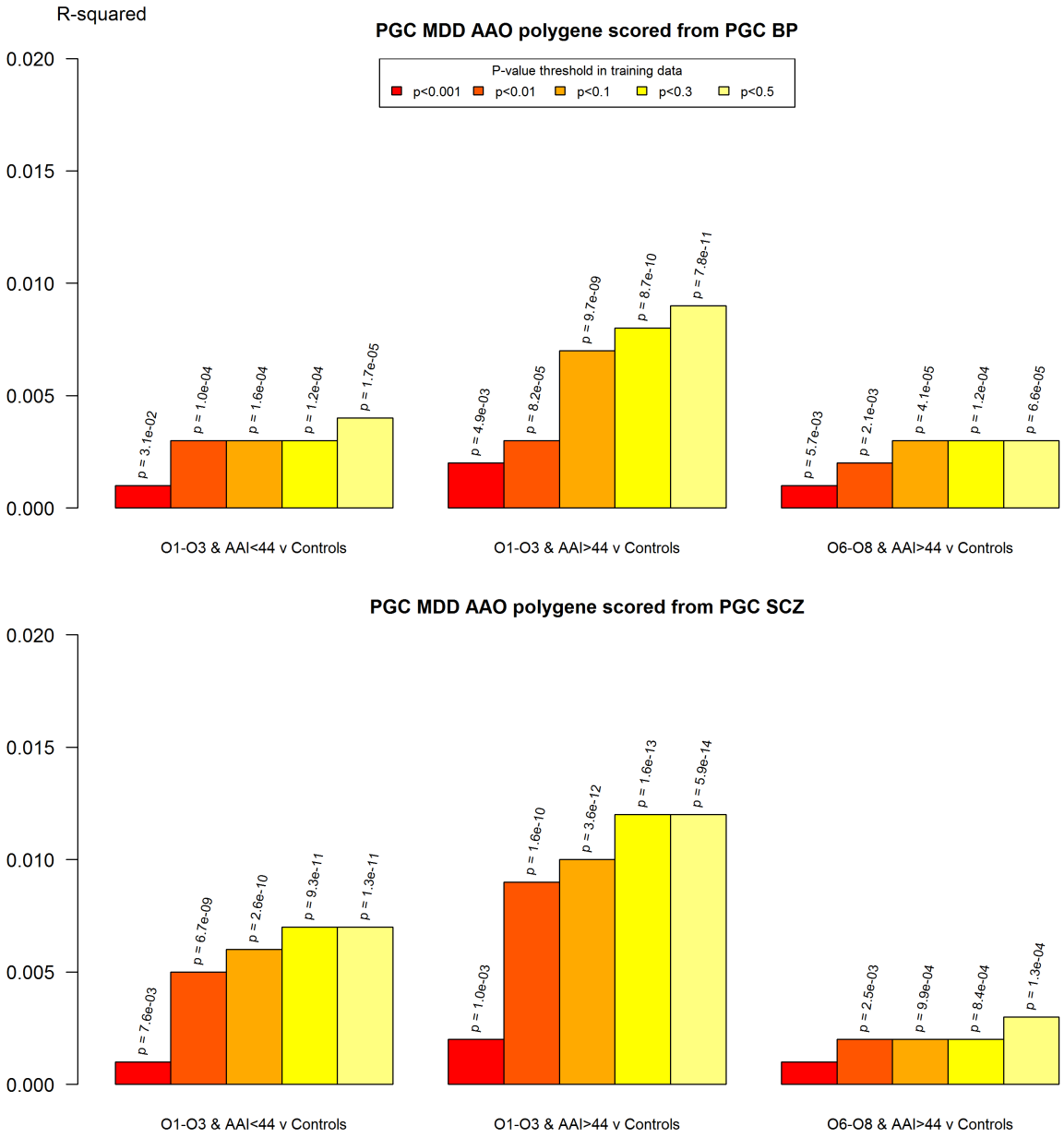

Figure S7. Polygenic risk score of schizophrenia and bipolar disorder within MDD stratifying by both age at onset and age at interview (AAI). The results show the increased overlap with bipolar disorder (BP) and schizophrenia (SCZ) in early-onset MDD (O1-3) was not driven by cases with earlier AAI (in fact the opposite). This tentatively suggests it reflects true genetic overlap rather than misdiagnosed MDD cases that eventually develop SCZ or BP. AAI of 44 was used a cut-off as this was the median of the sample. We calculated the proportion of variance explained (Nagelkerke's R^2) by subtraction of a full model (covariates + RPS) score from a reduced model (covariates only).

Supplemental Tables

Table S1. Genotyping and Imputation status of rs7647854 by study with info score.

Stage	Study	Genotyped?	Info
Discovery	GAIN	Genotyped	N/A
Discovery	GSK	Genotyped	N/A
Discovery	MDD2K_600k	Mixed	0.89
Discovery	MDD2K_317k	Mixed	0.81
Discovery	MPIP	Genotyped	N/A
Discovery	RADIANT_Bonn/Mannheim	Genotyped	N/A
Discovery	RADIANT_UK	Genotyped	N/A
Discovery	STAR*D	Imputed	0.62
Replication	TwinGene	Genotyped	N/A
Replication	PsyCoLaus	Imputed	0.8959
Replication	SHIP-LEGEND	Imputed	0.87
Replication	GenRED2/DepGenesNetworks	Genotyped	0.94
Replication	deCODE	Mixed	0.997
Replication	University of Münster	Genotyped	N/A
Replication	Combined Danish	Mixed	1.01
Replication	Generation Scotland	Genotyped	N/A
Replication	Converge	Mixed	0.98

Table S2. Results from polygenic score analysis using the genetic association results from the PGC Bipolar Disorder (2), PGC Schizophrenia (3), GERAD1 Alzheimer's disease (4), and CARDIoGRAM coronary heart disease (CAD) (5). GWAS to score into MDD discovery studies (excluding GenRED and Bonn-Mannheim). We calculated the proportion of variance explained (Nagelkerke's R^2 for logistic regression and R^2 for linear regression; reported as a percentage) by subtraction of a full model (covariates + RPS) score from a reduced model (covariates only). All results presented were corrected for sex, 20 population principal components and study indicators.

Subset	Bin	*p*-value Threshold	Bipolar Disorder		Schizophrenia		Alzheimer's Disease		CAD	
			R^2 (%)	*p*-value	R^2 (%)	*p*-value	R^2 (%)	*p*-value	R^2 (%)	*p*-value
Youngest 3/8 v. controls	1	0.001	0.2	$4.13*10^{-4}$	0.1	$2.23*10^{-3}$	<0.01	0.695	<0.01	0.562
	2	0.01	0.4	$3.39*10^{-8}$	0.7	$2.60*10^{-12}$	<0.01	0.415	<0.01	0.746
	3	0.1	0.5	$1.61*10^{-9}$	0.8	$1.05*10^{-13}$	<0.01	0.542	0.1	0.067
	4	0.2	0.5	$4.81*10^{-9}$	0.8	$1.59*10^{-13}$	<0.01	0.686	0.1	0.044
	5	0.3	0.5	$7.06*10^{-10}$	0.9	$1.24*10^{-14}$	<0.01	0.923	0.1	0.032
	6	0.4	0.6	$7.00*10^{-11}$	0.9	$2.89*10^{-15}$	<0.01	0.906	0.1	0.012
	7	0.5	0.6	$5.75*10^{-11}$	0.9	$2.22*10^{-15}$	<0.01	0.868	0.1	0.013
Oldest 3/8 v. controls	1	0.001	<0.01	0.022	<0.01	0.380	<0.01	0.688	<0.01	0.602
	2	0.01	0.1	$4.52*10^{-3}$	0.10	$5.69*10^{-3}$	<0.01	0.433	<0.01	0.505
	3	0.1	0.1	$9.61*10^{-4}$	0.10	$4.10*10^{-3}$	<0.01	0.199	0.1	0.062
	4	0.2	0.1	$1.22*10^{-3}$	0.10	$5.37*10^{-3}$	<0.01	0.201	0.1	0.029
	5	0.3	0.1	$7.90*10^{-4}$	0.10	$5.75*10^{-3}$	<0.01	0.346	0.1	0.018
	6	0.4	0.1	$7.28*10^{-4}$	0.10	$9.31*10^{-4}$	<0.01	0.385	0.1	0.012
	7	0.5	0.1	$4.52*10^{-4}$	0.10	$8.24*10^{-4}$	<0.01	0.223	0.1	0.017
All cases v. controls Cases only included if had age of onset information	1	0.001	0.1	$1.94*10^{-4}$	0.10	$1.83*10^{-3}$	<0.01	0.811	<0.01	0.262
	2	0.01	0.1	$6.13*10^{-8}$	0.40	$1.05*10^{-11}$	<0.01	0.544	<0.01	0.223
	3	0.1	0.3	$1.63*10^{-9}$	0.50	$1.23*10^{-13}$	<0.01	0.424	<0.01	$4.28*10^{-3}$
	4	0.2	0.3	$9.59*10^{-9}$	0.50	$1.38*10^{-13}$	<0.01	0.402	0.1	$8.01*10^{-4}$
	5	0.3	0.3	$3.61*10^{-10}$	0.50	$1.13*10^{-14}$	<0.01	0.758	0.1	$5.34*10^{-4}$
	6	0.4	0.4	$1.43*10^{-10}$	0.60	$2.22*10^{-16}$	<0.01	0.852	0.1	$1.84*10^{-4}$
	7	0.5	0.4	$5.93*10^{-11}$	0.60	$2.22*10^{-16}$	<0.01	0.753	0.1	$2.57*10^{-4}$
Youngest 3/8 v. Oldest 3/8	1	0.001	<0.010	0.252	<0.00	0.073	<0.01	0.564	<0.01	0.989
	2	0.01	0.1	0.016	0.30	$5.58*10^{-4}$	<0.01	0.907	<0.01	0.779
	3	0.1	0.1	0.019	0.30	$1.44*10^{-4}$	<0.01	0.408	<0.01	0.818
	4	0.2	0.1	0.029	0.30	$2.10*10^{-4}$	<0.01	0.307	<0.01	0.815
	5	0.3	0.1	0.011	0.40	$5.25*10^{-5}$	<0.01	0.342	<0.01	0.756
	6	0.4	0.2	$6.31*10^{-3}$	0.30	$1.83*10^{-4}$	<0.01	0.270	<0.01	0.875
	7	0.5	0.1	$6.60*10^{-3}$	0.30	$1.67*10^{-4}$	<0.01	0.157	<0.01	0.947
AAO as continuous trait	1	0.001	0.03	0.144	0.01	0.440	0.01	0.455	<0.01	0.692
	2	0.01	0.09	$8.16*10^{-3}$	0.09	0.010	<0.01	0.799	<0.01	0.781
	3	0.1	0.09	$7.82*10^{-3}$	0.11	$3.89*10^{-3}$	0.01	0.346	<0.01	0.595
	4	0.2	0.10	$6.07*10^{-3}$	0.10	$6.21*10^{-3}$	0.02	0.269	<0.01	0.636
	5	0.3	0.10	$4.55*10^{-3}$	0.13	$1.19*10^{-3}$	0.01	0.347	<0.01	0.765
	6	0.4	0.11	$2.83*10^{-3}$	0.11	$2.82*10^{-3}$	0.02	0.244	<0.01	0.852
	7	0.5	0.11	$3.21*10^{-3}$	0.12	$2.52*10^{-3}$	0.03	0.125	<0.01	0.954

Table S3. Results of the GCTA analysis estimating the variance captured by genotyped SNPs in early-onset cases (O1-3) and late-onset cases (O6-8). No difference in SNP-heritability was observed across early and late-onset MDD. A bivariate model looking at the overlap of heritability between early and late onset cases when both compared to controls separately gave a genetic correlation (r_G) of 99.77%.

		All Cases			Recurrent Cases		
Cases	**Controls**	**Cases**	**h_p^2 (SE)**	***p*-value**	**Cases**	**h_p^2 (SE)**	***p*-value**
O1-O3	9519	3969	0.220 (0.036)	$4x10^{-11}$	3120	0.245 (0.042)	$1x10^{-9}$
O6-O8	9519	2779	0.231 (0.046)	$1x10^{-7}$	1968	0.262 (0.059)	$2x10^{-6}$

Table S4. Associations of rs7647854 with other conditions.

SNP	Chr.	Ref. allele	Discovery		Alzheimer's GWAS		CAD GWAS	
			OR	***P***	**OR**	***P***	**OR**	***P***
rs7647854	3	G	1.30	$3.4x10^{-11}$	0.95	0.19	1.04	0.04

Supplemental Methods

Genome-wide Complex Trait Analysis

In order to estimate the heritability of AAO within MDD, Genome-wide Complex Trait Analysis (GCTA) was used to estimate the proportion of AAO phenotypic variance explained by common SNPs across the genome (6). SNPs were included with MAF > 0.01 and imputation R^2 > 0.6 in all nine studies, leaving a total of 962,903 SNPs. One individual was removed from each pair of individuals sharing more than 5% of their genetic material. Two analyses were run, analyzing cases in O1-3 against all controls and O6-8 cases against all controls. Each analysis was also run restricting to cases with recurrent depression only. Study indicators, twenty principal components and sex were included as covariates. Prevalence for MDD was set at 16.5% from Kessler *et al.* (8). A bivariate model was implemented within GCTA to examine the genetic covariance between early onset (O1-3) cases and later onset cases (O6-8). Controls were randomly split between the two groups and did not different significantly based on gender or originating study. Bivariate analysis was run covarying for 20 population principal components, study indicators and gender. Results are outlined in Table S1.

Description of Replication Studies

PsyCoLaus

Subjects were selected from subjects of European ancestry from a community survey (CoLaus) carried out in the city of Lausanne, Switzerland (9). Subjects were randomly selected from a complete list of the Lausanne inhabitants aged 35-75 years. All 35 to 66-year old participants were invited by letters also to participate in the psychiatric evaluation (PsyCoLaus) (10). Sixty-seven percent of the participants of the CoLaus study in the age range between 35-66 years accepted the psychiatric evaluation, which resulted in a sample of 3,719 individuals, of whom 92% were of European ancestry. Psychiatric assessment in the PsyCoLaus sub-study included the semi structured Diagnostic Interview for Genetic Studies (DIGS), French version (11). Cases met DSM-IV criteria for MDD and controls were devoid of any psychiatric disorders. A subset of the 3,419 European subjects who received full psychiatric assessment and gave consent for genetic testing were selected for GWAS genotyping. This research was approved by the local institutional review board. All participants received a detailed description of the goal and funding of the study and signed a written informed consent.

SHIP-LEGEND

Data from the Study of Health in Pomerania (SHIP) were used (12; 13). The target population was comprised of adult German residents in northeastern Germany living in 3 cities and 29 communities, with a total population of 212,157. A two-stage stratified cluster sample of adults aged 20-79 years (baseline) was randomly drawn from local population registries. The net sample (without migrated or deceased persons) comprised 6,267 eligible subjects of whom 4,308 Caucasian subjects participated at baseline SHIP-0 between 1997 and 2001. Follow-up examination (SHIP-1) was conducted 5 years after baseline and included 3,300 subjects. In 2007, the "Life-Events and Gene-Environment Interaction in Depression" (LEGEND) study was started based on SHIP (14). The lifetime diagnosis of MDD was assessed with the Munich-Composite International Diagnostic Interview (M-CIDI). The M-CIDI is a standardized fully structured instrument for assessing psychiatric disorders over the life span according to DSM-IV criteria. The computerized version of the interview was used by clinically experienced interviewers (psychologists) in a face-to-face situation. All interviewers had undergone intensive and continuous training in the diagnostic procedures. SHIP and LEGEND were approved by the local Institutional Review Board and conformed to the principles of the Declaration of Helsinki.

TwinGene

The TwinGene project, conducted between 2004 and 2008, is a population-based Swedish study of twins born between 1911 and 1958 drawn from the Swedish Twin Registry (15). All subjects in this investigation were independent (i.e., one twin selected per twin pair). The study participants previously participated in a telephone interview called Screening Across the Lifespan Twin Study (SALT). Data from the SALT study were used to identify MDD cases as either reporting antidepressant use or meeting DSM-IV criteria for MDD using the Composite International Diagnostic Interview Short Form (CIDI-SF) criteria. The study was approved by the local ethics committee at Karolinska Institutet and all participants gave informed consent.

Genetics of Recurrent Early-Onset Depression Phase II & Depression Genes and Networks

The second phase of GenRED was included as a replication sample (the first phase was a discovery sample). GenRED2 included new cases meeting the same criteria as in GenRED, plus new controls. Dr. Janet Sobell (University of Southern California) contributed 287 post-QC controls from the Mayo DNA Bank which consists of long-term, community medicine patients (Mayo Clinic, Rochester, MN) who were undergoing venipuncture for any reason. Consenting individuals ages 45 and above completed a brief demographic and psychiatric screening questionnaire. Extensive medical records were screened for evidence of psychiatric illness. Individuals were excluded if they were judged likely to have had a mood or psychotic disorder on the basis of a review of medical records, taking into account the recorded diagnoses and treatment in each case (including major disorders as well as possible proxies for a mood disorder in older nomenclature such as adjustment disorders, depression NOS, anxiety state, etc.). The final subset was selected to roughly match the proportions of self-reported ancestry in the GenRED 1+2 sample. Drs. Carlos Pato and James Knowles contributed 187 post-QC controls from the Genomic Psychiatry Consortium, an ongoing study of schizophrenia and bipolar disorder. Controls were recruited opportunistically in the Los Angeles area and screened with a self-report questionnaire. We selected individuals who reported European ancestry in all grandparents and answered negatively to five screening questions for lifetime bipolar disorder, five for lifetime schizophrenia, and four for lifetime MDD. Note that these 1,305 subjects were genotyped at the same lab (Centrillion Biosciences, Mountain View, CA) and with the same GWAS array (Illumina Omni1-Quad) as the Depression Genes and Networks sample (below) collected by a subset of the GenRED investigators, so that these samples were combined for the PGC replication analysis.

The Depression Genes and Networks (DGN) sample was genotyped and analyzed in combination with the GenRED2 sample (above). A survey research company (Knowledge Networks, Menlo Park, CA) recruited the 471 post-QC recurrent MDD cases and 470 never-depressed controls from participants in an online survey panel that is recruited on an ongoing basis using random digit dialing of nationally-representative US households. (Note that the same panel was used to recruit the Molecular Genetics of Schizophrenia control sample for the NIMH repository, but individuals who were invited to be screened for MGS and who were still members of the panel were not invited to be screened for DGN.) Online screening was carried out using the CIDI-SF depression and alcohol and substance dependence modules; prospective controls were selected who reported two or more episodes meeting criteria for MDD but denied lifetime substance dependence, while prospective controls denied ever having two or more weeks of depressed mood or anhedonia and two or more other MDD criteria outside of acute bereavement. These individuals were then interviewed (SCID) and individuals not meeting the initial eligibility criteria (based on final review by the site PI) were excluded. Note that these cases all reported recurrent MDD, but were not required to meet the additional criteria required for the GenRED project.

Danish Replication Sample

The Danish replication sample was made up of samples from 3 sources: additional RADIANT cases recruited in Denmark with genotype data available; a subset of Danish cases and screened controls recruited for the DEMO and PRISME studies genotyped specifically for these SNPs; and a cohort of unscreened controls from the Danish population already genotyped and imputed. As each sample individually was relatively small and minor allele frequencies were roughly in line across all samples, they were combined in their analysis.

The combined DEMO and PRISME samples came from 3 cohorts. The Denmark 1 cohort includes 162 cases with depression according to the ICD-10 diagnostic criteria. Diagnoses were obtained using a semi-structured diagnostic interview (Schedules for Clinical Assessment in Neuropsychiatry (SCAN version 2.1)). The subjects were all part of the Danish PRISME study and employees within large public service workplaces in a Danish county (16; 17). The Denmark 2 and 3 cohort includes 104 and 70 individuals from the Danish DEMO trial 1 and 2, respectively. The Denmark 2 cohort is described in detail by Krogh *et al.* (18; 19). All cases fulfilled the ICD-10 diagnostic criteria for depression and the diagnoses were obtained using the Major Depression Inventory (MDI) (20). The control sample consisted of 289 healthy, screened individuals with no diagnoses of affective disorders or anxiety disorders. The controls were all part of the Danish PRISME study. All cases and controls were Caucasian of origin and gave written informed consent. This study was approved by the Danish Data Protection Agency and the ethics

committees in Denmark. Genotyping for SNPs was done within this sample specifically for those requiring replication, as genome-wide data was not available. PCR reactions were composed of 10 ng DNA in a total volume of 9 µl. DNA amplification was performed as a multiplex reaction with either two (rs9323497 and rs7647854), two (rs10184299 and rs7950328) or four (rs625527, rs7807320, rs4379463 and rs1969420) markers simultaneously, except for rs1276324, which was amplified alone. Following PCR, primers and nucleotides were degraded by treatment with exonuclease and shrimp alkaline phosphatase and a primer extension reaction was performed according to the SNaPshot protocol using fluorescently labeled nucleotides (Applied Biosystems, Fostercity, USA). Genotyping was performed on an ABI 3130 Prism Genetic Analyzer, and the fluorescent peaks were analysed using Genemapper version 4.0 (Applied Biosystems, Fostercity, CA) and independently checked by two experienced investigators. Additional method conditions and primer sequences are available on request.

The 155 RADIANT cases were ascertained from two studies: DeNT, a retrospective study of depression in sibling pairs; and GENDEP, a pharmacogenetic study of antidepressant response. Both studies required moderate to severe depression as diagnosed by DSM-IV or ICD-10 criteria, with DeNT further requiring at least 2 episodes over their lifetime. All cases were recruited in Aarhus. Individuals were excluded if their genotypic data showed a missing rate >1%, abnormal heterozygosity, a sex assignment that conflicted with phenotypic data, if they were related (up to second degree) with other study members, or were of non-European ancestry. SNPs with a low minor allele frequency (<1%) or showing departure from Hardy–Weinberg equilibrium (p < 1E-5) were excluded. No imputation method was used. Full details of genotyping methods and quality control procedures has been published previously, with respect to the UK subset of the RADIANT studies (21).

The final cohort of Danish individuals were 883 controls from a schizophrenia GWAS conducted in Denmark on all individuals born in Denmark since 1981 having a schizophrenia diagnosis in the nationwide Danish Psychiatric Central Register as of 2006 (22). The controls were matched on sex, date of birth and age, and had no history of schizophrenia on the date of first diagnosis of schizophrenia of the case. By this procedure 915 controls were identified and subsequently dried blood spots from the individuals were obtained from the Danish Newborn Screening Biobank (DNSB) (23). Sufficient biological material was available for 899 controls. DNA was extracted from the dried blood spots using Extract-N-Amp Blood PCR kit (Sigma Aldrich) and subsequently whole-genome-amplified in triplicates using the RepliG kit (Qiagen) (24). The three separate reactions were pooled before genotyping, which was done using the Illumina Human 610-quad beadchip. Altogether 883 controls were successfully genotyped. SNPs with a deviation from Hardy-Weinberg equilibrium (p < 0.0001) and a MAF below 0.01 were

excluded as were SNPs and individuals with more than 2% missing data. Furthermore, test for relatedness, estimation of individual heterozygosity and test for non-random missingness of SNPs between cases and controls were conducted. One individual was excluded this way, leaving 882. Imputation was conducted using Impute v2.3.0 using standard settings and based on 1000 genome v3 and the strand file provided at the impute web site (25).

University of Münster Depression Cohorts

Data were pooled from the Münster Neuroimaging study and the Moodinflame study recruited from the same geographical area conducted at the Department of Psychiatry, University of Münster, Germany. From the Münster Neuroimaging Study, 516 healthy subjects, all adult, participated in the present study. All included subjects were thoroughly investigated by experienced psychologists and were free from any lifetime history of psychiatric disorders according to DSM-IV criteria (26), as ascertained by the SCID interview (27). Additional scales were employed (e.g., CTQ, LEQ, BDI). Exclusion criteria were scores ≥ 10 on the Beck Depression Inventory (BDI) (28), any neurological abnormalities, history of seizures, head trauma or unconsciousness, intake of any psychotropic medication, and the usual MRI contraindications. Depression cases were derived from two Münster Depression cohorts (Moodinflame and Münster Neuroimaging Study). As part of the Münster Neuroimaging Study of depression, 167 depressed adult subjects recruited since 2005 at the University of Münster, Germany. All included subjects were thoroughly investigated by experienced psychologists and major depressive disorder (MDD) was ascertained according to DSM-IV criteria (24), as diagnosed with the SCID interview (25). Patients were recruited from the inpatient service of the University of Münster's Department of Psychiatry. Exclusion criteria were any neurologic abnormalities; substance-related disorders; psychotic symptoms; a history of mania or hypomania; treatment with benzodiazepine; and previous electroconvulsive therapy; and the usual MRI-contraindications. Clinical assessment included a minimum of measures such as HAM-D-21, BDI, number of episodes of depression, age of onset, duration of illness, medication history, education age and sex. According to similar inclusion and exclusion criteria, a second cohort (Moodinflame) of 238 adult cases was also recruited at the University of Münster, Germany, as part of the Moodinflame study. Psychiatric diagnoses were ascertained using a structured clinical interview (SCID) (25). Clinical and pathological features were assessed in a standardized manner using various scales among which were Inventory of Depressive Symptoms - Clinician Rated (IDS-C), Young Mania Rating Scale (YMRS), Childhood Trauma Questionnaire (CTQ), HAM-D, medication and psychiatric history. In addition to age, sex, and education, clinical characteristics such as number of episodes of depression, age of onset of depression, duration of illness and medication history were assessed.

Genotyping was conducted blind to phenotypic data. The ABI PRSIM 7900HT Sequence Detection System (Applied Biosystems Inc., Foster City, CA, USA) was used to genotype using KASPtm genotyping assays (LGC Genomics Ltd, Hoddesdon, Herts, UK). Positive and negative controls were included four times on each 384-well plate run, and 100 samples were run in duplicate for each assay (with no conflicts). Deviation from Hardy Weinberg equilibrium was tested using chi-squared tests.

deCODE

Cases and controls were all Icelandic and were recruited from all over Iceland. For patients, diagnoses were assigned according to DSM-III or ICD-10 criteria. Controls were recruited as a part of various genetic programs at deCODE (excluding the schizophrenia, bipolar disorder, and anxiety projects) and were not screened for psychiatric disorders. Age at onset was obtained from hospital records and was defined as the age at first hospital admission. Approval for the study was granted by the National Bioethics Committee of Iceland and the Icelandic Data Protection Authority. Informed consent was obtained for all participants.

CONVERGE

CONVERGE (CONVERGE: China Oxford and VCU Experimental Research on Genetic Epidemiology) is a collaboration between the University of Oxford, Hua Shan Hospital at Fudan University, China, and Virginia Commonwealth University. Recurrent MD cases and controls were recruited from 53 provincial mental-health centers in China, were exclusively female and of Han Chinese ancestry. Critically, sampled controls have been carefully screened to ensure a low liability to depressive illness (>30 years old). Genetic material was extracted from saliva samples; sparse genome sequencing (~1.2X) was conducted for 12,000 cases and controls by Beijing Genomics Institute (BGI). Stringent quality control measures were implemented, with consideration to individual- and SNP-level metrics.

Generation Scotland

GS:SFHS consists of over 24,000 participants recruited at random from general medical practices across Scotland between 2006 and 2011. Probands (*n* = 7,953) were aged between 35 and 65 years and were registered with participating general medical practitioners. These individuals were not ascertained on the basis of having any particular disorder. Eligibility criteria specified that participants were over 18 years of age and had one first-degree relative also willing to participate. 20,223 individuals had phenotypic information for major depressive disorder (cases *n* = 2751, controls *n* = 17472; www.generationscotland.org/) (29; 30). Genome-wide SNP data were ascertained for 10,000 individuals, and after quality control, genotype data was available for 9863 participants. 18.1% of the genotyped

individuals had a diagnosis of single or recurrent episode depression. A shared family identity number was given to groups where each member was a first-degree relative of at least one other person. The current sample of unrelated individuals was ascertained by removing individuals with a shared family ID. Individuals with depression were preferentially selected from families. A diagnosis of MDD was made using the Structured Clinical Interview for DSM-IV Disorders (SCID); trained researchers administered the screening questions after a period of training and reliability assessment. Participants who screened positive (21.7%) were invited to continue the interview that focused on mood disorders, from which information on the presence or absence of a lifetime history of MDD, age of onset and number of depressive episodes was provided.

GERAD1 Consortium Study Description

Cases and elderly screened controls were recruited by the Medical Research Council (MRC) Genetic Resource for AD (Cardiff University; Institute of Psychiatry, London; Cambridge University; Trinity College Dublin), the Alzheimer's Research UK (ARUK) Collaboration (University of Nottingham; University of Manchester; University of Southampton; University of Bristol; Queen's University Belfast; the Oxford Project to Investigate Memory and Ageing (OPTIMA), Oxford University); Washington University, St Louis, United States; MRC PRION Unit, University College London; London and the South East Region AD project (LASER-AD), University College London; Competence Network of Dementia (CND) and Department of Psychiatry, University of Bonn, Germany; the National Institute of Mental Health (NIMH) AD Genetics Initiative. 6,129 population controls were drawn from large existing cohorts with available GWAS data, including the 1958 British Birth Cohort (1958BC) (http://www.b58cgene.sgul.ac.uk), the KORA F4 Study and the Heinz Nixdorf Recall Study. All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. Genotypes from all cases and 4,617 controls were previously included in the AD GWAS by Harold and colleagues (4). Genotypes for the remaining 2,660 population controls were obtained from WTCCC2. Imputation of the dataset was performed using IMPUTE2 and the 1000 genomes (http://www.1000genomes.org/) Dec2010 reference panel (NCBI build 37.1). The imputed data were then analyzed using logistic regression including covariates for country of origin, sex, age and 3 principal components obtained with EIGENSTRAT software based on individual genotypes for the GERAD study participants.

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