Original Article

Causal effects of serum sex hormone binding protein levels on the risk of amyotrophic lateral sclerosis: a mendelian randomization study

Ya-Nan Ou[1], Liu Yang[2], Bang-Sheng Wu[2], Lan Tan[1], Jin-Tai Yu[2]

[1]Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China; [2]Department of Neurology and Institute of Neurology, Huashan Hospital, State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Shanghai Medical College, Fudan University, Shanghai, China

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Correspondence to: Prof. Jin-Tai Yu, MD, PhD. Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, 12th WulumuqiZhong Road, Shanghai 200040, China. Email: jintai_yu@fudan.edu.cn. Prof. Lan Tan, MD, PhD. Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao 266071, China. Email: dr.tanlan@163.com.

Background: Extensive observational studies have suggested an association between serum sex-hormone binding globulin (SHBG) and Alzheimer's disease (AD); however, causality remains unclear. Furthermore, the effects on other neurodegenerative diseases have been poorly investigated. We aimed to explore the causal effects of genetically predicted SHBG serum levels on common neurodegenerative diseases.

Methods: A two-sample Mendelian randomization (MR) approach was used. Genetic variants of SHBG levels in the serum, detected using the chemiluminescent two-step sandwich immunoassay method, were identified from a genome-wide association meta-analysis from the UK Biobank (N=363,228). Summary-level data for AD, and other common neurodegenerative diseases including Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD) were adopted from the corresponding large genome-wide association studies of individuals of European ancestry, which were either clinically or autopsy-diagnosed. Causal estimates were calculated using the inverse-variance weighted (IVW) method and several sensitivity methods (MR-Egger, weighted median, and weighted mode). Egger intercept, MR-PRESSO, and leave-one-out analyses were used to identify potential violations.

Results: Genetically determined serum SHBG levels [odds ratio (OR_{IVW}) =1.113, 95% CI: 1.019–1.215, P=0.017] were associated with an increased risk of ALS. This causal effect was confirmed using sensitivity analyses, including the MR-Egger (OR =1.229, 95% CI: 1.049–1.441, P=0.012), weighted median (OR =1.231, 95% CI: 1.077–1.406, P=0.002), and weighted mode (OR =1.235, 95% CI: 1.067–1.431, P=0.005) methods. No notable heterogeneity or directional pleiotropy was observed. However, leave-one-out analysis showed that rs9892297 drove the observed effects. There was no evidence that genetically predicted serum SHBG levels affect other neurodegenerative diseases, including AD, PD, MS, DLB, and FTD (all P>0.05).

Conclusions: This MR analysis found that genetically determined serum SHBG was associated with an increased risk of ALS rather than AD, which is inconsistent with previous observational studies. This novel finding highlights the potential of SHBG in peripheral serum for ALS prevention. Further research into the effects of SHBG on other neurodegenerative diseases is required, especially because of the increased utilization of hormone therapy.

Keywords: Sex hormone binding protein; amyotrophic lateral sclerosis (ALS); Alzheimer's disease (AD); neurodegenerative diseases; Mendelian randomization (MR)

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Introduction

Because of extended lifespans, the prevalence of age-related neurodegenerative disorders is increasing (1). These disorders impair individuals' memory, cognition, mood, and movement, but currently none are curable; existing treatments can only manage the symptoms or delay disease progression. Thus, viable biomarkers of aging-related neurodegenerative diseases, especially in peripheral blood, are crucial for the early warning, diagnosis, and treatment of these diseases (2).

Sex hormones have been reported to play an important role in human brain development, showing neuroprotective effects by preserving neural function and promoting neuronal survival (3). Sex-hormone binding globulin (SHBG) is a hepatically secreted binding protein for sex hormones in plasma that prevents hormones from binding to intracellular androgen or estrogen receptors (4). Thus, it is considered the major factor controlling the balance between biologically active testosterone and estradiol (4). Emerging evidence indicates that peripheral SHBG levels might be an effective indicator of the occurrence or progression of neurodegenerative disorders (5). However, inconsistencies and uncertainties exist and causality remains unclear. Higher SHBG has been found to be associated with worse cognitive performance and an increased risk of developing Alzheimer's disease (AD) and all-cause dementia (6). Recently, by integrating information from two databases, the Chinese Alzheimer's Biomarker and LifestylE (CABLE) study and Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, our research team found that plasma SHBG could be a predictive biomarker for AD progression (5). However, the effects of SHBG on other neurodegenerative diseases have been poorly investigated. A previous Polish study revealed no difference in SHBG levels between Parkinson's disease (PD) patients and healthy subjects (7). In addition, a subtle relationship between SHBG and amyotrophic lateral sclerosis (ALS) has been revealed, which might be explained by the possible involvement of testosterone in ALS causation (8). However, the exploration of other neurological disorders remains controversial.

In addition, existing studies are limited to observational designs, which are subject to confounding bias and reverse causation (9). Although epidemiological studies have adjusted for confounding factors observed in study participants, confounding bias is inevitable (10). Reverse causality bias arises if preclinical states that lead to outcomes also affect their risk factors (10). People consciously reduce their exposure to risk factors after acquiring an illness. Mendelian randomization (MR) is a technique that allows the examination of causal relationships (10). This method minimizes confounding bias because genetic variants are randomly allocated during conception. Reverse causality bias is also precluded because the genotypes are not affected by the disease. MR assesses lifelong exposure to health-related outcomes; thus, it can reveal potential causal associations (11). It is becoming increasingly viable, as data from numerous large genome-wide association studies (GWAS) over the past decade are now publicly available. The MR approach has been employed to uncover the causal effects of many risk factors regarding the incidence of neurodegenerative diseases (12-15).

We conducted a two-sample MR study to explore the causal effects of genetically predicted SHBG levels in the serum on common neurodegenerative diseases such as AD, including maternal/paternal family history of AD, as well as PD, ALS, multiple sclerosis (MS), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). We present the following article in accordance with the STROBE-MR reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1156/rc).

Methods

Study design and instrument identification

Two-sample MR analysis is a genetic instrumental variable (IV) analysis based on summary-level data with single nucleotide polymorphisms (SNPs) as instruments for risk factors. This method has been widely used. The MR approach is based on three assumptions as follows: (I) the genetic variants are significantly associated with SHBG levels in serum; (II) the IVs (namely, SNPs) have no association with confounding factors; and (III) the risks of outcomes (the six neurodegenerative diseases) are influenced only by exposure (serum SHBG), not by other pathways (16) (*Figure 1*). This study analyzed publicly available summary

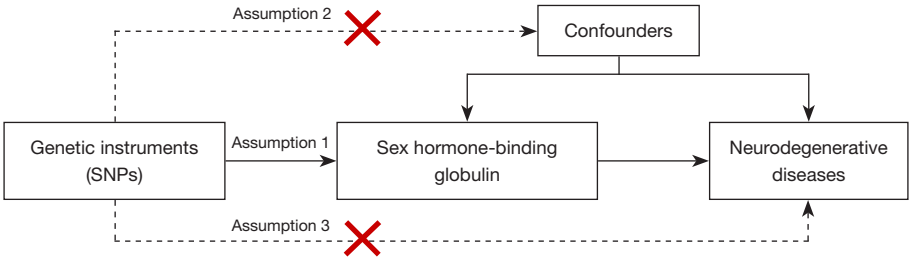

Figure 1 Scheme diagram of the Mendelian randomization design. The MR approach should satisfy three assumptions. 1: the genetic variants significantly associate with the exposures; in this study, the two exposures are serum SHBG levels and neurological disorders; 2: the IVs (namely, SNPs) have no association with confounding factors; 3: the risk of outcome (neurological disorders) is influenced only by the exposure (serum SHBG), not by other pathways. MR, Mendelian randomization; SHBG, sex-hormone binding globulin; SNP, single nucleotide polymorphism.

level data from large GWASs. Informed consents and ethical approvals were obtained for the original studies. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Significant SNPs ($P<5\times10^{-8}$) for serum SHBG levels were identified in a GWAS meta-analysis that included 363,228 individuals of European ancestry drawn from the UK Biobank (UKB) (17). The UKB was established in 2006 and enrolled participants from the entire UK population, with a recruitment age of 45–69 years. This study evaluated the genetic basis of 35 blood and urine laboratory measurements and identified 1,857 loci associated with at least one trait. Serum SHBG level was one of the 35 variables. Serum SHBG levels (nmol/L) were detected using the chemiluminescent two-step sandwich immunoassay method in Beckman Coulter DXI 800 (Beckman Coulter, UK), Ltd. The good or acceptable distribution rate was 95%. Further detailed information is provided in Table S1.

Outcome databases

The outcomes of AD, PD, ALS, MS, DLB, and FTD were all clinically diagnosed or autopsy-diagnosed. The genetic variants associated with AD were extracted from the following GWAS summary statistics: (I) the International Genomics of Alzheimer's Project (IGAP) GWAS Stage 1 result (N=21,982 cases, 41,944 controls) (18); (II) maternal family history of AD (N=27,696 cases, 260,980 controls); and (III) paternal family history of AD (N=14,338 cases, 245,941 controls) (19). Late-onset AD was either autopsy-confirmed or clinically confirmed. Maternal and paternal family histories of AD were self-reported (Table S1). The data of maternal and paternal family history of AD were extracted from the same dataset (UKB) as SHBG; thus, there was considerable overlap between the exposure and outcome samples. We only considered this part of the analysis as supplementary to support our main findings.

A recently published PD GWAS meta-analysis, which included three sources of data (three previously published GWAS studies, 13 new datasets, and proxy-case data from the UKB), was used as the PD GWAS source (N=37,688 cases, 18,618 UKB proxy-cases, and 1.4 million controls) (20). Summary statistics for ALS were obtained from a large GWAS involving 80,610 participants of European descent (20,806 ALS cases and 59,804 controls) (21). Patients were diagnosed with probable or definite ALS according to the EI Escorial criteria (22). The MS GWAS data leveraged genotype data from 47,429 MS cases and 68,374 controls of European descent from the International Multiple Sclerosis Genetics Consortium (23). DLB data were obtained from whole-genome sequencing of a cohort of 2,981 patients diagnosed with DLB and 4,391 neurologically healthy individuals (24). Participants were recruited from 44 institutions/consortia and diagnosed according to the established consensus criteria. FTD data were obtained from a two-stage GWAS with samples from 3,526 clinical FTD patients and 9,402 healthy controls (25). To reduce genetic heterogeneity, all the participants were of European ancestry (Table S1).

Instrument selection

We estimated the overall effect of serum SHBG on multiple neurodegenerative diseases by combining the effects of genome-wide significant SNPs ($P<5\times10^{-8}$) from the GWAS,

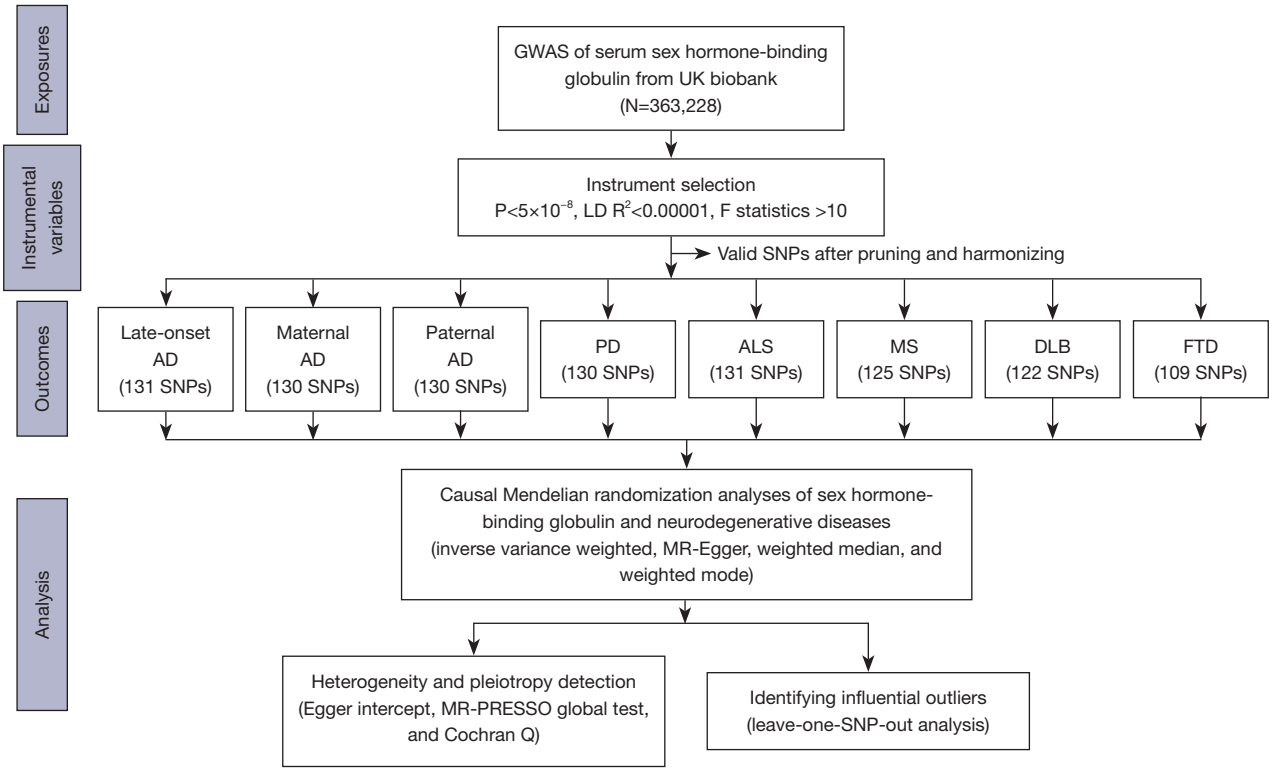

Figure 2 A flow diagram of the process in this MR analysis. SNP, single nucleotide polymorphism; GWAS, genome-wide association studies; IV, instrumental variable; LD, linkage disequilibrium; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MR, Mendelian randomization; SHBG, sex hormone binding globulin.

which were then clumped based on the European 1000 Genomes panel to a stringent LD threshold (R^2<0.00001) and then a default LD threshold (R^2<0.001). Several SNPs were further excluded to eliminate the genetic bias produced by the palindrome with intermediate allele frequencies. Eventually, 131 SNPs were included in late-onset AD, 130 SNPs for maternal AD, 130 SNPs for paternal AD, 130 SNPs for PD, 131 SNPs for ALS, 125 SNPs for MS, 122 SNPs for DLB, and 109 SNPs for FTD. There were no SNPs with F-statistics <10. The screening process is shown in *Figure 2*, and the included SNPs are shown in Tables S2-S9.

Statistical analyses

Causal effects were estimated using the random-effects maximum likelihood estimation method. We applied four complementary methods [inverse variance weighted (IVW), MR-Egger, weighted median, and weighted mode], which provided different assumptions regarding horizontal pleiotropy (26). The IVW method was performed as our primary method, which combined the Wald ratio estimates of the causal effects obtained from different SNPs. The intercept was assumed to be zero and associated with a weighted regression of SNP-exposure effects with SNP-outcome effects (27). MR-Egger regression is not constrained to have a slope of zero; therefore, its causal estimate represents a genotype-outcome dose-response relationship that takes pleiotropic effects into account (26,28). The weighted median approach is defined as the median of a weighted empirical density function of the ratio estimates, giving more weight to more precise IVs. The estimate is consistent even when up to 50% of the information comes from invalid or weak instruments (10). Results were presented as odds ratios (ORs) and 95% CIs. The MR-Egger intercept, MR-PRESSO global test, and Cochran Q statistics were used to test for the presence of heterogeneity or directional pleiotropy (29). The leave-one-SNP-out analysis was performed by systematic removal of

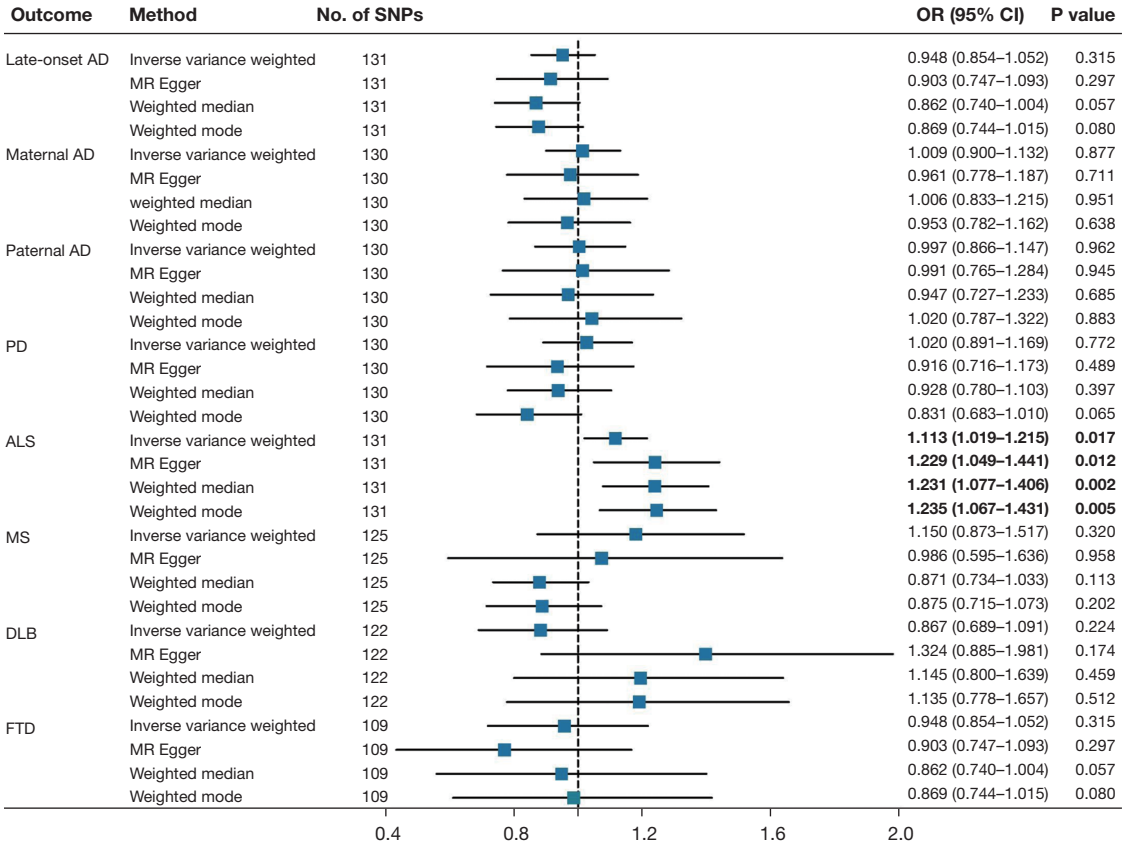

Figure 3 Mendelian randomization results of serum SHBG level and neurodegenerative diseases. Genome-wide significantly associated ($P<5\times10^{-8}$) independent (linkage disequilibrium $R^2=0.00001$, clumping distance =10,000 kb) SNPs were used as instruments. Bold fonts represent significant results. SNP, single nucleotide polymorphism; OR, odds ratio; MR, Mendelian randomization; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; SHBG, sex-hormone binding globulin.

genetic instruments from MR analysis to identify influential outliers. F-statistics were used to measure the strength of the genetic instruments in IVW (30). The F-statistics were >10, indicating that the instrument strength was sufficient for MR analysis and less likely to be influenced by weak instrument bias (31).

Statistical significance of the above analyses was set at a 2-sided P value of <0.05. Statistical analyses were conducted using R (version 3.6.3), and MR analyses were conducted using "TwoSampleMR".

Results

Genetically determined serum SHBG levels and AD risk

No obvious significant causal association between genetically determined serum SHBG levels and the risk of late-onset AD was found (OR_{IVW} =0.948, 95% CI: 0.854–1.052, P=0.315; SNPs =131; *Figure 3*, Figure S1), whereas the results of the sensitivity analysis using the weighted median method were suggestive of protective effects with an OR of 0.862 (95% CI: 0.740–1.004, P=0.057). Additional analysis applying an $R^2<0.001$ showed similar results (Figures S2,S3). There was evidence of heterogeneity in the causal effect estimates (P for MR-Egger =4.71E-05, P for IVW =5.37E-05; *Table 1*). The MR-PRESSO global test revealed horizontal pleiotropic effects (P<0.001). However, no significant outliers were observed. Similar null associations between maternal and paternal AD were identified using 130 IVs. No evidence for heterogeneity of effect sizes (Cochran Q statistic, P>0.05) or pleiotropy (intercept: 2.39E-04, P=0.959; P for MR-PRESSO global test =0.953) was found for paternal AD, while evidence of heterogeneity

Table 1 Heterogeneity, pleiotropy and F-statistics analysis

Neurodegenerative diseases	No. of SNPs	Heterogeneity analysis			Pleiotropy analysis			MR-PRESSO				Leave-one-out analysis	F-statistics
		Method	Q	P	Egger intercept	SE	P	Global test (P)	Outlier test	Distortion test (P)	Outlier-corrected P		
Late-onset AD	131	MR Egger	201.419	4.71E-05	0.002	0.003	0.553	<0.001	No outliers	NA	NA	No	162.09
		IVW	201.971	5.37E-05									
Maternal AD	130	MR Egger	160.291	0.028	0.002	0.004	0.588	0.044	No outliers	NA	NA	No	153.85
		IVW	160.66	0.031									
Paternal AD	130	MR Egger	102.755	9.51E-01	2.39E-04	0.005	0.959	0.953	NA	NA	NA	No	153.85
		IVW	102.758	9.57E-01									
PD	130	MR Egger	202.163	3.20E-05	0.005	0.004	0.309	0.202	NA	NA	NA	No	153.85
		IVW	203.811	2.96E-05									
ALS	131	MR Egger	155.66	0.055	-0.004	0.003	0.144	0.051	NA	NA	NA	rs9892297	166.54
		IVW	158.268	0.046									
MS	125	MR Egger	966.791	5.13E-131	0.006	0.009	0.478	<0.001	rs10069690, rs10838681 rs12569576, rs17826544, rs2618566, rs2642420, rs62580767, rs6736913, rs7694379, rs7994151	0.038	0.465	No	166.54
		IVW	970.77	2.53E-131									
DLB	122	MR Egger	127.707	0.298	−0.018	0.007	0.014	0.189	NA	NA	NA	No	146.97
		IVW	134.263	0.193									
FTD	109	MR Egger	105.083	0.534	0.011	0.009	0.203	0.534	NA	NA	NA	No	158.91
		IVW	106.726	0.517									

SNP, single nucleotide polymorphism; MR, Mendelian randomization; IVW, inverse-variance weighted; SE, standard error; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; DLB, Dementia with Lewy Bodies; FTD frontotemporal dementia; NA, not available.

existed in the causal effect estimates for maternal AD (P for MR Egger =0.028, P for IVW =0.031; P for MR-PRESSO global test =0.044). There was no distortion in the leave-one-out and single-SNP plots, suggesting that no single SNP was driving the observed effect in any of the analyses (Figures S4-S6). The F-statistics for the three association pairs were 162.19, 153.85, and 153.85.

Genetically determined serum SHBG and other neurodegenerative diseases

The IVW method failed to support a causal relationship between serum SHBG and PD, with an OR of 1.020 (95% CI: 0.891–1.169, P=0.772; SNPs =130; *Figure 3*, Figure S1). This effect was supported by the weighted mode method (OR =0.831, 95% CI: 0.683–1.010, P=0.065). Additional analyses (LD R^2<0.001) using MR-Egger (OR =795, 95% CI: 0.638–0.990, P=0.042; SNPs =193) and weighted mode (OR =0.827, 95% CI: 0.700–0.977, P=0.027; SNPs =193) methods showed a supportive association (Figures S2,S3). Evidence for the heterogeneity of effect sizes (P for MR Egger =3.20E-05, P for IVW =2.96E-05; *Table 1*) was revealed. Nonetheless, horizontal pleiotropic effects were absent (intercept: 0.005, P=0.309; P for the MR-PRESSO global test =0.202). We did not find a single genetic variant of SHBG that influenced the association in the leave-one-out analysis (Figure S7). The F-statistic value was 153.85.

Interestingly, the results showed a statistically significant causal effect of genetically predicted serum SHBG levels on ALS (OR_{IVW} =1.113, 95% CI: 1.019–1.215, P=0.017; *Figure 3*, Figure S1). The causal effect was confirmed by sensitivity analyses including MR-Egger ($OR_{MR\text{-}Egger}$ =1.229, 95% CI: 1.049–1.441, P=0.012), weighted median ($OR_{weighted\ median}$ =1.231, 95% CI: 1.077–1.406, P=0.002), and weighted mode ($OR_{weighted\ mode}$ =1.235, 95% CI: 1.067–1.431, P=0.005) methods (Figures S2,S3). Almost no evidence of heterogeneity of effect sizes (P for MR Egger =0.055, P for IVW =0.046; *Table 1*) or directional pleiotropy (intercept: −0.004, P=0.144; P for MR-PRESSO global test =0.051) was found. However, rs9892297 significantly drove the overall direction (Figure S8). The F statistics of 166.54 indicated that the association was less likely to be affected by weak instrumental bias.

No causal effects of SHBG on MS (125 SNPs), DLB (122 SNPs), or FTD (109 SNPs) were observed (*Figure 3*, Figure S1). Additional analyses supported these findings (Figures S2,S3). Cochran's Q statistics (P for MR Egger =5.13E-131, P for IVW =2.53E-131) indicated notable heterogeneity across instrument SNP effects for MS (*Table 1*). The MR-PRESSO global test indicated pleiotropy (P<0.001). Although several outliers were identified, the overall null causal effect remained unchanged. Directional pleiotropy by Egger analysis was found for DLB (intercept: −0.018, P=0.014). No heterogeneity or pleiotropy was detected in the FTD analysis (all P>0.05). No single SNP was found to drive the above associations (Figures S9-S11). The F-statistics for the three association pairs were 166.54, 146.97, and 158.91, respectively.

Discussion

To the best of our knowledge, this is the first two-sample MR study to examine the causal associations between serum SHBG levels and several common neurodegenerative diseases. We revealed that genetically predicted serum SHBG levels were associated with the risk of developing ALS but did not provide solid MR evidence to support the causal effects on AD (including maternal and paternal family history of AD), PD, MS, DLB, or FTD. These results should be interpreted with caution, given that some of our results may be driven by genetic pleiotropy and heterogeneity. However, the consistency of our results across MR methods strengthens our inference of causality. Overall, these results will help interpret the results from current observational studies and indicate the direction of future application of hormone replacement therapy (HRT).

Our MR study revealed the deleterious effects of SHBG on ALS. Few observational studies have explored the association between SHBG and ALS. ALS is a progressive neurodegenerative disorder characterized by the involvement of both upper and lower motor neurons (32). It has been postulated that testosterone may play a role in ALS (8). In patients susceptible to ALS, there is possibly a sort of "testosterone resistance" at the level of the blood-brain barrier (BBB) commencing from birth (8). In these patients, testosterone at low levels can penetrate the BBB and enter the central neural axis. Then, 5 α-reductase in the anterior pituitary converts testosterone into dihydrotestosterone (DHT). DHT deficiency can lead to motor neuron death, ultimately leading to ALS. SHBG is a major factor controlling the balance between biologically active sex hormones (4). Higher SHBG levels are associated with lower levels of biologically active free testosterone. Obviously, with advancing age, the circadian excursion in free non-SHBG-binding testosterone declines, resulting

in a decrease in free testosterone available for intracerebral transport. Thus, susceptibility to ALS increases in individuals with BBB "testosterone resistance" (4). This is probably the reason for the increased incidence of ALS with age. To our knowledge, this is the first MR study to use genetic instruments, showing that genetically determined serum SHBG levels are causally associated with ALS. Our study sheds light on the causal relationship between SHBG and ALS, and highlights the potential of SHBG as a biomarker for ALS.

Accumulating observational studies have revealed significant associations between SHBG and AD risk (6) and pathologies (5,33). Nevertheless, the present MR analysis failed to support causality. We acknowledge several reasons for this finding. First, previous observational studies may have been affected by reverse causality and confounding bias (9). Increased SHBG levels are a surrogate marker for other known risk factors for dementia, especially age (34). Furthermore, many previous studies have demonstrated that high SHBG levels are associated with smoking, alcohol intake, lower physical activity, hyperinsulinemia, and metabolic syndrome (35,36), all of which have been reported to be related to AD development. Thus, it may be useful to consider SHBG as an early indicator of AD rather than as a direct modifier of AD risk. Second, the relationship between SHBG and AD may be complex and nonlinear, and could not be fully explored in our study. Thus, SHBG may exert stronger effects on later disease development. The association between SHBG and these diseases also largely depends on heterogeneous features (e.g., age, sex, and HRT). Therefore, further detailed studies are warranted. Third, the strength of current genetic variants may have contributed to discrepancies between phenotypic and MR associations, and the results may require updating as new genetic discoveries become available. Although previous observational studies have highlighted the association between serum SHBG and incident AD, it was not supported in the MR analysis.

Apart from AD, other null results should be interpreted with caution. The prevalence of PD is 1.5 times higher in men than in women (37). This evident sex difference in the occurrence of the disease suggests that sex hormones may alter an individual's susceptibility to the disease (38). However, a previous Polish study revealed no difference in SHBG levels between patients with PD (N=36) and healthy controls (N=69) (7). Therefore, further research is required to explore the effects of sex hormones and SHBG on PD. To the best of our knowledge, few studies have investigated the effects of SHBG on MS, DLB, and FTD, and these associations warrant further investigation.

There are significant sex differences in the onset and progression of neurodegenerative diseases (39,40). Estrogens have been reported to exert neuroprotective effects through their action on cognate nuclear and membrane receptors (39). In the brain, sex hormones might affect a variety of signaling pathways, including catecholaminergic and acetylcholine pathways, which regulate cognition, motor, emotion, and other functions (41). Correspondingly, sex hormone receptors can induce various signaling cascades that mediate sex differences in neurodegenerative disorders (42). Furthermore, the preventive effects of HRT on cognitive impairment and dementia have been extensively studied (43). Unfortunately, these trials were not successful. Previous randomized controlled trials (RCTs) tended to focus on hormones (44,45) and rarely considered hormone transporters such as SHBG. Our MR research systematically interpreted the relationship between SHBG and neurodegenerative diseases, extending traditional observational associations to gene-mediated causality. It may be crucial for SHBG to be more widely included as a measure, along with other blood biomarkers, in hormone therapy studies or clinical trials.

Our study had several limitations that merit consideration. First, to avoid horizontal pleiotropy, a general challenge for MR, we used MR-PRESSO and MR-Egger regressions to estimate the extent to which heterogeneity and pleiotropy may bias the reported results. However, the possibility of heterogeneity and pleiotropy cannot be ruled out. Second, we cannot exclude the possibility of inflating the type 1 error rate because there were overlaps between exposure GWAS and outcome GWASs, especially for maternal and paternal family histories of AD. Third, it is important to recognize that MR measures the cumulative effect of lifelong exposure to genetic variants related to serum SHBG levels, unlike studies of the effects of discrete clinical interventions in adult life. Therefore, these MR results should not be extrapolated to determine the effect of SHBG on outcomes at a particular time period. Finally, the serum SHBG data were extracted from the UK biobank, a more educated, less deprived cohort, whose age range was 40–70 years, and thus might have poor representativeness of the UK general population. Moreover, since the majority of participants were of European ancestry, the results of this study are not necessarily applicable to other ethnicities.

Conclusions

Our findings highlight the important role of serum SHBG levels in neurodegenerative diseases, particularly ALS. Since the evaluation of sex hormones and SHBG in peripheral blood can be readily performed, they have the potential to be useful screening biomarkers for aging-related diseases. Further research is required regarding to study the role of SHBG, especially because of the increasing utilization of hormone therapy.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1156/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1156/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The current analyses based on publicly available summary data and therefore does not require ethical approval. Original studies have been approved by ethic committees and written informed consent was obtained from study participants or caregivers. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Table S1 Basic characteristics of included GWASs used in the present MR analysis

GWAS type	PMID	Sources	Sample size (case/control)	Phenotype ascertainment
SHBG	33462484	UK Biobank	363,228	Detected by Chemiluminescent immunoassay
Late-onset AD	30820047	-	21,982/41,994	-
		ADGC	14,428/14,562	Autopsy-confirmed or clinically-confirmed
		CHARGE	2,137/13,474	Autopsy-confirmed or clinically-confirmed
		EADI	2,240/6,631	Autopsy-confirmed or clinically-confirmed
		GERAD/PERADES	3,177/7,277	Autopsy-confirmed or clinically-confirmed
Paternal AD	29777097	UK Biobank	14,338/245,941	Self-reported
Maternal AD	29777097	UK Biobank	27,696/260,980	Self-reported
PD	31701892	Nalls and colleagues	13,708/95,282	Clinically-confirmed
		IPDGC-NeuroX	5,851/5,866	Clinically-confirmed
		PDWBS	6,476/302,042	Clinically-confirmed
		UK Biobank	18,618/436,419	Self-reported
		SGPD	1,169/968	Clinically-confirmed
		IPDGC	8,036/5,803	Clinically-confirmed
		Post-Chang, 23andMe	2,448/571,411	Clinically-confirmed
ALS	29566793	-	20,806/59,804	-
		Italy	2,853/2,143	Clinically-confirmed
		United Kingdom	449/226	Clinically-confirmed
		Belgium/France	1,150/595	Clinically-confirmed
		USA	3,777/33,365	Clinically-confirmed
		Van Rheenen Study	12,577/23,475	Clinically-confirmed
MS	31604244	International Multiple Sclerosis Genetics Consortium	47,429/68,374	Clinically-confirmed
DLB	33589841	44 institutions/consortia	2,981/4,391	Clinically-confirmed or pathologically-confirmed
FTD	24943344	44 international research groups	3,526/9,402	Clinically-confirmed or pathologically-confirmed

SHBG, serum sex hormone binding protein; GWAS, Genome wide association study; MR, Mendelian randomization; ADGC, Alzheimer Disease Genetics Consortium; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; EADI, Genetic and Environmental Risk in AD/Defining Genetic; GERAD/PERADES, Polygenic and Environmental Risk for Alzheimer's Disease Consortium; UKB, UK Biobank; IPDGC, International Parkinson's Disease Genomics Consortium; PDWBS, Parkinson's disease web-based study; SGPD, Systems genomics of Parkinson's disease consortium; IPDGC, International Parkinson's Disease Genomics Consortium; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; DLB, Dementia with Lewy Bodies; FTD, frontotemporal dementia.

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Table S2 SNP identified in AD GWAS

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs10069690	T	C	NA	NA	-0.017	0.0028	2.13E-09	-0.0322	0.0215	0.1336
rs1060817	G	A	NA	NA	-0.0176	0.0025	5.12E-12	-0.0065	0.0147	0.6587
rs1076540	T	C	NA	NA	0.0169	0.0029	8.14E-09	0.0031	0.0168	0.8532
rs10838681	A	G	NA	NA	0.0162	0.0028	8.80E-09	0.0045	0.0165	0.7842
rs10871777	G	A	NA	NA	-0.0227	0.0029	8.41E-15	-0.0347	0.0168	0.03837
rs1106766	T	C	NA	NA	0.0357	0.0029	5.41E-34	0.0018	0.0171	0.9168
rs11075253	A	C	NA	NA	0.023	0.0028	6.30E-17	-0.0112	0.0159	0.48
rs11078405	T	G	NA	NA	-0.0293	0.0026	1.40E-29	-0.0324	0.0146	0.02596
rs1126670	A	C	NA	NA	-0.028	0.0027	1.35E-24	0.029	0.0156	0.06277
rs1128249	T	G	NA	NA	0.0286	0.0026	8.43E-29	-0.02	0.0145	0.1672
rs11550348	A	G	NA	NA	0.0536	0.0038	5.40E-46	-5.00E-04	0.0224	0.9816
rs116189680	A	G	NA	NA	0.1439	0.0077	6.52E-78	0.0036	0.059	0.9519
rs11626364	C	T	NA	NA	0.0237	0.0035	9.61E-12	0.0124	0.0199	0.5315
rs11636917	C	T	NA	NA	-0.0247	0.0026	1.06E-20	0.0315	0.0149	0.03406
rs11647008	C	T	NA	NA	-0.0249	0.0025	6.86E-23	0.0034	0.0144	0.8111
rs11655704	C	T	NA	NA	0.0785	0.0027	1.30E-189	-0.0124	0.0156	0.4284
rs11739158	T	C	NA	NA	0.0148	0.0025	4.85E-09	0.003	0.0143	0.8352
rs11748288	G	A	NA	NA	0.0167	0.0025	5.85E-11	0.0407	0.0145	0.005182
rs1183910	A	G	NA	NA	-0.0261	0.0027	6.73E-22	-0.0073	0.0154	0.638
rs11856886	G	A	NA	NA	0.0194	0.0027	1.27E-12	-0.0504	0.0155	0.001162
rs11887329	G	A	NA	NA	-0.0213	0.003	7.13E-13	-0.0108	0.0168	0.5217
rs11918018	A	G	NA	NA	-0.0153	0.0025	1.03E-09	0.0025	0.0143	0.8634
rs11935444	C	T	NA	NA	-0.0165	0.0026	4.11E-10	-0.0304	0.0144	0.03545
rs12192649	A	G	NA	NA	0.022	0.003	9.97E-14	-0.0021	0.0172	0.9039
rs12325400	G	C	NA	NA	-0.016	0.0026	4.03E-10	-0.0402	0.0148	0.006624
rs12414178	T	C	NA	NA	-0.0269	0.0029	5.57E-20	0.002	0.0169	0.9066
rs12569576	G	A	NA	NA	-0.017	0.0025	1.25E-11	0.006	0.0145	0.6804
rs12575636	G	T	NA	NA	-0.027	0.0033	1.36E-16	0.0294	0.0182	0.1055
rs1260326	C	T	NA	NA	0.0772	0.0026	4.58E-198	-0.0147	0.0145	0.3099
rs12748152	T	C	NA	NA	-0.0668	0.0046	2.79E-47	0.0207	0.0265	0.4358
rs12941564	G	C	NA	NA	0.0239	0.0028	1.31E-17	0.0205	0.0159	0.1952
rs13094241	G	T	NA	NA	0.0172	0.0028	1.04E-09	0.0194	0.0164	0.2364
rs13354321	C	T	NA	NA	0.0144	0.0025	1.44E-08	0.0144	0.015	0.3379
rs1421085	C	T	NA	NA	-0.0183	0.0026	8.91E-13	0.0026	0.0145	0.8601
rs1497406	G	A	NA	NA	0.027	0.0025	1.56E-26	0.0058	0.0145	0.69
rs1547014	C	T	NA	NA	-0.0293	0.0027	5.70E-28	-0.0283	0.0155	0.06867
rs1556562	T	G	NA	NA	0.0243	0.003	8.54E-16	-0.0262	0.0176	0.1379
rs157934	C	T	NA	NA	0.0229	0.0027	4.25E-17	-0.0216	0.0158	0.1702
rs1635852	C	T	NA	NA	0.0187	0.0025	6.54E-14	0.0376	0.0142	0.00836
rs16845803	G	A	NA	NA	-0.0251	0.0037	1.08E-11	0.0497	0.021	0.01808
rs17041868	C	T	NA	NA	-0.0346	0.005	6.49E-12	0.0232	0.0301	0.4405
rs1716403	C	T	NA	NA	-0.0168	0.0027	3.75E-10	0.0205	0.0153	0.1806
rs17202341	G	A	NA	NA	0.0157	0.0026	2.86E-09	-0.0157	0.015	0.296
rs17377148	G	T	NA	NA	0.0401	0.0048	1.13E-16	-0.029	0.0291	0.319
rs174601	T	C	NA	NA	-0.0252	0.0026	1.80E-22	-0.0032	0.0154	0.8335
rs1755618	T	G	NA	NA	-0.0252	0.0035	1.17E-12	0.0231	0.0215	0.2819
rs17580	A	T	NA	NA	0.0535	0.0059	1.54E-19	0.0636	0.0331	0.05506
rs17628931	C	T	NA	NA	0.0294	0.0041	4.71E-13	-0.0267	0.0228	0.2433
rs1772183	A	G	NA	NA	-0.022	0.0025	1.30E-18	-0.0026	0.0142	0.8518
rs17794619	A	G	NA	NA	-0.0347	0.0037	3.61E-21	0.0029	0.021	0.889
rs17826544	G	A	NA	NA	0.029	0.0026	3.87E-29	-0.0337	0.0148	0.02224
rs1801282	G	C	NA	NA	0.0377	0.0039	1.41E-22	-0.0267	0.022	0.2236
rs1801689	C	A	NA	NA	-0.0912	0.0074	6.69E-35	-0.0572	0.0465	0.2192
rs1832007	G	A	NA	NA	-0.0483	0.0035	3.66E-43	-0.0194	0.02	0.3328
rs1935	G	C	NA	NA	0.1198	0.0025	1.00E-200	-0.012	0.0142	0.3991
rs1982151	G	A	NA	NA	-0.049	0.0028	9.23E-67	0.0233	0.0161	0.1478
rs2081687	C	T	NA	NA	0.0247	0.0026	1.03E-20	0.0013	0.015	0.9326
rs2205262	A	C	NA	NA	-0.0167	0.0025	4.00E-11	-0.0309	0.0144	0.0323
rs2254069	A	G	NA	NA	-0.0265	0.0038	2.11E-12	0.0234	0.022	0.286
rs2266782	A	G	NA	NA	-0.0163	0.0025	1.25E-10	-0.0025	0.0145	0.8605
rs2335077	G	A	NA	NA	0.0463	0.0026	1.71E-69	-0.0043	0.0151	0.7761
rs2427530	A	G	NA	NA	0.0194	0.0029	2.99E-11	0.0263	0.0169	0.1196
rs2487826	C	T	NA	NA	0.0176	0.0025	3.56E-12	-0.0077	0.0143	0.592
rs2537855	G	A	NA	NA	0.0447	0.0028	3.56E-59	-0.0063	0.016	0.695
rs2618566	T	G	NA	NA	-0.0171	0.0026	8.57E-11	-0.0163	0.0154	0.292
rs2642420	A	C	NA	NA	-0.0247	0.0033	9.54E-14	-0.0295	0.0188	0.1176
rs2836950	G	C	NA	NA	-0.0154	0.0026	3.64E-09	-0.0052	0.0149	0.7274
rs2860075	G	A	NA	NA	-0.0289	0.0026	1.40E-28	-0.0187	0.0149	0.2105
rs28925904	T	C	NA	NA	-0.0576	0.0081	1.49E-12	0.0718	0.0595	0.2275
rs28929474	T	C	NA	NA	0.219	0.0091	5.87E-129	-0.0678	0.0562	0.2274
rs2943641	C	T	NA	NA	-0.0322	0.0026	6.16E-35	0.0123	0.0147	0.4024

Table S2 (*continued*)

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Table S2 (*continued*)

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs3132469	G	A	NA	NA	-0.033	0.0035	8.29E-21	-0.0492	0.0219	0.02476
rs34145453	G	A	NA	NA	0.0189	0.0026	2.90E-13	0.0188	0.0151	0.2138
rs34372369	A	G	NA	NA	0.037	0.0057	6.20E-11	-0.0137	0.0341	0.6869
rs35371479	T	C	NA	NA	0.0256	0.0033	7.00E-15	-0.0075	0.0182	0.6777
rs35386490	C	T	NA	NA	0.1118	0.003	1.00E-200	0.0271	0.022	0.2188
rs35627524	G	T	NA	NA	-0.0433	0.0067	1.09E-10	0.0337	0.0396	0.3949
rs3749237	A	G	NA	NA	-0.0257	0.0027	8.87E-22	-0.0094	0.0154	0.5388
rs3779195	A	T	NA	NA	-0.0768	0.0032	2.35E-126	-0.0019	0.0185	0.9191
rs3818247	T	G	NA	NA	-0.0247	0.0026	2.95E-21	-0.0084	0.0165	0.61
rs3848375	T	C	NA	NA	0.0231	0.0032	3.11E-13	-0.0253	0.0182	0.164
rs41302867	A	G	NA	NA	-0.0342	0.0039	8.26E-19	-0.0101	0.0225	0.6524
rs4149056	C	T	NA	NA	-0.067	0.0035	9.39E-81	0.0074	0.0198	0.7085
rs4381968	T	C	NA	NA	-0.0138	0.0025	4.23E-08	0.0092	0.0148	0.5345
rs440837	G	A	NA	NA	0.0466	0.0031	1.16E-50	0.0251	0.0171	0.1414
rs45512696	T	C	NA	NA	0.0407	0.0033	2.72E-34	-0.0012	0.0196	0.9494
rs45535039	C	T	NA	NA	0.0204	0.0028	3.34E-13	0.0064	0.016	0.6915
rs4639796	A	G	NA	NA	-0.0296	0.0034	3.23E-18	0.0078	0.0194	0.689
rs464605	T	C	NA	NA	-0.0323	0.0029	1.25E-29	0.0027	0.0167	0.8727
rs4660293	G	A	NA	NA	-0.0295	0.003	5.90E-23	0.0149	0.0167	0.3717
rs4690098	T	C	NA	NA	-0.0498	0.003	1.01E-61	-0.011	0.0175	0.5308
rs4822455	T	C	NA	NA	-0.0184	0.0025	3.48E-13	0.0055	0.0145	0.705
rs4983559	A	G	NA	NA	-0.0179	0.0026	2.85E-12	0.0213	0.0148	0.1489
rs555754	A	G	NA	NA	0.0343	0.0025	5.02E-42	0.0318	0.0143	0.02598
rs55707100	T	C	NA	NA	-0.1171	0.0081	1.76E-47	0.0253	0.0392	0.5184
rs55840085	A	G	NA	NA	0.0195	0.0026	6.35E-14	-0.0326	0.0153	0.03391
rs56196860	A	C	NA	NA	0.0478	0.0073	5.01E-11	0.0015	0.055	0.9788
rs5745687	T	C	NA	NA	0.0307	0.0051	2.07E-09	0.0158	0.0281	0.5739
rs57506806	G	A	NA	NA	0.0351	0.003	2.25E-32	-0.0162	0.0175	0.3548
rs58941251	T	C	NA	NA	-0.0241	0.0041	2.74E-09	0.0226	0.0229	0.3232
rs6129800	A	G	NA	NA	0.0239	0.003	1.35E-15	-0.0277	0.0177	0.1166
rs61935507	T	C	NA	NA	-0.0295	0.0037	1.50E-15	-0.0435	0.0217	0.04533
rs62576339	C	T	NA	NA	0.03	0.0029	8.22E-25	0.0309	0.0173	0.07435
rs62580767	C	T	NA	NA	0.0234	0.0033	8.54E-13	-0.0116	0.0186	0.5305
rs62618693	T	C	NA	NA	0.041	0.0061	1.93E-11	0.0205	0.0389	0.5985
rs6356	T	C	NA	NA	0.0199	0.0026	2.43E-14	0.0055	0.0154	0.7215
rs645040	T	G	NA	NA	-0.0691	0.003	9.86E-120	-0.035	0.017	0.03902
rs6736913	G	A	NA	NA	-0.0712	0.0089	1.12E-15	0.0521	0.0607	0.3909
rs6756943	A	G	NA	NA	-0.0448	0.0027	5.62E-61	0.0137	0.0156	0.3829
rs6954673	T	C	NA	NA	-0.0185	0.0026	1.27E-12	0.0137	0.0149	0.36
rs7221345	A	G	NA	NA	-0.0325	0.0026	3.13E-37	-0.0436	0.0147	0.003118
rs7239151	A	G	NA	NA	0.0155	0.0027	6.50E-09	0.0085	0.0156	0.5884
rs724577	C	A	NA	NA	-0.0186	0.0028	6.04E-11	0.0197	0.0162	0.2234
rs7250351	A	G	NA	NA	0.0229	0.0041	2.17E-08	-0.0131	0.026	0.6141
rs7250425	T	C	NA	NA	0.0179	0.0025	7.64E-13	-0.0091	0.0143	0.5266
rs72683923	C	T	NA	NA	0.0774	0.0092	5.67E-17	-0.1035	0.0504	0.03993
rs72756074	G	A	NA	NA	0.023	0.0038	1.65E-09	-0.044	0.0223	0.04856
rs7314285	G	T	NA	NA	0.0764	0.0048	3.82E-56	0.0525	0.0287	0.06707
rs738409	G	C	NA	NA	0.0486	0.003	5.06E-58	-0.0115	0.0176	0.5138
rs7429135	G	T	NA	NA	0.0199	0.0034	5.92E-09	-0.0107	0.0193	0.5778
rs750472	C	A	NA	NA	-0.0216	0.0025	4.22E-18	-0.0029	0.0146	0.84
rs76610881	G	A	NA	NA	0.0418	0.0041	7.29E-25	-0.05	0.026	0.05442
rs7694379	A	G	NA	NA	-0.042	0.0025	4.75E-62	-0.0142	0.0144	0.3236
rs7697204	T	C	NA	NA	-0.0295	0.0028	4.24E-25	0.0306	0.0162	0.05929
rs78025076	T	C	NA	NA	0.0503	0.0089	1.62E-08	-5.00E-04	0.0599	0.9927
rs78444298	A	G	NA	NA	-0.0613	0.0093	5.44E-11	-0.0322	0.0671	0.6314
rs7922067	A	G	NA	NA	-0.0211	0.0025	1.18E-16	0.0043	0.0146	0.7668
rs7947951	G	A	NA	NA	-0.0283	0.0027	9.37E-26	0.0308	0.0153	0.04386
rs7994151	G	A	NA	NA	-0.0206	0.0035	2.89E-09	-0.0116	0.02	0.5602
rs8017377	A	G	NA	NA	-0.0342	0.0025	3.92E-42	0.0025	0.0146	0.8614
rs8023580	C	T	NA	NA	0.073	0.0028	1.52E-150	-0.0196	0.016	0.2196
rs9316500	G	T	NA	NA	-0.0172	0.0027	3.05E-10	-0.0203	0.0154	0.1878
rs9332817	C	G	NA	NA	0.05	0.0079	3.09E-10	0.0029	0.0515	0.9553
rs9388768	A	C	NA	NA	-0.0197	0.0027	1.39E-13	0.0032	0.0153	0.8341
rs9427104	T	C	NA	NA	0.027	0.0025	4.04E-27	0.0102	0.0142	0.4726
rs9556403	G	A	NA	NA	0.0205	0.0026	4.66E-15	0.0097	0.0148	0.5152
rs9644032	G	T	NA	NA	-0.0159	0.0026	1.03E-09	0.0165	0.0151	0.2729
rs976002	G	A	NA	NA	0.035	0.0029	1.60E-33	-0.04	0.0208	0.05491
rs9892297	G	A	NA	NA	-0.1366	0.0026	1.00E-200	0.0206	0.0156	0.1862
rs9987289	G	A	NA	NA	0.0437	0.0043	3.22E-24	-0.027	0.0256	0.2921

SNP, single nucleotide polymorphism; AD, Alzheimer's disease; GWAS, genome-wide association studies; NA, not available.

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Table S3 SNPs identified in maternal AD GWAS

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs10069690	T	C	NA	NA	-0.017	0.0028	2.13E-09	-0.04975	0.020069	0.013183
rs1060817	G	A	NA	NA	-0.0176	0.0025	5.12E-12	0.011114	0.017727	0.530698
rs1076540	T	C	NA	NA	0.0169	0.0029	8.14E-09	-0.03771	0.020537	0.066347
rs10838681	A	G	NA	NA	0.0162	0.0028	8.80E-09	-0.02157	0.019742	0.274476
rs10871777	G	A	NA	NA	-0.0227	0.0029	8.41E-15	0.00919	0.02051	0.654094
rs1106766	T	C	NA	NA	0.0357	0.0029	5.41E-34	0.00723	0.020317	0.721935
rs11075253	A	C	NA	NA	0.023	0.0028	6.30E-17	0.009964	0.019106	0.602009
rs11078405	T	G	NA	NA	-0.0293	0.0026	1.40E-29	-0.06038	0.018153	0.00088
rs1126670	A	C	NA	NA	-0.028	0.0027	1.35E-24	0.042508	0.019103	0.026072
rs1128249	T	G	NA	NA	0.0286	0.0026	8.43E-29	-0.00314	0.017889	0.860462
rs11550348	A	G	NA	NA	0.0536	0.0038	5.40E-46	0.012394	0.02658	0.641011
rs116189680	A	G	NA	NA	0.1439	0.0077	6.52E-78	0.059445	0.05313	0.263204
rs11626364	C	T	NA	NA	0.0237	0.0035	9.61E-12	-0.00935	0.024285	0.700375
rs11636917	C	T	NA	NA	-0.0247	0.0026	1.06E-20	-0.00127	0.018388	0.944799
rs11647008	C	T	NA	NA	-0.0249	0.0025	6.86E-23	0.002747	0.017494	0.875211
rs11655704	C	T	NA	NA	0.0785	0.0027	1.30E-189	-0.00822	0.018772	0.661595
rs11739158	T	C	NA	NA	0.0148	0.0025	4.85E-09	0.030774	0.017659	0.08138
rs11748288	G	A	NA	NA	0.0167	0.0025	5.85E-11	0.035954	0.017768	0.04302
rs1183910	A	G	NA	NA	-0.0261	0.0027	6.73E-22	-0.02844	0.018986	0.134127
rs11856886	G	A	NA	NA	0.0194	0.0027	1.27E-12	-0.02242	0.018997	0.237999
rs11887329	G	A	NA	NA	-0.0213	0.003	7.13E-13	0.04302	0.020576	0.036543
rs11918018	A	G	NA	NA	-0.0153	0.0025	1.03E-09	-0.00128	0.017497	0.941567
rs11935444	C	T	NA	NA	-0.0165	0.0026	4.11E-10	-0.02784	0.017681	0.115325
rs12192649	A	G	NA	NA	0.022	0.003	9.97E-14	0.007127	0.020465	0.727665
rs12325400	G	C	NA	NA	-0.016	0.0026	4.03E-10	-0.05864	0.017852	0.00102
rs12414178	T	C	NA	NA	-0.0269	0.0029	5.57E-20	0.020264	0.02059	0.325038
rs12569576	G	A	NA	NA	-0.017	0.0025	1.25E-11	0.017522	0.017551	0.318111
rs12575636	G	T	NA	NA	-0.027	0.0033	1.36E-16	0.010212	0.022352	0.647784
rs1260326	C	T	NA	NA	0.0772	0.0026	4.58E-198	-0.02535	0.017866	0.155885
rs12748152	T	C	NA	NA	-0.0668	0.0046	2.79E-47	-0.05651	0.032357	0.080711
rs13094241	G	T	NA	NA	0.0172	0.0028	1.04E-09	0.028171	0.019659	0.151856
rs13354321	C	T	NA	NA	0.0144	0.0025	1.44E-08	-0.01184	0.017704	0.503463
rs1421085	C	T	NA	NA	-0.0183	0.0026	8.91E-13	-0.00103	0.017845	0.954007
rs1497406	G	A	NA	NA	0.027	0.0025	1.56E-26	0.009239	0.017692	0.601512
rs1547014	C	T	NA	NA	-0.0293	0.0027	5.70E-28	-0.01447	0.018588	0.436271
rs1556562	T	G	NA	NA	0.0243	0.003	8.54E-16	0.023992	0.020888	0.250723
rs157934	C	T	NA	NA	0.0229	0.0027	4.25E-17	0.041666	0.018926	0.027695
rs1635852	C	T	NA	NA	0.0187	0.0025	6.54E-14	0.037209	0.017447	0.032952
rs16845803	G	A	NA	NA	-0.0251	0.0037	1.08E-11	0.037215	0.02577	0.148706
rs17041868	C	T	NA	NA	-0.0346	0.005	6.49E-12	0.006253	0.035595	0.860559
rs1716403	C	T	NA	NA	-0.0168	0.0027	3.75E-10	0.000292	0.018711	0.987564
rs17202341	G	A	NA	NA	0.0157	0.0026	2.86E-09	-0.04017	0.018355	0.028618
rs17377148	G	T	NA	NA	0.0401	0.0048	1.13E-16	0.013581	0.033107	0.681663
rs174601	T	C	NA	NA	-0.0252	0.0026	1.80E-22	-0.0187	0.018059	0.300449
rs1755618	T	G	NA	NA	-0.0252	0.0035	1.17E-12	0.009397	0.025121	0.708361
rs17580	A	T	NA	NA	0.0535	0.0059	1.54E-19	0.032912	0.040338	0.414556
rs17628931	C	T	NA	NA	0.0294	0.0041	4.71E-13	0.034494	0.027983	0.217693
rs1772183	A	G	NA	NA	-0.022	0.0025	1.30E-18	-0.02406	0.017482	0.168719
rs17794619	A	G	NA	NA	-0.0347	0.0037	3.61E-21	0.017153	0.025239	0.496728
rs17826544	G	A	NA	NA	0.029	0.0026	3.87E-29	-0.01124	0.017917	0.530472
rs1801282	G	C	NA	NA	0.0377	0.0039	1.41E-22	-0.0397	0.027007	0.141575
rs1801689	C	A	NA	NA	-0.0912	0.0074	6.69E-35	0.039163	0.051242	0.444705
rs1832007	G	A	NA	NA	-0.0483	0.0035	3.66E-43	-0.01493	0.02418	0.536866
rs1935	G	C	NA	NA	0.1198	0.0025	1.00E-200	-0.01143	0.017513	0.514074
rs1982151	G	A	NA	NA	-0.049	0.0028	9.23E-67	0.00278	0.020023	0.889559
rs2081687	C	T	NA	NA	0.0247	0.0026	1.03E-20	0.025985	0.018514	0.160452
rs2205262	A	C	NA	NA	-0.0167	0.0025	4.00E-11	-0.01439	0.017643	0.41474
rs2254069	A	G	NA	NA	-0.0265	0.0038	2.11E-12	-0.02883	0.02696	0.28482
rs2266782	A	G	NA	NA	-0.0163	0.0025	1.25E-10	0.005005	0.017706	0.777443
rs2335077	G	A	NA	NA	0.0463	0.0026	1.71E-69	-0.01536	0.018375	0.403286
rs2427530	A	G	NA	NA	0.0194	0.0029	2.99E-11	0.032276	0.020215	0.110356
rs2487826	C	T	NA	NA	0.0176	0.0025	3.56E-12	0.003413	0.017699	0.847065
rs2537855	G	A	NA	NA	0.0447	0.0028	3.56E-59	0.002748	0.019308	0.886805
rs2618566	T	G	NA	NA	-0.0171	0.0026	8.57E-11	-0.00288	0.018439	0.875742
rs2642420	A	C	NA	NA	-0.0247	0.0033	9.54E-14	0.02142	0.023035	0.352429
rs2836950	G	C	NA	NA	-0.0154	0.0026	3.64E-09	-0.01037	0.018258	0.56994
rs2860075	G	A	NA	NA	-0.0289	0.0026	1.40E-28	-0.02624	0.018203	0.149397
rs28925904	T	C	NA	NA	-0.0576	0.0081	1.49E-12	0.049009	0.055511	0.377306
rs28929474	T	C	NA	NA	0.219	0.0091	5.87E-129	-0.07902	0.06239	0.205299
rs2943641	C	T	NA	NA	-0.0322	0.0026	6.16E-35	0.02516	0.018311	0.169429
rs3132469	G	A	NA	NA	-0.033	0.0035	8.29E-21	-0.0687	0.024243	0.004601

Table S3 (*continued*)

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Table S3 (*continued*)

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs34145453	G	A	NA	NA	0.0189	0.0026	2.90E-13	-0.01572	0.018144	0.386369
rs34372369	A	G	NA	NA	0.037	0.0057	6.20E-11	-0.02866	0.039921	0.472773
rs35371479	T	C	NA	NA	0.0256	0.0033	7.00E-15	-0.00291	0.022764	0.898447
rs35627524	G	T	NA	NA	-0.0433	0.0067	1.09E-10	-0.00499	0.046822	0.915169
rs3749237	A	G	NA	NA	-0.0257	0.0027	8.87E-22	0.031401	0.018598	0.091345
rs3779195	A	T	NA	NA	-0.0768	0.0032	2.35E-126	-0.00276	0.022467	0.902223
rs3818247	T	G	NA	NA	-0.0247	0.0026	2.95E-21	-0.02154	0.018208	0.23677
rs3848375	T	C	NA	NA	0.0231	0.0032	3.11E-13	-0.03109	0.022016	0.157866
rs41302867	A	G	NA	NA	-0.0342	0.0039	8.26E-19	-0.01366	0.026657	0.608229
rs4149056	C	T	NA	NA	-0.067	0.0035	9.39E-81	0.003491	0.024447	0.88646
rs4381968	T	C	NA	NA	-0.0138	0.0025	4.23E-08	-0.02557	0.017605	0.146309
rs440837	G	A	NA	NA	0.0466	0.0031	1.16E-50	0.014053	0.021725	0.517711
rs45512696	T	C	NA	NA	0.0407	0.0033	2.72E-34	-0.00257	0.023011	0.911089
rs45535039	C	T	NA	NA	0.0204	0.0028	3.34E-13	-0.00715	0.019683	0.716432
rs4639796	A	G	NA	NA	-0.0296	0.0034	3.23E-18	-0.01633	0.023883	0.494162
rs464605	T	C	NA	NA	-0.0323	0.0029	1.25E-29	0.009331	0.020068	0.641944
rs4660293	G	A	NA	NA	-0.0295	0.003	5.90E-23	-0.00076	0.020617	0.970436
rs4690098	T	C	NA	NA	-0.0498	0.003	1.01E-61	0.011287	0.020936	0.589816
rs4822455	T	C	NA	NA	-0.0184	0.0025	3.48E-13	0.01906	0.017717	0.282014
rs4983559	A	G	NA	NA	-0.0179	0.0026	2.85E-12	0.011058	0.017972	0.53837
rs555754	A	G	NA	NA	0.0343	0.0025	5.02E-42	-0.02461	0.017535	0.160432
rs55707100	T	C	NA	NA	-0.1171	0.0081	1.76E-47	0.020801	0.056002	0.710315
rs55840085	A	G	NA	NA	0.0195	0.0026	6.35E-14	-0.02055	0.018251	0.260097
rs56196860	A	C	NA	NA	0.0478	0.0073	5.01E-11	-0.00018	0.050003	0.99711
rs5745687	T	C	NA	NA	0.0307	0.0051	2.07E-09	0.014957	0.035291	0.671705
rs57506806	G	A	NA	NA	0.0351	0.003	2.25E-32	-0.00537	0.020742	0.795552
rs58941251	T	C	NA	NA	-0.0241	0.0041	2.74E-09	0.013725	0.028079	0.624973
rs6129800	A	G	NA	NA	0.0239	0.003	1.35E-15	-0.0062	0.020984	0.767685
rs61935507	T	C	NA	NA	-0.0295	0.0037	1.50E-15	0.02591	0.025598	0.311451
rs62576339	C	T	NA	NA	0.03	0.0029	8.22E-25	-0.01467	0.020522	0.47478
rs62580767	C	T	NA	NA	0.0234	0.0033	8.54E-13	0.018203	0.022597	0.420494
rs62618693	T	C	NA	NA	0.041	0.0061	1.93E-11	-0.06838	0.042581	0.108315
rs6356	T	C	NA	NA	0.0199	0.0026	2.43E-14	-0.00908	0.018221	0.618297
rs645040	T	G	NA	NA	-0.0691	0.003	9.86E-120	-0.01156	0.020855	0.5793
rs6736913	G	A	NA	NA	-0.0712	0.0089	1.12E-15	-0.06239	0.059873	0.297373
rs6756943	A	G	NA	NA	-0.0448	0.0027	5.62E-61	-0.04132	0.018983	0.029502
rs6954673	T	C	NA	NA	-0.0185	0.0026	1.27E-12	-0.04428	0.018208	0.015024
rs7221345	A	G	NA	NA	-0.0325	0.0026	3.13E-37	-0.0089	0.017841	0.61772
rs7239151	A	G	NA	NA	0.0155	0.0027	6.50E-09	-0.0092	0.018766	0.624028
rs724577	C	A	NA	NA	-0.0186	0.0028	6.04E-11	0.022927	0.019904	0.249355
rs7250351	A	G	NA	NA	0.0229	0.0041	2.17E-08	-0.0278	0.028758	0.333641
rs7250425	T	C	NA	NA	0.0179	0.0025	7.64E-13	0.011914	0.017454	0.494877
rs72683923	C	T	NA	NA	0.0774	0.0092	5.67E-17	-0.0454	0.063072	0.471632
rs72756074	G	A	NA	NA	0.023	0.0038	1.65E-09	0.016589	0.026625	0.533237
rs7314285	G	T	NA	NA	0.0764	0.0048	3.82E-56	-0.01136	0.034788	0.744064
rs738409	G	C	NA	NA	0.0486	0.003	5.06E-58	-0.01398	0.021208	0.50988
rs7429135	G	T	NA	NA	0.0199	0.0034	5.92E-09	0.033432	0.024004	0.163703
rs750472	C	A	NA	NA	-0.0216	0.0025	4.22E-18	0.024473	0.01745	0.160785
rs76610881	G	A	NA	NA	0.0418	0.0041	7.29E-25	-0.02824	0.028044	0.313925
rs7694379	A	G	NA	NA	-0.042	0.0025	4.75E-62	0.036783	0.017637	0.037014
rs7697204	T	C	NA	NA	-0.0295	0.0028	4.24E-25	0.01365	0.020044	0.495877
rs78025076	T	C	NA	NA	0.0503	0.0089	1.62E-08	0.025575	0.060588	0.672943
rs78444298	A	G	NA	NA	-0.0613	0.0093	5.44E-11	0.028472	0.063222	0.65246
rs7922067	A	G	NA	NA	-0.0211	0.0025	1.18E-16	-0.00241	0.017788	0.892303
rs7947951	G	A	NA	NA	-0.0283	0.0027	9.37E-26	0.023058	0.018943	0.223507
rs7994151	G	A	NA	NA	-0.0206	0.0035	2.89E-09	0.020986	0.024318	0.388133
rs8017377	A	G	NA	NA	-0.0342	0.0025	3.92E-42	-0.0082	0.017474	0.639014
rs8023580	C	T	NA	NA	0.073	0.0028	1.52E-150	0.034249	0.019539	0.079625
rs9316500	G	T	NA	NA	-0.0172	0.0027	3.05E-10	0.01171	0.01918	0.541516
rs9332817	C	G	NA	NA	0.05	0.0079	3.09E-10	0.064675	0.053767	0.229026
rs9388768	A	C	NA	NA	-0.0197	0.0027	1.39E-13	-0.0004	0.018594	0.982711
rs9427104	T	C	NA	NA	0.027	0.0025	4.04E-27	0.014845	0.017468	0.395426
rs9556403	G	A	NA	NA	0.0205	0.0026	4.66E-15	-0.0097	0.018275	0.59571
rs9644032	G	T	NA	NA	-0.0159	0.0026	1.03E-09	0.015264	0.018172	0.400912
rs976002	G	A	NA	NA	0.035	0.0029	1.60E-33	0.005158	0.020218	0.798654
rs9892297	G	A	NA	NA	-0.1366	0.0026	1.00E-200	-0.00086	0.018475	0.96286
rs9987289	G	A	NA	NA	0.0437	0.0043	3.22E-24	0.000249	0.030219	0.993415

SNP, single nucleotide polymorphism; AD, Alzheimer's disease; GWAS, genome-wide association studies; NA, not available.

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Table S4 SNPs identified in paternal AD GWAS

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs10069690	T	C	NA	NA	-0.017	0.0028	2.13E-09	-0.01726	0.027397	0.528738
rs1060817	G	A	NA	NA	-0.0176	0.0025	5.12E-12	0.024213	0.024324	0.319521
rs1076540	T	C	NA	NA	0.0169	0.0029	8.14E-09	0.011428	0.028008	0.683255
rs10838681	A	G	NA	NA	0.0162	0.0028	8.80E-09	0.026146	0.026969	0.33231
rs10871777	G	A	NA	NA	-0.0227	0.0029	8.41E-15	-0.03334	0.02825	0.237888
rs1106766	T	C	NA	NA	0.0357	0.0029	5.41E-34	0.051032	0.027693	0.065361
rs11075253	A	C	NA	NA	0.023	0.0028	6.30E-17	0.034992	0.026121	0.180381
rs11078405	T	G	NA	NA	-0.0293	0.0026	1.40E-29	-0.02072	0.024829	0.404094
rs1126670	A	C	NA	NA	-0.028	0.0027	1.35E-24	0.009118	0.026138	0.727216
rs1128249	T	G	NA	NA	0.0286	0.0026	8.43E-29	0.008612	0.024496	0.725181
rs11550348	A	G	NA	NA	0.0536	0.0038	5.40E-46	-0.02038	0.036599	0.577632
rs116189680	A	G	NA	NA	0.1439	0.0077	6.52E-78	-0.03822	0.074373	0.607307
rs11626364	C	T	NA	NA	0.0237	0.0035	9.61E-12	0.026225	0.033104	0.428235
rs11636917	C	T	NA	NA	-0.0247	0.0026	1.06E-20	0.024139	0.02516	0.337347
rs11647008	C	T	NA	NA	-0.0249	0.0025	6.86E-23	-0.00473	0.023977	0.843495
rs11655704	C	T	NA	NA	0.0785	0.0027	1.30E-189	-0.03368	0.025783	0.191442
rs11739158	T	C	NA	NA	0.0148	0.0025	4.85E-09	0.017594	0.024218	0.467525
rs11748288	G	A	NA	NA	0.0167	0.0025	5.85E-11	0.007204	0.02433	0.76717
rs1183910	A	G	NA	NA	-0.0261	0.0027	6.73E-22	0.001102	0.025978	0.966161
rs11856886	G	A	NA	NA	0.0194	0.0027	1.27E-12	-0.01344	0.026039	0.60573
rs11887329	G	A	NA	NA	-0.0213	0.003	7.13E-13	0.018684	0.028274	0.508715
rs11918018	A	G	NA	NA	-0.0153	0.0025	1.03E-09	0.00342	0.023985	0.88663
rs11935444	C	T	NA	NA	-0.0165	0.0026	4.11E-10	0.016706	0.024238	0.49067
rs12192649	A	G	NA	NA	0.022	0.003	9.97E-14	0.022407	0.027993	0.423448
rs12325400	G	C	NA	NA	-0.016	0.0026	4.03E-10	-0.01461	0.024431	0.549885
rs12414178	T	C	NA	NA	-0.0269	0.0029	5.57E-20	0.020827	0.028237	0.460767
rs12569576	G	A	NA	NA	-0.017	0.0025	1.25E-11	0.037942	0.024032	0.114387
rs12575636	G	T	NA	NA	-0.027	0.0033	1.36E-16	-0.02882	0.030827	0.349909
rs1260326	C	T	NA	NA	0.0772	0.0026	4.58E-198	0.017181	0.024542	0.483903
rs12748152	T	C	NA	NA	-0.0668	0.0046	2.79E-47	-0.05414	0.04449	0.223663
rs13094241	G	T	NA	NA	0.0172	0.0028	1.04E-09	0.027326	0.026971	0.310976
rs13354321	C	T	NA	NA	0.0144	0.0025	1.44E-08	-0.02213	0.024269	0.361757
rs1421085	C	T	NA	NA	-0.0183	0.0026	8.91E-13	0.047446	0.024373	0.051578
rs1497406	G	A	NA	NA	0.027	0.0025	1.56E-26	0.006581	0.024242	0.78604
rs1547014	C	T	NA	NA	-0.0293	0.0027	5.70E-28	0.035575	0.025566	0.164088
rs1556562	T	G	NA	NA	0.0243	0.003	8.54E-16	-0.04309	0.028412	0.129369
rs157934	C	T	NA	NA	0.0229	0.0027	4.25E-17	0.018735	0.025997	0.471124
rs1635852	C	T	NA	NA	0.0187	0.0025	6.54E-14	0.009417	0.023915	0.693744
rs16845803	G	A	NA	NA	-0.0251	0.0037	1.08E-11	0.041381	0.035293	0.240993
rs17041868	C	T	NA	NA	-0.0346	0.005	6.49E-12	-0.00603	0.049011	0.902105
rs1716403	C	T	NA	NA	-0.0168	0.0027	3.75E-10	-0.02929	0.025578	0.252107
rs17202341	G	A	NA	NA	0.0157	0.0026	2.86E-09	0.000678	0.025102	0.978446
rs17377148	G	T	NA	NA	0.0401	0.0048	1.13E-16	-0.06589	0.045992	0.151978
rs174601	T	C	NA	NA	-0.0252	0.0026	1.80E-22	0.036673	0.024675	0.137216
rs1755618	T	G	NA	NA	-0.0252	0.0035	1.17E-12	-0.03087	0.03465	0.373031
rs17580	A	T	NA	NA	0.0535	0.0059	1.54E-19	0.074347	0.054619	0.173454
rs17628931	C	T	NA	NA	0.0294	0.0041	4.71E-13	-0.00498	0.038533	0.897123
rs1772183	A	G	NA	NA	-0.022	0.0025	1.30E-18	0.023934	0.023945	0.317534
rs17794619	A	G	NA	NA	-0.0347	0.0037	3.61E-21	-0.03372	0.034832	0.333041
rs17826544	G	A	NA	NA	0.029	0.0026	3.87E-29	0.014959	0.024578	0.542785
rs1801282	G	C	NA	NA	0.0377	0.0039	1.41E-22	-0.01791	0.036891	0.627365
rs1801689	C	A	NA	NA	-0.0912	0.0074	6.69E-35	0.039955	0.070165	0.569054
rs1832007	G	A	NA	NA	-0.0483	0.0035	3.66E-43	0.034156	0.03291	0.299334
rs1935	G	C	NA	NA	0.1198	0.0025	1.00E-200	-0.03211	0.024014	0.181224
rs1982151	G	A	NA	NA	-0.049	0.0028	9.23E-67	-0.02417	0.027408	0.377795
rs2081687	C	T	NA	NA	0.0247	0.0026	1.03E-20	0.019819	0.02537	0.43468
rs2205262	A	C	NA	NA	-0.0167	0.0025	4.00E-11	0.002921	0.024182	0.903857
rs2254069	A	G	NA	NA	-0.0265	0.0038	2.11E-12	0.016988	0.036768	0.644051
rs2266782	A	G	NA	NA	-0.0163	0.0025	1.25E-10	-0.00945	0.024251	0.696659
rs2335077	G	A	NA	NA	0.0463	0.0026	1.71E-69	0.02181	0.02513	0.385439
rs2427530	A	G	NA	NA	0.0194	0.0029	2.99E-11	-0.01379	0.027853	0.620633
rs2487826	C	T	NA	NA	0.0176	0.0025	3.56E-12	-0.01498	0.024285	0.537404
rs2537855	G	A	NA	NA	0.0447	0.0028	3.56E-59	0.011132	0.026458	0.673933
rs2618566	T	G	NA	NA	-0.0171	0.0026	8.57E-11	0.003685	0.025268	0.884057
rs2642420	A	C	NA	NA	-0.0247	0.0033	9.54E-14	-0.0221	0.031722	0.485938
rs2836950	G	C	NA	NA	-0.0154	0.0026	3.64E-09	-0.02417	0.025063	0.334947
rs2860075	G	A	NA	NA	-0.0289	0.0026	1.40E-28	0.009192	0.024991	0.713009
rs28925904	T	C	NA	NA	-0.0576	0.0081	1.49E-12	0.148139	0.074298	0.04617
rs28929474	T	C	NA	NA	0.219	0.0091	5.87E-129	-0.06488	0.085376	0.447262
rs2943641	C	T	NA	NA	-0.0322	0.0026	6.16E-35	-0.00914	0.025032	0.715124
rs3132469	G	A	NA	NA	-0.033	0.0035	8.29E-21	-0.00655	0.033507	0.845024

Table S4 (*continued*)

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Table S4 (*continued*)

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs34145453	G	A	NA	NA	0.0189	0.0026	2.90E-13	-0.00726	0.024863	0.770353
rs34372369	A	G	NA	NA	0.037	0.0057	6.20E-11	-0.14677	0.056158	0.00896
rs35371479	T	C	NA	NA	0.0256	0.0033	7.00E-15	-0.03178	0.031314	0.310106
rs35627524	G	T	NA	NA	-0.0433	0.0067	1.09E-10	0.009379	0.06397	0.883439
rs3749237	A	G	NA	NA	-0.0257	0.0027	8.87E-22	0.022343	0.025506	0.381048
rs3779195	A	T	NA	NA	-0.0768	0.0032	2.35E-126	0.010341	0.030714	0.736358
rs3818247	T	G	NA	NA	-0.0247	0.0026	2.95E-21	0.015571	0.024915	0.53199
rs3848375	T	C	NA	NA	0.0231	0.0032	3.11E-13	-0.02232	0.030155	0.459143
rs41302867	A	G	NA	NA	-0.0342	0.0039	8.26E-19	-0.02121	0.036611	0.562456
rs4149056	C	T	NA	NA	-0.067	0.0035	9.39E-81	-0.03428	0.033676	0.30874
rs4381968	T	C	NA	NA	-0.0138	0.0025	4.23E-08	0.011557	0.024151	0.632273
rs440837	G	A	NA	NA	0.0466	0.0031	1.16E-50	-0.01537	0.029872	0.606892
rs45512696	T	C	NA	NA	0.0407	0.0033	2.72E-34	0.020937	0.031422	0.505199
rs45535039	C	T	NA	NA	0.0204	0.0028	3.34E-13	-0.05577	0.027105	0.039642
rs4639796	A	G	NA	NA	-0.0296	0.0034	3.23E-18	-0.00825	0.032714	0.800969
rs464605	T	C	NA	NA	-0.0323	0.0029	1.25E-29	0.045261	0.027593	0.100939
rs4660293	G	A	NA	NA	-0.0295	0.003	5.90E-23	0.002038	0.028232	0.942459
rs4690098	T	C	NA	NA	-0.0498	0.003	1.01E-61	-0.02998	0.028826	0.298342
rs4822455	T	C	NA	NA	-0.0184	0.0025	3.48E-13	-0.03383	0.024229	0.162612
rs4983559	A	G	NA	NA	-0.0179	0.0026	2.85E-12	-0.02573	0.024624	0.296063
rs555754	A	G	NA	NA	0.0343	0.0025	5.02E-42	0.037596	0.024003	0.117276
rs55707100	T	C	NA	NA	-0.1171	0.0081	1.76E-47	-0.03056	0.07737	0.692872
rs55840085	A	G	NA	NA	0.0195	0.0026	6.35E-14	0.00406	0.024955	0.870755
rs56196860	A	C	NA	NA	0.0478	0.0073	5.01E-11	-0.01378	0.068707	0.841072
rs5745687	T	C	NA	NA	0.0307	0.0051	2.07E-09	0.022354	0.048347	0.643816
rs57506806	G	A	NA	NA	0.0351	0.003	2.25E-32	-0.03413	0.028525	0.23155
rs58941251	T	C	NA	NA	-0.0241	0.0041	2.74E-09	-0.04286	0.038827	0.269696
rs6129800	A	G	NA	NA	0.0239	0.003	1.35E-15	-0.03177	0.028835	0.270503
rs61935507	T	C	NA	NA	-0.0295	0.0037	1.50E-15	-0.0216	0.035301	0.540645
rs62576339	C	T	NA	NA	0.03	0.0029	8.22E-25	-0.00374	0.028104	0.894238
rs62580767	C	T	NA	NA	0.0234	0.0033	8.54E-13	0.002738	0.031014	0.929657
rs62618693	T	C	NA	NA	0.041	0.0061	1.93E-11	0.089546	0.056422	0.112498
rs6356	T	C	NA	NA	0.0199	0.0026	2.43E-14	-0.00107	0.024953	0.965692
rs645040	T	G	NA	NA	-0.0691	0.003	9.86E-120	0.032156	0.028717	0.26281
rs6736913	G	A	NA	NA	-0.0712	0.0089	1.12E-15	-0.08076	0.081646	0.322598
rs6756943	A	G	NA	NA	-0.0448	0.0027	5.62E-61	-0.00496	0.026105	0.849376
rs6954673	T	C	NA	NA	-0.0185	0.0026	1.27E-12	0.013553	0.024893	0.586123
rs7221345	A	G	NA	NA	-0.0325	0.0026	3.13E-37	0.005746	0.02446	0.81427
rs7239151	A	G	NA	NA	0.0155	0.0027	6.50E-09	0.01719	0.025767	0.504677
rs724577	C	A	NA	NA	-0.0186	0.0028	6.04E-11	0.023265	0.027271	0.393603
rs7250351	A	G	NA	NA	0.0229	0.0041	2.17E-08	0.018732	0.039663	0.636724
rs7250425	T	C	NA	NA	0.0179	0.0025	7.64E-13	-0.00779	0.023925	0.744589
rs72683923	C	T	NA	NA	0.0774	0.0092	5.67E-17	-0.15275	0.088591	0.084679
rs72756074	G	A	NA	NA	0.023	0.0038	1.65E-09	0.017928	0.036502	0.623319
rs7314285	G	T	NA	NA	0.0764	0.0048	3.82E-56	0.039957	0.047256	0.397809
rs738409	G	C	NA	NA	0.0486	0.003	5.06E-58	-0.02489	0.029092	0.392318
rs7429135	G	T	NA	NA	0.0199	0.0034	5.92E-09	-0.01008	0.032709	0.757907
rs750472	C	A	NA	NA	-0.0216	0.0025	4.22E-18	-0.00383	0.023932	0.872961
rs76610881	G	A	NA	NA	0.0418	0.0041	7.29E-25	-0.03675	0.038569	0.340643
rs7694379	A	G	NA	NA	-0.042	0.0025	4.75E-62	-0.03434	0.024209	0.156057
rs7697204	T	C	NA	NA	-0.0295	0.0028	4.24E-25	-0.01931	0.027393	0.480888
rs78025076	T	C	NA	NA	0.0503	0.0089	1.62E-08	0.056965	0.082557	0.49019
rs78444298	A	G	NA	NA	-0.0613	0.0093	5.44E-11	-0.02181	0.087354	0.802838
rs7922067	A	G	NA	NA	-0.0211	0.0025	1.18E-16	0.005266	0.024388	0.829037
rs7947951	G	A	NA	NA	-0.0283	0.0027	9.37E-26	0.03278	0.025974	0.206929
rs7994151	G	A	NA	NA	-0.0206	0.0035	2.89E-09	-0.00099	0.033438	0.976361
rs8017377	A	G	NA	NA	-0.0342	0.0025	3.92E-42	-0.0229	0.023948	0.339014
rs8023580	C	T	NA	NA	0.073	0.0028	1.52E-150	0.016433	0.026841	0.540377
rs9316500	G	T	NA	NA	-0.0172	0.0027	3.05E-10	-0.00653	0.026328	0.803995
rs9332817	C	G	NA	NA	0.05	0.0079	3.09E-10	0.017483	0.074191	0.8137
rs9388768	A	C	NA	NA	-0.0197	0.0027	1.39E-13	-0.01245	0.025453	0.624764
rs9427104	T	C	NA	NA	0.027	0.0025	4.04E-27	0.007817	0.023958	0.744205
rs9556403	G	A	NA	NA	0.0205	0.0026	4.66E-15	0.007567	0.025027	0.762388
rs9644032	G	T	NA	NA	-0.0159	0.0026	1.03E-09	-0.02142	0.024853	0.388697
rs976002	G	A	NA	NA	0.035	0.0029	1.60E-33	-0.01877	0.027792	0.499477
rs9892297	G	A	NA	NA	-0.1366	0.0026	1.00E-200	0.007712	0.025278	0.7603
rs9987289	G	A	NA	NA	0.0437	0.0043	3.22E-24	0.013842	0.041485	0.738632

SNP, single nucleotide polymorphism; AD, Alzheimer's disease; GWAS, genome-wide association studies; NA, not available.

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Table S5 SNPs identified in ALS GWAS

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome	samplesize
rs10069690	T	C	NA	0.2613	-0.017	0.0028	2.13E-09	0.0099	0.0177	0.5772	80610
rs1060817	G	A	NA	0.5145	-0.0176	0.0025	5.12E-12	0.0076	0.0138	0.5811	80610
rs1076540	T	C	NA	0.24	0.0169	0.0029	8.14E-09	-0.0078	0.0158	0.6227	80610
rs10838681	A	G	NA	0.2554	0.0162	0.0028	8.80E-09	0.0259	0.0156	0.09735	80610
rs10871777	G	A	NA	0.2408	-0.0227	0.0029	8.41E-15	-4.00E-04	0.016	0.9802	80610
rs1106766	T	C	NA	0.2261	0.0357	0.0029	5.41E-34	0.0353	0.0171	0.03868	80610
rs11075253	A	C	NA	0.3032	0.023	0.0028	6.30E-17	-0.0178	0.0148	0.2304	80610
rs11078405	T	G	NA	0.4745	-0.0293	0.0026	1.40E-29	-0.0299	0.014	0.03249	80610
rs1126670	A	C	NA	0.685	-0.028	0.0027	1.35E-24	-0.0025	0.0146	0.8612	80610
rs1128249	T	G	NA	0.3946	0.0286	0.0026	8.43E-29	0.0091	0.0142	0.5207	80610
rs11550348	A	G	NA	0.1282	0.0536	0.0038	5.40E-46	0.0261	0.0205	0.2038	80610
rs116189680	A	G	NA	0.0266	0.1439	0.0077	6.52E-78	-0.0303	0.0491	0.5364	80610
rs11626364	C	T	NA	0.1558	0.0237	0.0035	9.61E-12	-0.008	0.0188	0.6686	80610
rs11636917	C	T	NA	0.3656	-0.0247	0.0026	1.06E-20	0.0181	0.0142	0.2012	80610
rs11647008	C	T	NA	0.4711	-0.0249	0.0025	6.86E-23	-0.0101	0.0136	0.4582	80610
rs11655704	C	T	NA	0.3026	0.0785	0.0027	1.30E-189	0.0127	0.015	0.3964	80610
rs11739158	T	C	NA	0.4252	0.0148	0.0025	4.85E-09	0.0061	0.0137	0.6564	80610
rs11748288	G	A	NA	0.5177	0.0167	0.0025	5.85E-11	0.0147	0.0138	0.288	80610
rs1183910	A	G	NA	0.3181	-0.0261	0.0027	6.73E-22	0.0062	0.0146	0.6696	80610
rs11856886	G	A	NA	0.3042	0.0194	0.0027	1.27E-12	0.0032	0.015	0.8334	80610
rs11887329	G	A	NA	0.2463	-0.0213	0.003	7.13E-13	0.0024	0.0159	0.8808	80610
rs11918018	A	G	NA	0.4609	-0.0153	0.0025	1.03E-09	-0.0129	0.0137	0.3456	80610
rs11935444	C	T	NA	0.5112	-0.0165	0.0026	4.11E-10	0.0021	0.0138	0.8802	80610
rs12192649	A	G	NA	0.2176	0.022	0.003	9.97E-14	-0.0225	0.0166	0.1739	80610
rs12325400	G	C	NA	0.3859	-0.016	0.0026	4.03E-10	-0.0179	0.014	0.2002	80610
rs12414178	T	C	NA	0.2407	-0.0269	0.0029	5.57E-20	0.0053	0.016	0.7427	80610
rs12569576	G	A	NA	0.449	-0.017	0.0025	1.25E-11	0.0177	0.0138	0.1994	80610
rs12575636	G	T	NA	0.1998	-0.027	0.0033	1.36E-16	0.0351	0.017	0.03927	80610
rs1260326	C	T	NA	0.5768	0.0772	0.0026	4.58E-198	-0.0085	0.0137	0.535	80610
rs12748152	T	C	NA	0.0775	-0.0668	0.0046	2.79E-47	-0.0172	0.0261	0.5094	80610
rs12941564	G	C	NA	0.294	0.0239	0.0028	1.31E-17	-0.0178	0.0151	0.2383	80610
rs13094241	G	T	NA	0.7259	0.0172	0.0028	1.04E-09	-0.0179	0.0152	0.2374	80610
rs13354321	C	T	NA	0.393	0.0144	0.0025	1.44E-08	0.0053	0.0142	0.7094	80610
rs1421085	C	T	NA	0.412	-0.0183	0.0026	8.91E-13	-0.0242	0.0138	0.07934	80610
rs1497406	G	A	NA	0.5173	0.027	0.0025	1.56E-26	0.024	0.0138	0.082	80610
rs1547014	C	T	NA	0.7082	-0.0293	0.0027	5.70E-28	0.0227	0.0157	0.1463	80610
rs1556562	T	G	NA	0.7963	0.0243	0.003	8.54E-16	-0.0031	0.0169	0.8562	80610
rs157934	C	T	NA	0.295	0.0229	0.0027	4.25E-17	-0.0176	0.015	0.2416	80610
rs1635852	C	T	NA	0.4949	0.0187	0.0025	6.54E-14	0.0041	0.0137	0.7613	80610
rs16845803	G	A	NA	0.132	-0.0251	0.0037	1.08E-11	0.013	0.021	0.5351	80610
rs17041868	C	T	NA	0.0657	-0.0346	0.005	6.49E-12	0.0238	0.0277	0.3904	80610
rs1716403	C	T	NA	0.6831	-0.0168	0.0027	3.75E-10	0.0019	0.0146	0.8941	80610
rs17202341	G	A	NA	0.3418	0.0157	0.0026	2.86E-09	-0.0032	0.0143	0.8232	80610
rs17377148	G	T	NA	0.0682	0.0401	0.0048	1.13E-16	-0.0089	0.0275	0.7458	80610
rs174601	T	C	NA	0.3627	-0.0252	0.0026	1.80E-22	-0.0019	0.0146	0.899	80610
rs1755618	T	G	NA	0.1441	-0.0252	0.0035	1.17E-12	-0.0059	0.0193	0.7612	80610
rs17580	A	T	NA	0.0496	0.0535	0.0059	1.54E-19	-0.0067	0.0353	0.8485	80610
rs17628931	C	T	NA	0.1037	0.0294	0.0041	4.71E-13	-0.014	0.0226	0.536	80610
rs1772183	A	G	NA	0.496	-0.022	0.0025	1.30E-18	0.0033	0.0136	0.8076	80610
rs17794619	A	G	NA	0.1348	-0.0347	0.0037	3.61E-21	-0.0076	0.0208	0.716	80610
rs17826544	G	A	NA	0.5258	0.029	0.0026	3.87E-29	0.0023	0.0141	0.8699	80610
rs1801282	G	C	NA	0.1204	0.0377	0.0039	1.41E-22	-0.0241	0.0212	0.2553	80610
rs1801689	C	A	NA	0.0355	-0.0912	0.0074	6.69E-35	-0.0326	0.0469	0.4871	80610
rs1832007	G	A	NA	0.147	-0.0483	0.0035	3.66E-43	0.0175	0.0194	0.3653	80610
rs1935	G	C	NA	0.4851	0.1198	0.0025	1.00E-200	-0.0055	0.0136	0.6871	80610
rs1982151	G	A	NA	0.7255	-0.049	0.0028	9.23E-67	-0.0441	0.0155	0.004471	80610
rs2081687	C	T	NA	0.654	0.0247	0.0026	1.03E-20	0.0054	0.0143	0.7038	80610
rs2205262	A	C	NA	0.5884	-0.0167	0.0025	4.00E-11	-0.0072	0.0138	0.6016	80610
rs2254069	A	G	NA	0.1229	-0.0265	0.0038	2.11E-12	-0.0118	0.0211	0.5753	80610
rs2266782	A	G	NA	0.4096	-0.0163	0.0025	1.25E-10	0.0072	0.0138	0.603	80610
rs2335077	G	A	NA	0.3434	0.0463	0.0026	1.71E-69	-0.0138	0.0144	0.3361	80610
rs2427530	A	G	NA	0.2286	0.0194	0.0029	2.99E-11	-9.00E-04	0.0173	0.9574	80610
rs2487826	C	T	NA	0.4437	0.0176	0.0025	3.56E-12	0.0187	0.0137	0.1732	80610
rs2537855	G	A	NA	0.2916	0.0447	0.0028	3.56E-59	0.0383	0.0155	0.01379	80610
rs2618566	T	G	NA	0.6495	-0.0171	0.0026	8.57E-11	0.0123	0.015	0.411	80610
rs2642420	A	C	NA	0.1716	-0.0247	0.0033	9.54E-14	-0.025	0.018	0.1647	80610
rs2836950	G	C	NA	0.3618	-0.0154	0.0026	3.64E-09	-0.0048	0.0145	0.742	80610
rs2860075	G	A	NA	0.5282	-0.0289	0.0026	1.40E-28	-0.0156	0.0143	0.2745	80610
rs28925904	T	C	NA	0.0212	-0.0576	0.0081	1.49E-12	-0.0336	0.0579	0.562	80610
rs28929474	T	C	NA	0.0177	0.219	0.0091	5.87E-129	-0.0465	0.0582	0.4245	80610
rs2943641	C	T	NA	0.6348	-0.0322	0.0026	6.16E-35	-0.0271	0.0141	0.05403	80610

Table S5 (*continued*)

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Table S5 (*continued*)

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome	samplesize
rs3132469	G	A	NA	0.8678	-0.033	0.0035	8.29E-21	-0.0135	0.0208	0.5166	80610
rs34145453	G	A	NA	0.3681	0.0189	0.0026	2.90E-13	0.0215	0.0142	0.132	80610
rs34372369	A	G	NA	0.0575	0.037	0.0057	6.20E-11	0.0027	0.0299	0.9274	80610
rs35371479	T	C	NA	0.1843	0.0256	0.0033	7.00E-15	-0.0213	0.0176	0.2253	80610
rs35386490	C	T	NA	0.2041	0.1118	0.003	1.00E-200	0.0308	0.0192	0.1088	80610
rs35627524	G	T	NA	0.042	-0.0433	0.0067	1.09E-10	-4.00E-04	0.0357	0.99	80610
rs3749237	A	G	NA	0.3071	-0.0257	0.0027	8.87E-22	0.0374	0.0147	0.01085	80610
rs3779195	A	T	NA	0.1787	-0.0768	0.0032	2.35E-126	-8.00E-04	0.0182	0.9654	80610
rs3818247	T	G	NA	0.3415	-0.0247	0.0026	2.95E-21	0.012	0.015	0.4266	80610
rs3848375	T	C	NA	0.7996	0.0231	0.0032	3.11E-13	-0.0218	0.0193	0.258	80610
rs41302867	A	G	NA	0.1234	-0.0342	0.0039	8.26E-19	0.0284	0.0217	0.1906	80610
rs4149056	C	T	NA	0.1574	-0.067	0.0035	9.39E-81	-2.00E-04	0.0187	0.9929	80610
rs4381968	T	C	NA	0.5417	-0.0138	0.0025	4.23E-08	-0.0165	0.0139	0.2338	80610
rs440837	G	A	NA	0.2285	0.0466	0.0031	1.16E-50	0.0124	0.0161	0.4428	80610
rs45512696	T	C	NA	0.1579	0.0407	0.0033	2.72E-34	-5.00E-04	0.019	0.9796	80610
rs45535039	C	T	NA	0.2859	0.0204	0.0028	3.34E-13	-0.0213	0.0151	0.1592	80610
rs4639796	A	G	NA	0.1608	-0.0296	0.0034	3.23E-18	0.0295	0.0184	0.1099	80610
rs464605	T	C	NA	0.74	-0.0323	0.0029	1.25E-29	-0.0296	0.0157	0.05913	80610
rs4660293	G	A	NA	0.2341	-0.0295	0.003	5.90E-23	0.0135	0.0163	0.4074	80610
rs4690098	T	C	NA	0.2358	-0.0498	0.003	1.01E-61	0.0033	0.017	0.8464	80610
rs4822455	T	C	NA	0.577	-0.0184	0.0025	3.48E-13	-0.0056	0.0138	0.6832	80610
rs4983559	A	G	NA	0.5156	-0.0179	0.0026	2.85E-12	0.0025	0.014	0.8582	80610
rs555754	A	G	NA	0.4872	0.0343	0.0025	5.02E-42	-0.0074	0.0136	0.5886	80610
rs55707100	T	C	NA	0.0327	-0.1171	0.0081	1.76E-47	-0.0387	0.0411	0.3472	80610
rs55840085	A	G	NA	0.3617	0.0195	0.0026	6.35E-14	-0.0135	0.0144	0.3499	80610
rs56196860	A	C	NA	0.0321	0.0478	0.0073	5.01E-11	-0.1333	0.0489	0.00643	80610
rs5745687	T	C	NA	0.0667	0.0307	0.0051	2.07E-09	-0.0418	0.0282	0.1388	80610
rs57506806	G	A	NA	0.2263	0.0351	0.003	2.25E-32	-0.0037	0.0169	0.8271	80610
rs58941251	T	C	NA	0.1048	-0.0241	0.0041	2.74E-09	-0.0031	0.0225	0.8886	80610
rs6129800	A	G	NA	0.2181	0.0239	0.003	1.35E-15	0.0088	0.0169	0.6014	80610
rs61935507	T	C	NA	0.1415	-0.0295	0.0037	1.50E-15	-0.008	0.0205	0.6967	80610
rs62576339	C	T	NA	0.2438	0.03	0.0029	8.22E-25	0.0091	0.0161	0.5701	80610
rs62580767	C	T	NA	0.182	0.0234	0.0033	8.54E-13	0.0222	0.0178	0.2133	80610
rs62618693	T	C	NA	0.0417	0.041	0.0061	1.93E-11	0.0146	0.0363	0.6865	80610
rs6356	T	C	NA	0.378	0.0199	0.0026	2.43E-14	-0.0244	0.0149	0.1014	80610
rs645040	T	G	NA	0.7743	-0.0691	0.003	9.86E-120	-0.0089	0.0163	0.5845	80610
rs6736913	G	A	NA	0.9829	-0.0712	0.0089	1.12E-15	0.0978	0.0587	0.09571	80610
rs6756943	A	G	NA	0.6988	-0.0448	0.0027	5.62E-61	-5.00E-04	0.0149	0.9738	80610
rs6954673	T	C	NA	0.3421	-0.0185	0.0026	1.27E-12	-0.0089	0.0142	0.5297	80610
rs7221345	A	G	NA	0.6023	-0.0325	0.0026	3.13E-37	-0.023	0.0139	0.09781	80610
rs7239151	A	G	NA	0.7041	0.0155	0.0027	6.50E-09	0.0113	0.0149	0.4479	80610
rs724577	C	A	NA	0.7392	-0.0186	0.0028	6.04E-11	-0.0227	0.0154	0.141	80610
rs7250351	A	G	NA	0.8758	0.0229	0.0041	2.17E-08	-0.0038	0.0242	0.8753	80610
rs7250425	T	C	NA	0.4991	0.0179	0.0025	7.64E-13	-0.0061	0.0136	0.6538	80610
rs72683923	C	T	NA	0.0208	0.0774	0.0092	5.67E-17	-0.0038	0.0554	0.9449	80610
rs72756074	G	A	NA	0.1168	0.023	0.0038	1.65E-09	-0.0152	0.0226	0.5019	80610
rs7314285	G	T	NA	0.0728	0.0764	0.0048	3.82E-56	0.0275	0.0261	0.293	80610
rs738409	G	C	NA	0.233	0.0486	0.003	5.06E-58	-0.0238	0.0163	0.1451	80610
rs7429135	G	T	NA	0.8374	0.0199	0.0034	5.92E-09	-0.0047	0.0184	0.7962	80610
rs750472	C	A	NA	0.496	-0.0216	0.0025	4.22E-18	0.0045	0.0137	0.7431	80610
rs76610881	G	A	NA	0.0944	0.0418	0.0041	7.29E-25	-0.0192	0.0249	0.4411	80610
rs7694379	A	G	NA	0.4182	-0.042	0.0025	4.75E-62	0.0108	0.0138	0.4327	80610
rs7697204	T	C	NA	0.7338	-0.0295	0.0028	4.24E-25	-0.006	0.0155	0.6961	80610
rs78025076	T	C	NA	0.0235	0.0503	0.0089	1.62E-08	0.02	0.0572	0.727	80610
rs78444298	A	G	NA	0.0189	-0.0613	0.0093	5.44E-11	-0.0723	0.0597	0.2258	80610
rs7922067	A	G	NA	0.5118	-0.0211	0.0025	1.18E-16	-0.04	0.0137	0.003538	80610
rs7947951	G	A	NA	0.681	-0.0283	0.0027	9.37E-26	0.0028	0.0147	0.8503	80610
rs7994151	G	A	NA	0.1515	-0.0206	0.0035	2.89E-09	0.0372	0.0189	0.04937	80610
rs8017377	A	G	NA	0.47	-0.0342	0.0025	3.92E-42	-0.013	0.0136	0.3362	80610
rs8023580	C	T	NA	0.2948	0.073	0.0028	1.52E-150	0.0184	0.0153	0.2293	80610
rs9316500	G	T	NA	0.3059	-0.0172	0.0027	3.05E-10	0.0224	0.0147	0.1279	80610
rs9332817	C	G	NA	0.026	0.05	0.0079	3.09E-10	0.0354	0.0483	0.4635	80610
rs9388768	A	C	NA	0.6737	-0.0197	0.0027	1.39E-13	0.0082	0.0144	0.5696	80610
rs9427104	T	C	NA	0.4756	0.027	0.0025	4.04E-27	-0.0146	0.0136	0.2829	80610
rs9556403	G	A	NA	0.3616	0.0205	0.0026	4.66E-15	-0.0111	0.0142	0.4327	80610
rs9644032	G	T	NA	0.6264	-0.0159	0.0026	1.03E-09	-0.0125	0.014	0.3727	80610
rs976002	G	A	NA	0.2285	0.035	0.0029	1.60E-33	0.0533	0.0202	0.008376	80610
rs9892297	G	A	NA	0.3183	-0.1366	0.0026	1.00E-200	-0.0399	0.0149	0.00745	80610
rs9987289	G	A	NA	0.9151	0.0437	0.0043	3.22E-24	-0.0227	0.0246	0.3575	80610

SNP, single nucleotide polymorphism; ALS, amyotrophic lateral sclerosis; GWAS, genome-wide association studies; NA, not available.

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Table S6 SNPs identified in PD GWAS

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome	samplesize
rs10069690	T	C	NA	0.2636	-0.017	0.0028	2.13E-09	0.0324	0.0191	0.08932	482730
rs1060817	G	A	NA	0.5905	-0.0176	0.0025	5.12E-12	-0.0229	0.0199	0.2498	482730
rs1076540	T	C	NA	0.2443	0.0169	0.0029	8.14E-09	-0.0113	0.0258	0.6623	468692
rs10838681	A	G	NA	0.2482	0.0162	0.0028	8.80E-09	-0.0072	0.0195	0.7131	482730
rs10871777	G	A	NA	0.2345	-0.0227	0.0029	8.41E-15	-0.0018	0.0198	0.9273	482730
rs1106766	T	C	NA	0.2189	0.0357	0.0029	5.41E-34	0.0142	0.0203	0.4838	482730
rs11075253	A	C	NA	0.3046	0.023	0.0028	6.30E-17	0.0099	0.0183	0.5888	482730
rs11078405	T	G	NA	0.395	-0.0293	0.0026	1.40E-29	-0.0291	0.0172	0.0908	482730
rs1126670	A	C	NA	0.6821	-0.028	0.0027	1.35E-24	0.0164	0.0181	0.3659	482730
rs1128249	T	G	NA	0.3939	0.0286	0.0026	8.43E-29	-0.0015	0.0171	0.9321	482730
rs11550348	A	G	NA	0.1245	0.0536	0.0038	5.40E-46	0.0059	0.0296	0.8414	482730
rs116189680	A	G	NA	0.0276	0.1439	0.0077	6.52E-78	0.02	0.0727	0.7834	471013
rs11626364	C	T	NA	0.1566	0.0237	0.0035	9.61E-12	-0.0018	0.0241	0.9415	482730
rs11636917	C	T	NA	0.3587	-0.0247	0.0026	1.06E-20	-0.0047	0.0204	0.8192	482730
rs11647008	C	T	NA	0.476	-0.0249	0.0025	6.86E-23	0.0174	0.0182	0.3381	482730
rs11655704	C	T	NA	0.3053	0.0785	0.0027	1.30E-189	-0.0056	0.0207	0.7858	482730
rs11739158	T	C	NA	0.4262	0.0148	0.0025	4.85E-09	0.0111	0.0224	0.6214	468692
rs11748288	G	A	NA	0.5891	0.0167	0.0025	5.85E-11	0.0293	0.0196	0.1352	482730
rs1183910	A	G	NA	0.3183	-0.0261	0.0027	6.73E-22	0.0067	0.018	0.7085	482730
rs11856886	G	A	NA	0.3025	0.0194	0.0027	1.27E-12	-0.0654	0.0201	0.001146	482730
rs11887329	G	A	NA	0.2447	-0.0213	0.003	7.13E-13	-0.007	0.026	0.7871	468692
rs11918018	A	G	NA	0.466	-0.0153	0.0025	1.03E-09	-0.0056	0.0224	0.8027	468692
rs11935444	C	T	NA	0.5683	-0.0165	0.0026	4.11E-10	0.0805	0.0172	2.73E-06	482730
rs12192649	A	G	NA	0.2184	0.022	0.003	9.97E-14	-0.0017	0.0206	0.9333	482730
rs12325400	G	C	NA	0.3852	-0.016	0.0026	4.03E-10	-0.0354	0.018	0.04971	482730
rs12414178	T	C	NA	0.2444	-0.0269	0.0029	5.57E-20	0.0184	0.0258	0.4757	468692
rs12569576	G	A	NA	0.4529	-0.017	0.0025	1.25E-11	0.023	0.0219	0.2936	471013
rs12575636	G	T	NA	0.2011	-0.027	0.0033	1.36E-16	0.001	0.0215	0.9641	482730
rs1260326	C	T	NA	0.5801	0.0772	0.0026	4.58E-198	0.0678	0.0172	8.24E-05	482730
rs12748152	T	C	NA	0.077	-0.0668	0.0046	2.79E-47	0.0542	0.0315	0.0852	482730
rs13094241	G	T	NA	0.7236	0.0172	0.0028	1.04E-09	0.0092	0.0239	0.7008	470485
rs13354321	C	T	NA	0.3963	0.0144	0.0025	1.44E-08	-0.0171	0.0229	0.4537	468692
rs1421085	C	T	NA	0.4159	-0.0183	0.0026	8.91E-13	-0.0043	0.0171	0.8017	482730
rs1497406	G	A	NA	0.5813	0.027	0.0025	1.56E-26	-0.0177	0.0186	0.3404	482730
rs1547014	C	T	NA	0.6948	-0.0293	0.0027	5.70E-28	-0.0119	0.0183	0.5151	482730
rs1556562	T	G	NA	0.7995	0.0243	0.003	8.54E-16	0.032	0.0231	0.1658	27693
rs157934	C	T	NA	0.304	0.0229	0.0027	4.25E-17	-0.0127	0.0261	0.627	466555
rs1635852	C	T	NA	0.5049	0.0187	0.0025	6.54E-14	-0.0053	0.0168	0.7511	482730
rs16845803	G	A	NA	0.1365	-0.0251	0.0037	1.08E-11	0.0302	0.0326	0.3553	468692
rs17041868	C	T	NA	0.0664	-0.0346	0.005	6.49E-12	0.0027	0.0451	0.9527	468692
rs1716403	C	T	NA	0.6736	-0.0168	0.0027	3.75E-10	-0.0671	0.0213	0.001632	482730
rs17202341	G	A	NA	0.3369	0.0157	0.0026	2.86E-09	-0.0038	0.0234	0.8713	471013
rs17377148	G	T	NA	0.0735	0.0401	0.0048	1.13E-16	0.0497	0.042	0.237	468692
rs174601	T	C	NA	0.3619	-0.0252	0.0026	1.80E-22	0.0037	0.0179	0.8366	482730
rs1755618	T	G	NA	0.1539	-0.0252	0.0035	1.17E-12	-0.0386	0.0306	0.2066	468692
rs17580	A	T	NA	0.0563	0.0535	0.0059	1.54E-19	0.0219	0.0468	0.6397	482730
rs17628931	C	T	NA	0.111	0.0294	0.0041	4.71E-13	0.0981	0.0355	0.005677	468692
rs1772183	A	G	NA	0.4876	-0.022	0.0025	1.30E-18	-0.0317	0.0184	0.08504	482730
rs17794619	A	G	NA	0.141	-0.0347	0.0037	3.61E-21	-0.011	0.0317	0.7299	471013
rs17826544	G	A	NA	0.6193	0.029	0.0026	3.87E-29	-3.00E-04	0.0186	0.9884	482730
rs1801282	G	C	NA	0.1194	0.0377	0.0039	1.41E-22	-0.0136	0.0261	0.6008	482730
rs1801689	C	A	NA	0.0392	-0.0912	0.0074	6.69E-35	0.0012	0.0446	0.9779	482730
rs1832007	G	A	NA	0.1415	-0.0483	0.0035	3.66E-43	0.0071	0.0253	0.7792	480593
rs1935	G	C	NA	0.4896	0.1198	0.0025	1.00E-200	0.0122	0.017	0.4731	482730
rs1982151	G	A	NA	0.7336	-0.049	0.0028	9.23E-67	0.0329	0.019	0.08233	482730
rs2081687	C	T	NA	0.6564	0.0247	0.0026	1.03E-20	0.0119	0.0203	0.5564	482730
rs2205262	A	C	NA	0.5975	-0.0167	0.0025	4.00E-11	-0.0136	0.0202	0.5025	482730
rs2254069	A	G	NA	0.1199	-0.0265	0.0038	2.11E-12	-0.0536	0.0345	0.1201	468692
rs2266782	A	G	NA	0.4014	-0.0163	0.0025	1.25E-10	-0.0077	0.0171	0.6541	482730
rs2335077	G	A	NA	0.3375	0.0463	0.0026	1.71E-69	-0.0201	0.0199	0.3117	482730
rs2427530	A	G	NA	0.2258	0.0194	0.0029	2.99E-11	-0.0027	0.0203	0.8931	482730
rs2487826	C	T	NA	0.4472	0.0176	0.0025	3.56E-12	-0.0073	0.0184	0.6897	482730
rs2537855	G	A	NA	0.2857	0.0447	0.0028	3.56E-59	0.0318	0.0251	0.2056	468692
rs2618566	T	G	NA	0.6458	-0.0171	0.0026	8.57E-11	-0.01	0.0249	0.6877	466555
rs2642420	A	C	NA	0.185	-0.0247	0.0033	9.54E-14	0.0076	0.0237	0.7484	482730
rs2836950	G	C	NA	0.3642	-0.0154	0.0026	3.64E-09	0.0249	0.0199	0.21	482730
rs2860075	G	A	NA	0.6526	-0.0289	0.0026	1.40E-28	0.0212	0.0204	0.2975	482730
rs28925904	T	C	NA	0.0211	-0.0576	0.0081	1.49E-12	-0.1472	0.0638	0.0211	482730
rs28929474	T	C	NA	0.0174	0.219	0.0091	5.87E-129	-0.0862	0.0679	0.204	482730
rs2943641	C	T	NA	0.6386	-0.0322	0.0026	6.16E-35	0.0068	0.0175	0.6994	482730
rs3132469	G	A	NA	0.8715	-0.033	0.0035	8.29E-21	0.0093	0.0298	0.7561	480593

Table S6 (*continued*)

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Table S6 (*continued*)

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome	samplesize
rs34145453	G	A	NA	0.3663	0.0189	0.0026	2.90E-13	0.0204	0.0181	0.2579	482730
rs34372369	A	G	NA	0.0538	0.037	0.0057	6.20E-11	-0.0423	0.038	0.2657	482730
rs35371479	T	C	NA	0.1823	0.0256	0.0033	7.00E-15	0.0013	0.0219	0.9532	482730
rs35627524	G	T	NA	0.041	-0.0433	0.0067	1.09E-10	0.1131	0.0589	0.05491	468692
rs3749237	A	G	NA	0.3056	-0.0257	0.0027	8.87E-22	0.0032	0.0187	0.8634	482730
rs3779195	A	T	NA	0.1769	-0.0768	0.0032	2.35E-126	-0.0101	0.0289	0.7277	469486
rs3818247	T	G	NA	0.3454	-0.0247	0.0026	2.95E-21	-0.0074	0.0246	0.7634	468692
rs3848375	T	C	NA	0.8161	0.0231	0.0032	3.11E-13	0.0302	0.0288	0.2947	470485
rs41302867	A	G	NA	0.1283	-0.0342	0.0039	8.26E-19	-0.0614	0.0281	0.02862	480593
rs4149056	C	T	NA	0.1568	-0.067	0.0035	9.39E-81	-2.00E-04	0.0231	0.9915	482730
rs4381968	T	C	NA	0.5561	-0.0138	0.0025	4.23E-08	0.0479	0.0226	0.03398	468692
rs440837	G	A	NA	0.2243	0.0466	0.0031	1.16E-50	0.0121	0.0227	0.5942	482730
rs45512696	T	C	NA	0.162	0.0407	0.0033	2.72E-34	0.0081	0.0305	0.7921	468692
rs45535039	C	T	NA	0.2844	0.0204	0.0028	3.34E-13	-0.0097	0.0189	0.6086	482730
rs4639796	A	G	NA	0.1593	-0.0296	0.0034	3.23E-18	-0.0072	0.0231	0.7557	482730
rs464605	T	C	NA	0.7392	-0.0323	0.0029	1.25E-29	-0.0216	0.0239	0.3653	471013
rs4660293	G	A	NA	0.2343	-0.0295	0.003	5.90E-23	0.002	0.0199	0.9188	482730
rs4690098	T	C	NA	0.2325	-0.0498	0.003	1.01E-61	0.0279	0.0256	0.2764	27693
rs4822455	T	C	NA	0.5782	-0.0184	0.0025	3.48E-13	-0.0035	0.017	0.8361	482730
rs4983559	A	G	NA	0.6129	-0.0179	0.0026	2.85E-12	0.0058	0.0177	0.7419	482730
rs555754	A	G	NA	0.4866	0.0343	0.0025	5.02E-42	-0.0083	0.0177	0.6395	482730
rs55707100	T	C	NA	0.0329	-0.1171	0.0081	1.76E-47	0.0011	0.0477	0.9814	482730
rs55840085	A	G	NA	0.3526	0.0195	0.0026	6.35E-14	0.0242	0.0234	0.2991	468692
rs56196860	A	C	NA	0.0298	0.0478	0.0073	5.01E-11	0.0207	0.0769	0.7873	468692
rs5745687	T	C	NA	0.0664	0.0307	0.0051	2.07E-09	0.0087	0.0343	0.8006	482730
rs57506806	G	A	NA	0.2287	0.0351	0.003	2.25E-32	0.0066	0.0235	0.7797	482730
rs58941251	T	C	NA	0.1032	-0.0241	0.0041	2.74E-09	0.05	0.0313	0.1109	482730
rs6129800	A	G	NA	0.2198	0.0239	0.003	1.35E-15	0.0122	0.0211	0.5628	482730
rs61935507	T	C	NA	0.1351	-0.0295	0.0037	1.50E-15	-0.0535	0.0333	0.1087	468692
rs62576339	C	T	NA	0.2525	0.03	0.0029	8.22E-25	0.0421	0.0224	0.0603	482730
rs62580767	C	T	NA	0.1771	0.0234	0.0033	8.54E-13	0.0121	0.0291	0.6788	469691
rs62618693	T	C	NA	0.0409	0.041	0.0061	1.93E-11	8.00E-04	0.0444	0.9851	482730
rs6356	T	C	NA	0.3693	0.0199	0.0026	2.43E-14	-0.0532	0.0192	0.00548	482730
rs645040	T	G	NA	0.7687	-0.0691	0.003	9.86E-120	0.0149	0.0199	0.4552	482730
rs6736913	G	A	NA	0.9819	-0.0712	0.0089	1.12E-15	-0.0474	0.0667	0.4767	482730
rs6756943	A	G	NA	0.7016	-0.0448	0.0027	5.62E-61	-0.018	0.0243	0.4602	468692
rs6954673	T	C	NA	0.3485	-0.0185	0.0026	1.27E-12	-0.0232	0.0176	0.1875	482730
rs7221345	A	G	NA	0.6011	-0.0325	0.0026	3.13E-37	-0.0342	0.0177	0.05283	482730
rs7239151	A	G	NA	0.6978	0.0155	0.0027	6.50E-09	0.0223	0.0206	0.278	482730
rs724577	C	A	NA	0.7368	-0.0186	0.0028	6.04E-11	-0.0017	0.0193	0.9288	482730
rs7250351	A	G	NA	0.8885	0.0229	0.0041	2.17E-08	0.0508	0.0291	0.08128	482730
rs7250425	T	C	NA	0.5031	0.0179	0.0025	7.64E-13	0.0211	0.0186	0.2565	482730
rs72683923	C	T	NA	0.0168	0.0774	0.0092	5.67E-17	0.0608	0.0764	0.4257	482730
rs72756074	G	A	NA	0.1196	0.023	0.0038	1.65E-09	0.055	0.0273	0.04429	482730
rs7314285	G	T	NA	0.069	0.0764	0.0048	3.82E-56	0.0029	0.0382	0.9397	480937
rs738409	G	C	NA	0.2306	0.0486	0.003	5.06E-58	-0.0088	0.02	0.6613	482730
rs7429135	G	T	NA	0.8394	0.0199	0.0034	5.92E-09	-0.0302	0.0246	0.2196	482730
rs750472	C	A	NA	0.5031	-0.0216	0.0025	4.22E-18	0.0226	0.0176	0.1992	482730
rs76610881	G	A	NA	0.097	0.0418	0.0041	7.29E-25	-0.0251	0.0347	0.4692	482730
rs7694379	A	G	NA	0.4194	-0.042	0.0025	4.75E-62	-0.0261	0.0191	0.1721	482730
rs7697204	T	C	NA	0.7344	-0.0295	0.0028	4.24E-25	-0.0287	0.0225	0.2038	482730
rs78025076	T	C	NA	0.0203	0.0503	0.0089	1.62E-08	0.095	0.0866	0.2726	468692
rs78444298	A	G	NA	0.0159	-0.0613	0.0093	5.44E-11	0.2158	0.0795	0.006635	27693
rs7922067	A	G	NA	0.5802	-0.0211	0.0025	1.18E-16	0.0034	0.0185	0.8538	482730
rs7947951	G	A	NA	0.6843	-0.0283	0.0027	9.37E-26	0.0205	0.0213	0.3346	482730
rs7994151	G	A	NA	0.1531	-0.0206	0.0035	2.89E-09	-0.0677	0.0311	0.0294	468692
rs8017377	A	G	NA	0.4707	-0.0342	0.0025	3.92E-42	8.00E-04	0.0168	0.9621	482730
rs8023580	C	T	NA	0.2936	0.073	0.0028	1.52E-150	-0.0401	0.0245	0.1023	468692
rs9316500	G	T	NA	0.3028	-0.0172	0.0027	3.05E-10	-0.006	0.0182	0.7397	482730
rs9332817	C	G	NA	0.0269	0.05	0.0079	3.09E-10	-0.0445	0.0663	0.5019	480593
rs9388768	A	C	NA	0.6733	-0.0197	0.0027	1.39E-13	0.0177	0.0179	0.3227	482730
rs9427104	T	C	NA	0.4771	0.027	0.0025	4.04E-27	0.0289	0.0181	0.1101	482730
rs9556403	G	A	NA	0.361	0.0205	0.0026	4.66E-15	0.0043	0.0231	0.8529	468692
rs9644032	G	T	NA	0.62	-0.0159	0.0026	1.03E-09	-0.0081	0.0179	0.6495	482730
rs976002	G	A	NA	0.2222	0.035	0.0029	1.60E-33	0.0099	0.0212	0.6421	480593
rs9892297	G	A	NA	0.3233	-0.1366	0.0026	1.00E-200	0.0377	0.0182	0.0387	482730
rs9987289	G	A	NA	0.9115	0.0437	0.0043	3.22E-24	0.0615	0.031	0.04728	482730

SNP, single nucleotide polymorphism; PD, Parkinson's disease; GWAS, genome-wide association studies; NA, not available.

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Table S7 SNPs identified in MS GWAS

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome	samplesize
rs10069690	T	C	NA	0.3476	-0.017	0.0028	2.13E-09	0.125928	0.03811	0.000952	115000
rs1060817	G	A	NA	0.4884	-0.0176	0.0025	5.12E-12	-0.01582	0.016647	0.3418	115000
rs1076540	T	C	NA	0.1655	0.0169	0.0029	8.14E-09	-0.00682	0.019279	0.7234	115000
rs10838681	A	G	NA	0.4355	0.0162	0.0028	8.80E-09	0.082947	0.018379	6.39E-06	115000
rs10871777	G	A	NA	0.2458	-0.0227	0.0029	8.41E-15	0.003908	0.018958	0.8367	115000
rs1106766	T	C	NA	0.1392	0.0357	0.0029	5.41E-34	0.002002	0.019785	0.9194	115000
rs11075253	A	C	NA	0.1318	0.023	0.0028	6.30E-17	-0.0004	0.019696	0.9838	115000
rs11078405	T	G	NA	0.7282	-0.0293	0.0026	1.40E-29	0.018571	0.016658	0.2649	115000
rs1126670	A	C	NA	0.8472	-0.028	0.0027	1.35E-24	0.005982	0.017447	0.7317	115000
rs1128249	T	G	NA	0.394	0.0286	0.0026	8.43E-29	-0.00955	0.016717	0.568	115000
rs11550348	A	G	NA	0.1366	0.0536	0.0038	5.40E-46	-0.02225	0.026093	0.3938	115000
rs116189680	A	G	NA	0.0132	0.1439	0.0077	6.52E-78	0.200404	0.17565	0.2539	115000
rs11626364	C	T	NA	0.1254	0.0237	0.0035	9.61E-12	0.002002	0.023601	0.9324	115000
rs11636917	C	T	NA	0.1623	-0.0247	0.0026	1.06E-20	-0.03256	0.017117	0.05711	115000
rs11647008	C	T	NA	0.2061	-0.0249	0.0025	6.86E-23	0.009142	0.016493	0.5794	115000
rs11655704	C	T	NA	0.3385	0.0785	0.0027	1.30E-189	-0.01134	0.017803	0.5243	115000
rs11739158	T	C	NA	0.4135	0.0148	0.0025	4.85E-09	0.005616	0.01636	0.7314	115000
rs11748288	G	A	NA	0.3808	0.0167	0.0025	5.85E-11	-0.00723	0.016587	0.6631	115000
rs1183910	A	G	NA	0.2955	-0.0261	0.0027	6.73E-22	-0.00866	0.01751	0.6208	115000
rs11856886	G	A	NA	0.2752	0.0194	0.0027	1.27E-12	-0.001	0.018115	0.956	115000
rs11887329	G	A	NA	0.2097	-0.0213	0.003	7.13E-13	0.012883	0.018914	0.4958	115000
rs11918018	A	G	NA	0.47	-0.0153	0.0025	1.03E-09	-0.01654	0.016291	0.3101	115000
rs11935444	C	T	NA	0.4978	-0.0165	0.0026	4.11E-10	-0.01298	0.016621	0.4347	115000
rs12192649	A	G	NA	0.102	0.022	0.003	9.97E-14	0.016129	0.019279	0.4028	115000
rs12325400	G	C	NA	0.3339	-0.016	0.0026	4.03E-10	0.067423	0.016707	5.45E-05	115000
rs12414178	T	C	NA	0.387	-0.0269	0.0029	5.57E-20	0.003305	0.019184	0.8632	115000
rs12569576	G	A	NA	0.356	-0.017	0.0025	1.25E-11	-0.01843	0.01708	0.2806	115000
rs12575636	G	T	NA	0.1354	-0.027	0.0033	1.36E-16	0.082078	0.020717	7.44E-05	115000
rs1260326	C	T	NA	0.7067	0.0772	0.0026	4.58E-198	0.009243	0.016562	0.5768	115000
rs12748152	T	C	NA	0.0387	-0.0668	0.0046	2.79E-47	0.038117	0.030147	0.2061	115000
rs12941564	G	C	NA	0.2929	0.0239	0.0028	1.31E-17	0.008662	0.017857	0.6276	115000
rs13094241	G	T	NA	0.6342	0.0172	0.0028	1.04E-09	-0.00628	0.018388	0.7327	115000
rs13354321	C	T	NA	0.3281	0.0144	0.0025	1.44E-08	0.010353	0.016853	0.539	115000
rs1421085	C	T	NA	0.2286	-0.0183	0.0026	8.91E-13	0.031491	0.016436	0.05537	115000
rs1497406	G	A	NA	0.4421	0.027	0.0025	1.56E-26	0.015873	0.016553	0.3376	115000
rs1547014	C	T	NA	0.6867	-0.0293	0.0027	5.70E-28	-0.0313	0.017634	0.07586	115000
rs1556562	T	G	NA	0.91993	0.0243	0.003	8.54E-16	-0.01461	0.020108	0.4676	115000
rs157934	C	T	NA	0.3215	0.0229	0.0027	4.25E-17	-0.01331	0.018272	0.4663	115000
rs1635852	C	T	NA	0.3089	0.0187	0.0025	6.54E-14	-0.0472	0.016236	0.003651	115000
rs16845803	G	A	NA	0.2021	-0.0251	0.0037	1.08E-11	-0.01005	0.024046	0.676	115000
rs17041868	C	T	NA	0.1054	-0.0346	0.005	6.49E-12	0.036525	0.033795	0.2798	115000
rs1716403	C	T	NA	0.7726	-0.0168	0.0027	3.75E-10	-0.0028	0.017492	0.873	115000
rs17202341	G	A	NA	0.1675	0.0157	0.0026	2.86E-09	0.057523	0.017904	0.001314	115000
rs17377148	G	T	NA	0.0248	0.0401	0.0048	1.13E-16	0.006219	0.032753	0.8494	115000
rs174601	T	C	NA	0.4924	-0.0252	0.0026	1.80E-22	-0.00965	0.017997	0.5917	115000
rs1755618	T	G	NA	0.2079	-0.0252	0.0035	1.17E-12	-0.04574	0.023661	0.05323	115000
rs17580	A	T	NA	0.0196	0.0535	0.0059	1.54E-19	0.068921	0.06441	0.2846	115000
rs17628931	C	T	NA	0.0347	0.0294	0.0041	4.71E-13	0.017859	0.027215	0.5117	115000
rs1772183	A	G	NA	0.6026	-0.022	0.0025	1.30E-18	0.007571	0.016135	0.6389	115000
rs17794619	A	G	NA	0.0691	-0.0347	0.0037	3.61E-21	0.019897	0.024667	0.4199	115000
rs17826544	G	A	NA	0.3802	0.029	0.0026	3.87E-29	-0.01847	0.016761	0.2705	115000
rs1801282	G	C	NA	0.0703	0.0377	0.0039	1.41E-22	-0.02303	0.024737	0.3518	115000
rs1801689	C	A	NA	0.0164	-0.0912	0.0074	6.69E-35	0.021632	0.141156	0.8782	115000
rs1832007	G	A	NA	0.1024	-0.0483	0.0035	3.66E-43	-0.00985	0.022571	0.6625	115000
rs1935	G	C	NA	0.3922	0.1198	0.0025	1.00E-200	-0.00592	0.016241	0.7156	115000
rs1982151	G	A	NA	0.6711	-0.049	0.0028	9.23E-67	-0.07037	0.018302	0.000121	115000
rs2081687	C	T	NA	0.72	0.0247	0.0026	1.03E-20	-0.00793	0.01705	0.6418	115000
rs2205262	A	C	NA	0.6727	-0.0167	0.0025	4.00E-11	-0.02157	0.016437	0.1895	115000
rs2254069	A	G	NA	0.2686	-0.0265	0.0038	2.11E-12	0.0002	0.033956	0.9953	115000
rs2266782	A	G	NA	0.3478	-0.0163	0.0025	1.25E-10	-0.00339	0.016156	0.8336	115000
rs2335077	G	A	NA	0.3053	0.0463	0.0026	1.71E-69	0.02596	0.017373	0.1351	115000
rs2427530	A	G	NA	0.263	0.0194	0.0029	2.99E-11	0.06294	0.019664	0.001371	115000
rs2487826	C	T	NA	0.4163	0.0176	0.0025	3.56E-12	-0.00541	0.016375	0.7409	115000
rs2537855	G	A	NA	0.2997	0.0447	0.0028	3.56E-59	0.034799	0.018509	0.06009	115000
rs2618566	T	G	NA	0.5909	-0.0171	0.0026	8.57E-11	-0.01745	0.019551	0.3722	115000
rs2642420	A	C	NA	0.1258	-0.0247	0.0033	9.54E-14	0.00894	0.021496	0.6775	115000
rs2836950	G	C	NA	0.3055	-0.0154	0.0026	3.64E-09	0.007629	0.017601	0.6647	115000
rs2860075	G	A	NA	0.3766	-0.0289	0.0026	1.40E-28	-0.02342	0.017054	0.1696	115000
rs28925904	T	C	NA	0.0078	-0.0576	0.0081	1.49E-12	0.254763	0.434115	0.5573	115000
rs28929474	T	C	NA	0.004	0.219	0.0091	5.87E-129	0.100705	0.060153	0.0941	115000
rs2943641	C	T	NA	0.7508	-0.0322	0.0026	6.16E-35	0.052592	0.016947	0.001913	115000

Table S7 (*continued*)

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Table S7 (*continued*)

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome	samplesize
rs3132469	G	A	NA	0.94089	-0.033	0.0035	8.29E-21	-0.57501	0.021592	2.99E-156	115000
rs34145453	G	A	NA	0.4491	0.0189	0.0026	2.90E-13	-0.03237	0.018158	0.07463	115000
rs34372369	A	G	NA	0.0313	0.037	0.0057	6.20E-11	0.039157	0.039858	0.3259	115000
rs35371479	T	C	NA	0.0613	0.0256	0.0033	7.00E-15	-0.02557	0.020748	0.2178	115000
rs35386490	C	T	NA	0.0557	0.1118	0.003	1.00E-200	-0.06194	0.026522	0.01952	115000
rs3749237	A	G	NA	0.2384	-0.0257	0.0027	8.87E-22	0.024293	0.017463	0.1642	115000
rs3779195	A	T	NA	0.1991	-0.0768	0.0032	2.35E-126	-0.0008	0.022559	0.9717	115000
rs3818247	T	G	NA	0.4934	-0.0247	0.0026	2.95E-21	-0.0013	0.024468	0.9576	115000
rs3848375	T	C	NA	0.6448	0.0231	0.0032	3.11E-13	-0.01593	0.020925	0.4466	115000
rs41302867	A	G	NA	0.0469	-0.0342	0.0039	8.26E-19	-0.08149	0.029371	0.00553	115000
rs4149056	C	T	NA	0.0877	-0.067	0.0035	9.39E-81	0.019591	0.022269	0.379	115000
rs4381968	T	C	NA	0.6625	-0.0138	0.0025	4.23E-08	-0.00763	0.016644	0.6467	115000
rs440837	G	A	NA	0.4093	0.0466	0.0031	1.16E-50	0.030872	0.019824	0.1194	115000
rs45512696	T	C	NA	0.0645	0.0407	0.0033	2.72E-34	0.008563	0.0221	0.6984	115000
rs45535039	C	T	NA	0.3844	0.0204	0.0028	3.34E-13	0.005883	0.018029	0.7442	115000
rs4639796	A	G	NA	0.2973	-0.0296	0.0034	3.23E-18	0.01552	0.021789	0.4763	115000
rs464605	T	C	NA	0.6064	-0.0323	0.0029	1.25E-29	-0.01349	0.01877	0.4723	115000
rs4660293	G	A	NA	0.0962	-0.0295	0.003	5.90E-23	0.038949	0.018849	0.03879	115000
rs4690098	T	C	NA	0.2159	-0.0498	0.003	1.01E-61	0.017742	0.019944	0.3737	115000
rs4822455	T	C	NA	0.516	-0.0184	0.0025	3.48E-13	-0.00995	0.016542	0.5475	115000
rs4983559	A	G	NA	0.4046	-0.0179	0.0026	2.85E-12	0.01005	0.017213	0.5593	115000
rs555754	A	G	NA	0.4301	0.0343	0.0025	5.02E-42	-0.0008	0.01567	0.9593	115000
rs55707100	T	C	NA	0.0098	-0.1171	0.0081	1.76E-47	-0.02567	0.123762	0.8357	115000
rs55840085	A	G	NA	0.4069	0.0195	0.0026	6.35E-14	0.011237	0.017716	0.5259	115000
rs5745687	T	C	NA	0.0198	0.0307	0.0051	2.07E-09	0.066247	0.033149	0.04567	115000
rs57506806	G	A	NA	0.1567	0.0351	0.003	2.25E-32	0.025933	0.021977	0.238	115000
rs58941251	T	C	NA	0.0787	-0.0241	0.0041	2.74E-09	0.029326	0.026057	0.2604	115000
rs6129800	A	G	NA	0.3742	0.0239	0.003	1.35E-15	-0.05685	0.019756	0.004006	115000
rs61935507	T	C	NA	0.0909	-0.0295	0.0037	1.50E-15	-0.02235	0.024359	0.3589	115000
rs62576339	C	T	NA	0.2917	0.03	0.0029	8.22E-25	-0.00588	0.019117	0.7583	115000
rs62580767	C	T	NA	0.0769	0.0234	0.0033	8.54E-13	0.017044	0.021264	0.4228	115000
rs62618693	T	C	NA	0.0106	0.041	0.0061	1.93E-11	0.156069	0.097736	0.1103	115000
rs6356	T	C	NA	0.4305	0.0199	0.0026	2.43E-14	0.005385	0.017906	0.7636	115000
rs645040	T	G	NA	0.7638	-0.0691	0.003	9.86E-120	0.009142	0.019693	0.6425	115000
rs6736913	G	A	NA	0.996206	-0.0712	0.0089	1.12E-15	0.276115	0.308195	0.3703	115000
rs6756943	A	G	NA	0.7354	-0.0448	0.0027	5.62E-61	0.009041	0.017844	0.6124	115000
rs6954673	T	C	NA	0.3175	-0.0185	0.0026	1.27E-12	-0.00783	0.017058	0.6462	115000
rs7221345	A	G	NA	0.5445	-0.0325	0.0026	3.13E-37	-0.07775	0.017103	5.48E-06	115000
rs7239151	A	G	NA	0.5505	0.0155	0.0027	6.50E-09	-0.00411	0.018045	0.8199	115000
rs724577	C	A	NA	0.6855	-0.0186	0.0028	6.04E-11	0.037199	0.018332	0.04244	115000
rs7250351	A	G	NA	0.6558	0.0229	0.0041	2.17E-08	0.019607	0.037667	0.6027	115000
rs7250425	T	C	NA	0.5821	0.0179	0.0025	7.64E-13	0.058159	0.016587	0.000454	115000
rs72756074	G	A	NA	0.11	0.023	0.0038	1.65E-09	0.012376	0.025248	0.624	115000
rs7314285	G	T	NA	0.2526	0.0764	0.0048	3.82E-56	0.041135	0.034188	0.2289	115000
rs738409	G	C	NA	0.2622	0.0486	0.003	5.06E-58	0.013896	0.019634	0.4791	115000
rs7429135	G	T	NA	0.7742	0.0199	0.0034	5.92E-09	-0.02153	0.022148	0.331	115000
rs750472	C	A	NA	0.4443	-0.0216	0.0025	4.22E-18	-0.00521	0.017237	0.7623	115000
rs76610881	G	A	NA	0.031	0.0418	0.0041	7.29E-25	0.100262	0.04966	0.04349	115000
rs7694379	A	G	NA	0.3554	-0.042	0.0025	4.75E-62	0.005716	0.016405	0.7275	115000
rs7697204	T	C	NA	0.6226	-0.0295	0.0028	4.24E-25	-0.01918	0.018639	0.3034	115000
rs7922067	A	G	NA	0.2849	-0.0211	0.0025	1.18E-16	-0.0283	0.016893	0.09393	115000
rs7947951	G	A	NA	0.6014	-0.0283	0.0027	9.37E-26	-0.00558	0.017439	0.7488	115000
rs7994151	G	A	NA	0.2198	-0.0206	0.0035	2.89E-09	0.023781	0.022788	0.2967	115000
rs8017377	A	G	NA	0.2444	-0.0342	0.0025	3.92E-42	0.032213	0.01667	0.05331	115000
rs8023580	C	T	NA	0.3125	0.073	0.0028	1.52E-150	0.034695	0.018596	0.06208	115000
rs9316500	G	T	NA	0.3375	-0.0172	0.0027	3.05E-10	0.010353	0.017836	0.5616	115000
rs9332817	C	G	NA	0.0114	0.05	0.0079	3.09E-10	0.04877	0.116925	0.6766	115000
rs9388768	A	C	NA	0.504	-0.0197	0.0027	1.39E-13	0.050883	0.017461	0.003567	115000
rs9427104	T	C	NA	0.3958	0.027	0.0025	4.04E-27	0.003105	0.016242	0.8484	115000
rs9556403	G	A	NA	0.388	0.0205	0.0026	4.66E-15	-0.00421	0.016793	0.8021	115000
rs9644032	G	T	NA	0.7065	-0.0159	0.0026	1.03E-09	-0.01518	0.016895	0.3688	115000
rs9892297	G	A	NA	0.3482	-0.1366	0.0026	1.00E-200	0.026241	0.017705	0.1383	115000
rs9987289	G	A	NA	0.886	0.0437	0.0043	3.22E-24	0.022348	0.029139	0.4431	115000

SNP, single nucleotide polymorphism; MS, multiple sclerosis; GWAS, genome-wide association studies; NA, not available.

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Table S8 SNPs identified in DLB GWAS

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs10069690	T	C	NA	0.259871	-0.017	0.0028	2.13E-09	0.001479	0.042246	0.972028
rs1060817	G	A	NA	0.596598	-0.0176	0.0025	5.12E-12	0.056777	0.037772	0.132805
rs1076540	T	C	NA	0.240502	0.0169	0.0029	8.14E-09	0.002257	0.043422	0.958514
rs10838681	A	G	NA	0.240502	0.0162	0.0028	8.80E-09	0.012344	0.042933	0.773647
rs11075253	A	C	NA	0.313136	0.023	0.0028	6.30E-17	0.001748	0.039493	0.964768
rs11078405	T	G	NA	0.402781	-0.0293	0.0026	1.40E-29	-0.05894	0.038484	0.125619
rs1126670	A	C	NA	0.675317	-0.028	0.0027	1.35E-24	0.060169	0.039896	0.13152
rs1128249	T	G	NA	0.399181	0.0286	0.0026	8.43E-29	0.046559	0.037765	0.217645
rs11550348	A	G	NA	0.125031	0.0536	0.0038	5.40E-46	0.017093	0.055984	0.760083
rs116189680	A	G	NA	0.02297	0.1439	0.0077	6.52E-78	0.300542	0.116166	0.009677
rs11626364	C	T	NA	0.158182	0.0237	0.0035	9.61E-12	0.020038	0.051236	0.695713
rs11636917	C	T	NA	0.368016	-0.0247	0.0026	1.06E-20	-0.02352	0.038591	0.542287
rs11655704	C	T	NA	0.307177	0.0785	0.0027	1.30E-189	-0.03443	0.039913	0.388363
rs11739158	T	C	NA	0.434318	0.0148	0.0025	4.85E-09	-0.09833	0.037534	0.008798
rs11748288	G	A	NA	0.579339	0.0167	0.0025	5.85E-11	0.073746	0.037828	0.051233
rs1183910	A	G	NA	0.329898	-0.0261	0.0027	6.73E-22	0.042207	0.039347	0.283434
rs11856886	G	A	NA	0.302334	0.0194	0.0027	1.27E-12	0.040979	0.039594	0.3007
rs11887329	G	A	NA	0.237522	-0.0213	0.003	7.13E-13	-0.01171	0.043009	0.785398
rs11918018	A	G	NA	0.462627	-0.0153	0.0025	1.03E-09	-0.02809	0.037449	0.453224
rs11935444	C	T	NA	0.562329	-0.0165	0.0026	4.11E-10	0.018373	0.037969	0.62846
rs12192649	A	G	NA	0.214055	0.022	0.003	9.97E-14	0.022788	0.044747	0.610504
rs12325400	G	C	NA	0.390986	-0.016	0.0026	4.03E-10	-0.1301	0.038194	0.000659
rs12414178	T	C	NA	0.25118	-0.0269	0.0029	5.57E-20	0.00016	0.042843	0.997008
rs12569576	G	A	NA	0.436057	-0.017	0.0025	1.25E-11	0.0866	0.037424	0.020671
rs12575636	G	T	NA	0.200273	-0.027	0.0033	1.36E-16	0.048685	0.046164	0.291626
rs1260326	C	T	NA	0.565061	0.0772	0.0026	4.58E-198	0.02041	0.037293	0.584175
rs12748152	T	C	NA	0.070524	-0.0668	0.0046	2.79E-47	0.015568	0.070765	0.82592
rs13094241	G	T	NA	0.733673	0.0172	0.0028	1.04E-09	-0.0191	0.041357	0.644326
rs1421085	C	T	NA	0.420164	-0.0183	0.0026	8.91E-13	0.019469	0.037619	0.604807
rs1497406	G	A	NA	0.564813	0.027	0.0025	1.56E-26	0.021522	0.037193	0.562832
rs1547014	C	T	NA	0.705488	-0.0293	0.0027	5.70E-28	-0.06377	0.039973	0.1106
rs1556562	T	G	NA	0.811274	0.0243	0.003	8.54E-16	-0.11378	0.046483	0.014367
rs157934	C	T	NA	0.299106	0.0229	0.0027	4.25E-17	-0.0601	0.04018	0.134748
rs1635852	C	T	NA	0.505339	0.0187	0.0025	6.54E-14	-0.01758	0.03689	0.633554
rs16845803	G	A	NA	0.131487	-0.0251	0.0037	1.08E-11	0.032632	0.053855	0.544554
rs17041868	C	T	NA	0.060839	-0.0346	0.005	6.49E-12	-0.00601	0.078529	0.939001
rs1716403	C	T	NA	0.679662	-0.0168	0.0027	3.75E-10	0.026139	0.039877	0.512153
rs17202341	G	A	NA	0.341694	0.0157	0.0026	2.86E-09	-0.0327	0.038963	0.401366
rs17377148	G	T	NA	0.059722	0.0401	0.0048	1.13E-16	0.075961	0.075036	0.31138
rs174601	T	C	NA	0.35262	-0.0252	0.0026	1.80E-22	0.06634	0.038757	0.086969
rs1755618	T	G	NA	0.139806	-0.0252	0.0035	1.17E-12	0.031198	0.05268	0.553656
rs17580	A	T	NA	0.03489	0.0535	0.0059	1.54E-19	0.144014	0.093757	0.124531
rs17628931	C	T	NA	0.102682	0.0294	0.0041	4.71E-13	0.125372	0.059669	0.035627
rs1772183	A	G	NA	0.482493	-0.022	0.0025	1.30E-18	-0.01224	0.037342	0.743096
rs17794619	A	G	NA	0.13335	-0.0347	0.0037	3.61E-21	0.002477	0.05411	0.96355
rs17826544	G	A	NA	0.640055	0.029	0.0026	3.87E-29	-0.12952	0.038524	0.000774
rs1801689	C	A	NA	0.034641	-0.0912	0.0074	6.69E-35	0.070719	0.102279	0.489314
rs1832007	G	A	NA	0.139185	-0.0483	0.0035	3.66E-43	0.050512	0.05251	0.33607
rs1935	G	C	NA	0.494289	0.1198	0.0025	1.00E-200	0.038846	0.036827	0.291493
rs1982151	G	A	NA	0.719146	-0.049	0.0028	9.23E-67	0.046154	0.041751	0.268968
rs2081687	C	T	NA	0.647256	0.0247	0.0026	1.03E-20	-0.00095	0.039129	0.98067
rs2205262	A	C	NA	0.595853	-0.0167	0.0025	4.00E-11	-0.01411	0.037714	0.708311
rs2254069	A	G	NA	0.115843	-0.0265	0.0038	2.11E-12	0.020724	0.058165	0.721603
rs2266782	A	G	NA	0.401664	-0.0163	0.0025	1.25E-10	-0.01273	0.037757	0.736063
rs2335077	G	A	NA	0.347902	0.0463	0.0026	1.71E-69	-0.0759	0.039103	0.052238
rs2427530	A	G	NA	0.225602	0.0194	0.0029	2.99E-11	0.016995	0.043725	0.697585
rs2487826	C	T	NA	0.455302	0.0176	0.0025	3.56E-12	0.044237	0.03728	0.235366
rs2537855	G	A	NA	0.290539	0.0447	0.0028	3.56E-59	0.030481	0.040329	0.449709
rs2618566	T	G	NA	0.638813	-0.0171	0.0026	8.57E-11	0.030121	0.038709	0.436482
rs2642420	A	C	NA	0.17184	-0.0247	0.0033	9.54E-14	0.056862	0.04899	0.245781
rs2836950	G	C	NA	0.355972	-0.0154	0.0026	3.64E-09	-0.07527	0.039451	0.056397
rs2860075	G	A	NA	0.663645	-0.0289	0.0026	1.40E-28	-0.0049	0.039274	0.900735
rs28925904	T	C	NA	0.0185	-0.0576	0.0081	1.49E-12	0.108514	0.131759	0.410198
rs28929474	T	C	NA	0.016389	0.219	0.0091	5.87E-129	0.029908	0.140193	0.831056
rs2943641	C	T	NA	0.637447	-0.0322	0.0026	6.16E-35	0.004763	0.038196	0.900761
rs34145453	G	A	NA	0.375962	0.0189	0.0026	2.90E-13	-0.00391	0.038817	0.919813
rs34372369	A	G	NA	0.056245	0.037	0.0057	6.20E-11	-0.13479	0.08441	0.110289
rs35371479	T	C	NA	0.192575	0.0256	0.0033	7.00E-15	0.025629	0.047055	0.586062
rs35386490	C	T	NA	0.196052	0.1118	0.003	1.00E-200	-0.06884	0.046208	0.136283
rs3749237	A	G	NA	0.290911	-0.0257	0.0027	8.87E-22	0.02781	0.04032	0.490389
rs3779195	A	T	NA	0.172337	-0.0768	0.0032	2.35E-126	-0.00323	0.04883	0.947332

Table S8 (*continued*)

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Table S8 (*continued*)

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs3818247	T	G	NA	0.330767	-0.0247	0.0026	2.95E-21	0.016857	0.038899	0.664841
rs3848375	T	C	NA	0.816489	0.0231	0.0032	3.11E-13	-0.07451	0.047778	0.118874
rs41302867	A	G	NA	0.119444	-0.0342	0.0039	8.26E-19	-0.04102	0.056635	0.46887
rs4149056	C	T	NA	0.150981	-0.067	0.0035	9.39E-81	-0.00313	0.051724	0.951816
rs440837	G	A	NA	0.23181	0.0466	0.0031	1.16E-50	-0.02128	0.044604	0.633355
rs45512696	T	C	NA	0.152098	0.0407	0.0033	2.72E-34	-0.00898	0.050176	0.858041
rs45535039	C	T	NA	0.288428	0.0204	0.0028	3.34E-13	-0.02028	0.041364	0.623955
rs4639796	A	G	NA	0.16141	-0.0296	0.0034	3.23E-18	-0.07048	0.050735	0.164795
rs464605	T	C	NA	0.742985	-0.0323	0.0029	1.25E-29	0.042076	0.042286	0.319726
rs4660293	G	A	NA	0.232928	-0.0295	0.003	5.90E-23	0.007383	0.043254	0.864418
rs4690098	T	C	NA	0.23181	-0.0498	0.003	1.01E-61	-0.06162	0.043888	0.16034
rs4822455	T	C	NA	0.567917	-0.0184	0.0025	3.48E-13	0.00838	0.037555	0.823419
rs4983559	A	G	NA	0.622796	-0.0179	0.0026	2.85E-12	-0.03127	0.037885	0.409268
rs555754	A	G	NA	0.510678	0.0343	0.0025	5.02E-42	-0.0631	0.036812	0.086504
rs55840085	A	G	NA	0.371244	0.0195	0.0026	6.35E-14	-0.07872	0.038362	0.040155
rs56196860	A	C	NA	0.031041	0.0478	0.0073	5.01E-11	-0.10207	0.108608	0.347333
rs5745687	T	C	NA	0.073256	0.0307	0.0051	2.07E-09	-0.06318	0.074045	0.393509
rs57506806	G	A	NA	0.229451	0.0351	0.003	2.25E-32	-0.02601	0.044066	0.555086
rs58941251	T	C	NA	0.111622	-0.0241	0.0041	2.74E-09	-0.00215	0.059326	0.97109
rs6129800	A	G	NA	0.212317	0.0239	0.003	1.35E-15	0.005395	0.044497	0.903447
rs61935507	T	C	NA	0.141793	-0.0295	0.0037	1.50E-15	0.027498	0.053283	0.605827
rs62576339	C	T	NA	0.248945	0.03	0.0029	8.22E-25	0.019881	0.043206	0.645381
rs62580767	C	T	NA	0.184132	0.0234	0.0033	8.54E-13	-0.01178	0.048637	0.808604
rs62618693	T	C	NA	0.043705	0.041	0.0061	1.93E-11	-0.06574	0.090072	0.465456
rs6356	T	C	NA	0.370872	0.0199	0.0026	2.43E-14	0.044189	0.0383	0.248568
rs6736913	G	A	NA	0.98597	-0.0712	0.0089	1.12E-15	-0.12571	0.14852	0.39732
rs6756943	A	G	NA	0.689223	-0.0448	0.0027	5.62E-61	0.011513	0.040004	0.773499
rs6954673	T	C	NA	0.334741	-0.0185	0.0026	1.27E-12	0.078978	0.038955	0.04262
rs7221345	A	G	NA	0.60144	-0.0325	0.0026	3.13E-37	-0.00475	0.037421	0.899105
rs7239151	A	G	NA	0.700521	0.0155	0.0027	6.50E-09	0.020496	0.040513	0.612929
rs724577	C	A	NA	0.732804	-0.0186	0.0028	6.04E-11	0.081037	0.042269	0.055219
rs7250351	A	G	NA	0.896325	0.0229	0.0041	2.17E-08	-0.00444	0.059524	0.940562
rs7250425	T	C	NA	0.507946	0.0179	0.0025	7.64E-13	-0.01528	0.036954	0.679166
rs72683923	C	T	NA	0.015644	0.0774	0.0092	5.67E-17	-0.23903	0.154838	0.12266
rs72756074	G	A	NA	0.123417	0.023	0.0038	1.65E-09	-0.07891	0.057793	0.172139
rs7314285	G	T	NA	0.068413	0.0764	0.0048	3.82E-56	0.045079	0.071795	0.530119
rs738409	G	C	NA	0.234542	0.0486	0.003	5.06E-58	-0.06511	0.044247	0.141156
rs7429135	G	T	NA	0.835113	0.0199	0.0034	5.92E-09	0.019747	0.050787	0.697406
rs750472	C	A	NA	0.496896	-0.0216	0.0025	4.22E-18	0.039573	0.037268	0.288307
rs76610881	G	A	NA	0.094736	0.0418	0.0041	7.29E-25	0.068527	0.061505	0.265218
rs7694379	A	G	NA	0.415942	-0.042	0.0025	4.75E-62	-0.00325	0.037501	0.930974
rs7697204	T	C	NA	0.732804	-0.0295	0.0028	4.24E-25	0.068592	0.04261	0.107453
rs78025076	T	C	NA	0.017631	0.0503	0.0089	1.62E-08	0.023843	0.137623	0.862441
rs78444298	A	G	NA	0.01341	-0.0613	0.0093	5.44E-11	0.102809	0.152087	0.499062
rs7922067	A	G	NA	0.581202	-0.0211	0.0025	1.18E-16	-0.00152	0.03703	0.967229
rs7947951	G	A	NA	0.68078	-0.0283	0.0027	9.37E-26	0.013196	0.04006	0.741853
rs7994151	G	A	NA	0.156692	-0.0206	0.0035	2.89E-09	-0.06841	0.051743	0.186134
rs8017377	A	G	NA	0.475788	-0.0342	0.0025	3.92E-42	-0.00987	0.03729	0.791324
rs8023580	C	T	NA	0.297492	0.073	0.0028	1.52E-150	0.030646	0.040962	0.454405
rs9316500	G	T	NA	0.307673	-0.0172	0.0027	3.05E-10	0.033938	0.039851	0.394362
rs9332817	C	G	NA	0.028061	0.05	0.0079	3.09E-10	-0.17612	0.117168	0.132797
rs9388768	A	C	NA	0.674447	-0.0197	0.0027	1.39E-13	0.057391	0.039856	0.149884
rs9427104	T	C	NA	0.479017	0.027	0.0025	4.04E-27	0.01412	0.036981	0.70254
rs9556403	G	A	NA	0.365036	0.0205	0.0026	4.66E-15	0.025483	0.03841	0.507082
rs9644032	G	T	NA	0.626397	-0.0159	0.0026	1.03E-09	0.012262	0.03872	0.751479
rs976002	G	A	NA	0.219518	0.035	0.0029	1.60E-33	-0.00871	0.044898	0.846095
rs9892297	G	A	NA	0.328532	-0.1366	0.0026	1.00E-200	-0.04856	0.038982	0.212829
rs9987289	G	A	NA	0.922151	0.0437	0.0043	3.22E-24	0.033742	0.068998	0.624819

SNP, single nucleotide polymorphism; DLB, Dementia with Lewy Bodies; GWAS, genome-wide association studies; NA, not available.

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Table S9 SNPs identified in FTD GWAS

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs1060817	G	A	NA	NA	-0.0176	0.0025	5.12E-12	-0.0136	0.0398	0.7317
rs1076540	T	C	NA	NA	0.0169	0.0029	8.14E-09	0.0587	0.0453	0.1951
rs10838681	A	G	NA	NA	0.0162	0.0028	8.80E-09	-0.047	0.0462	0.3096
rs10871777	G	A	NA	NA	-0.0227	0.0029	8.41E-15	-0.056	0.0451	0.2146
rs1106766	T	C	NA	NA	0.0357	0.0029	5.41E-34	0.2205	0.0579	0.000138
rs11075253	A	C	NA	NA	0.023	0.0028	6.30E-17	0.0339	0.0624	0.5867
rs11078405	T	G	NA	NA	-0.0293	0.0026	1.40E-29	-0.0222	0.0456	0.6273
rs1126670	A	C	NA	NA	-0.028	0.0027	1.35E-24	0.1207	0.0426	0.004562
rs1128249	T	G	NA	NA	0.0286	0.0026	8.43E-29	-0.0555	0.048	0.2477
rs11550348	A	G	NA	NA	0.0536	0.0038	5.40E-46	-0.1076	0.0657	0.1015
rs11626364	C	T	NA	NA	0.0237	0.0035	9.61E-12	-0.0215	0.0531	0.6862
rs11636917	C	T	NA	NA	-0.0247	0.0026	1.06E-20	-0.0259	0.0412	0.5299
rs11647008	C	T	NA	NA	-0.0249	0.0025	6.86E-23	0.0365	0.0607	0.548
rs11655704	C	T	NA	NA	0.0785	0.0027	1.30E-189	0.0036	0.0426	0.9334
rs11739158	T	C	NA	NA	0.0148	0.0025	4.85E-09	0.0217	0.0393	0.5805
rs11748288	G	A	NA	NA	0.0167	0.0025	5.85E-11	0.0344	0.0394	0.3819
rs1183910	A	G	NA	NA	-0.0261	0.0027	6.73E-22	-0.0296	0.0428	0.4895
rs11856886	G	A	NA	NA	0.0194	0.0027	1.27E-12	0.075	0.0429	0.08064
rs11887329	G	A	NA	NA	-0.0213	0.003	7.13E-13	-0.0245	0.0466	0.5986
rs11918018	A	G	NA	NA	-0.0153	0.0025	1.03E-09	0.0037	0.0427	0.9306
rs11935444	C	T	NA	NA	-0.0165	0.0026	4.11E-10	-0.0102	0.0402	0.7998
rs12192649	A	G	NA	NA	0.022	0.003	9.97E-14	0.0027	0.0471	0.9541
rs12325400	G	C	NA	NA	-0.016	0.0026	4.03E-10	-0.0713	0.0406	0.07873
rs12414178	T	C	NA	NA	-0.0269	0.0029	5.57E-20	-0.042	0.0749	0.5747
rs12569576	G	A	NA	NA	-0.017	0.0025	1.25E-11	0.034	0.0419	0.4162
rs12575636	G	T	NA	NA	-0.027	0.0033	1.36E-16	0.0633	0.0494	0.1998
rs1260326	C	T	NA	NA	0.0772	0.0026	4.58E-198	0.0334	0.0392	0.3948
rs12748152	T	C	NA	NA	-0.0668	0.0046	2.79E-47	-0.1212	0.0831	0.1445
rs12941564	G	C	NA	NA	0.0239	0.0028	1.31E-17	0.0716	0.0438	0.1019
rs13094241	G	T	NA	NA	0.0172	0.0028	1.04E-09	-0.0309	0.0472	0.5131
rs1421085	C	T	NA	NA	-0.0183	0.0026	8.91E-13	-0.004	0.0393	0.9184
rs1497406	G	A	NA	NA	0.027	0.0025	1.56E-26	0.0528	0.0393	0.1789
rs1547014	C	T	NA	NA	-0.0293	0.0027	5.70E-28	-0.0165	0.0426	0.6988
rs1556562	T	G	NA	NA	0.0243	0.003	8.54E-16	0.0093	0.0479	0.8463
rs157934	C	T	NA	NA	0.0229	0.0027	4.25E-17	-0.0034	0.0425	0.9367
rs1635852	C	T	NA	NA	0.0187	0.0025	6.54E-14	-8.00E-04	0.0385	0.9833
rs16845803	G	A	NA	NA	-0.0251	0.0037	1.08E-11	0.0576	0.0605	0.3411
rs1716403	C	T	NA	NA	-0.0168	0.0027	3.75E-10	0.0186	0.0414	0.6531
rs17202341	G	A	NA	NA	0.0157	0.0026	2.86E-09	0.0059	0.0417	0.8884
rs17377148	G	T	NA	NA	0.0401	0.0048	1.13E-16	-0.0676	0.0849	0.4257
rs174601	T	C	NA	NA	-0.0252	0.0026	1.80E-22	0.0144	0.045	0.7489
rs1755618	T	G	NA	NA	-0.0252	0.0035	1.17E-12	0.0081	0.0561	0.885
rs17580	A	T	NA	NA	0.0535	0.0059	1.54E-19	-0.0283	0.1287	0.8262
rs17628931	C	T	NA	NA	0.0294	0.0041	4.71E-13	-0.0021	0.0641	0.9732
rs1772183	A	G	NA	NA	-0.022	0.0025	1.30E-18	-0.0121	0.0392	0.7565
rs17794619	A	G	NA	NA	-0.0347	0.0037	3.61E-21	-0.0324	0.0683	0.6357
rs17826544	G	A	NA	NA	0.029	0.0026	3.87E-29	-0.0147	0.0443	0.7392
rs1801282	G	C	NA	NA	0.0377	0.0039	1.41E-22	-0.0855	0.0623	0.1699
rs1832007	G	A	NA	NA	-0.0483	0.0035	3.66E-43	0.0259	0.0545	0.6348
rs1935	G	C	NA	NA	0.1198	0.0025	1.00E-200	0.0563	0.0459	0.2205
rs1982151	G	A	NA	NA	-0.049	0.0028	9.23E-67	0.0216	0.043	0.6145
rs2081687	C	T	NA	NA	0.0247	0.0026	1.03E-20	-0.0573	0.0409	0.1616
rs2205262	A	C	NA	NA	-0.0167	0.0025	4.00E-11	0.002	0.0401	0.9599
rs2254069	A	G	NA	NA	-0.0265	0.0038	2.11E-12	0.1602	0.0662	0.0156
rs2266782	A	G	NA	NA	-0.0163	0.0025	1.25E-10	-0.0548	0.039	0.1594
rs2335077	G	A	NA	NA	0.0463	0.0026	1.71E-69	-0.0865	0.047	0.06601
rs2427530	A	G	NA	NA	0.0194	0.0029	2.99E-11	0.0444	0.0637	0.4861
rs2487826	C	T	NA	NA	0.0176	0.0025	3.56E-12	0.0103	0.0401	0.7974
rs2537855	G	A	NA	NA	0.0447	0.0028	3.56E-59	-0.0711	0.0551	0.1969
rs2618566	T	G	NA	NA	-0.0171	0.0026	8.57E-11	0.0055	0.0563	0.9229
rs2642420	A	C	NA	NA	-0.0247	0.0033	9.54E-14	-0.0161	0.0514	0.7539
rs2836950	G	C	NA	NA	-0.0154	0.0026	3.64E-09	-0.0414	0.0482	0.3902
rs2860075	G	A	NA	NA	-0.0289	0.0026	1.40E-28	-0.0059	0.0409	0.885
rs2943641	C	T	NA	NA	-0.0322	0.0026	6.16E-35	-0.0618	0.0399	0.1214
rs34145453	G	A	NA	NA	0.0189	0.0026	2.90E-13	0.0226	0.051	0.6578
rs34372369	A	G	NA	NA	0.037	0.0057	6.20E-11	0.0218	0.0901	0.8093
rs35371479	T	C	NA	NA	0.0256	0.0033	7.00E-15	-0.024	0.0517	0.6426
rs35627524	G	T	NA	NA	-0.0433	0.0067	1.09E-10	-0.0539	0.1219	0.6581
rs3779195	A	T	NA	NA	-0.0768	0.0032	2.35E-126	-0.074	0.0603	0.2202
rs3818247	T	G	NA	NA	-0.0247	0.0026	2.95E-21	0.0169	0.057	0.7665
rs41302867	A	G	NA	NA	-0.0342	0.0039	8.26E-19	-0.0268	0.0813	0.7415

Table S9 (*continued*)

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Table S9 (*continued*)

SNP	effect_allele	other_allele	eaf.exposure	eaf.outcome	beta.exposure	se.exposure	pval.exposure	beta.outcome	se.outcome	pval.outcome
rs4149056	C	T	NA	NA	-0.067	0.0035	9.39E-81	0.1116	0.0556	0.04481
rs4381968	T	C	NA	NA	-0.0138	0.0025	4.23E-08	-0.0997	0.0411	0.0154
rs440837	G	A	NA	NA	0.0466	0.0031	1.16E-50	-0.0365	0.0456	0.4227
rs45512696	T	C	NA	NA	0.0407	0.0033	2.72E-34	-0.0092	0.0545	0.8656
rs45535039	C	T	NA	NA	0.0204	0.0028	3.34E-13	-0.0802	0.0506	0.1131
rs4639796	A	G	NA	NA	-0.0296	0.0034	3.23E-18	-0.0541	0.0642	0.3997
rs464605	T	C	NA	NA	-0.0323	0.0029	1.25E-29	0.0247	0.0501	0.6224
rs4660293	G	A	NA	NA	-0.0295	0.003	5.90E-23	0.0246	0.0479	0.6075
rs4690098	T	C	NA	NA	-0.0498	0.003	1.01E-61	-0.0202	0.0461	0.6604
rs4822455	T	C	NA	NA	-0.0184	0.0025	3.48E-13	-0.0074	0.0405	0.8558
rs4983559	A	G	NA	NA	-0.0179	0.0026	2.85E-12	-0.0513	0.0426	0.2283
rs555754	A	G	NA	NA	0.0343	0.0025	5.02E-42	-0.015	0.0392	0.7023
rs55707100	T	C	NA	NA	-0.1171	0.0081	1.76E-47	0.0607	0.1584	0.7018
rs55840085	A	G	NA	NA	0.0195	0.0026	6.35E-14	-0.0394	0.0417	0.3445
rs5745687	T	C	NA	NA	0.0307	0.0051	2.07E-09	0.0891	0.095	0.3486
rs57506806	G	A	NA	NA	0.0351	0.003	2.25E-32	0.0233	0.0582	0.6888
rs58941251	T	C	NA	NA	-0.0241	0.0041	2.74E-09	-0.1045	0.0655	0.1108
rs6129800	A	G	NA	NA	0.0239	0.003	1.35E-15	0.0186	0.0484	0.7003
rs62576339	C	T	NA	NA	0.03	0.0029	8.22E-25	0.0865	0.0503	0.0856
rs62580767	C	T	NA	NA	0.0234	0.0033	8.54E-13	-0.0198	0.0514	0.6994
rs62618693	T	C	NA	NA	0.041	0.0061	1.93E-11	-0.1912	0.1571	0.2237
rs6736913	G	A	NA	NA	-0.0712	0.0089	1.12E-15	0.0864	0.1714	0.6144
rs6756943	A	G	NA	NA	-0.0448	0.0027	5.62E-61	0.0112	0.044	0.7989
rs6954673	T	C	NA	NA	-0.0185	0.0026	1.27E-12	-0.0334	0.0405	0.4088
rs7221345	A	G	NA	NA	-0.0325	0.0026	3.13E-37	0.0271	0.0437	0.5353
rs7239151	A	G	NA	NA	0.0155	0.0027	6.50E-09	0.058	0.0451	0.1983
rs724577	C	A	NA	NA	-0.0186	0.0028	6.04E-11	0.0024	0.0442	0.9567
rs7250425	T	C	NA	NA	0.0179	0.0025	7.64E-13	0.0673	0.0391	0.08508
rs72683923	C	T	NA	NA	0.0774	0.0092	5.67E-17	0.0931	0.2179	0.669
rs7314285	G	T	NA	NA	0.0764	0.0048	3.82E-56	-0.0021	0.0755	0.9778
rs738409	G	C	NA	NA	0.0486	0.003	5.06E-58	-0.0674	0.0507	0.1844
rs7429135	G	T	NA	NA	0.0199	0.0034	5.92E-09	-0.0017	0.0525	0.9736
rs750472	C	A	NA	NA	-0.0216	0.0025	4.22E-18	0.0399	0.0459	0.3848
rs7694379	A	G	NA	NA	-0.042	0.0025	4.75E-62	0.0032	0.0393	0.935
rs7697204	T	C	NA	NA	-0.0295	0.0028	4.24E-25	0.0339	0.0435	0.4351
rs7922067	A	G	NA	NA	-0.0211	0.0025	1.18E-16	0.0321	0.041	0.4332
rs7947951	G	A	NA	NA	-0.0283	0.0027	9.37E-26	0.0112	0.0422	0.7914
rs7994151	G	A	NA	NA	-0.0206	0.0035	2.89E-09	-0.0014	0.0541	0.9799
rs8017377	A	G	NA	NA	-0.0342	0.0025	3.92E-42	0.0402	0.049	0.4126
rs8023580	C	T	NA	NA	0.073	0.0028	1.52E-150	-0.01	0.0459	0.8277
rs9316500	G	T	NA	NA	-0.0172	0.0027	3.05E-10	0.076	0.0413	0.06539
rs9388768	A	C	NA	NA	-0.0197	0.0027	1.39E-13	-0.0466	0.0434	0.2833
rs9427104	T	C	NA	NA	0.027	0.0025	4.04E-27	0.0235	0.0391	0.5472
rs9556403	G	A	NA	NA	0.0205	0.0026	4.66E-15	-0.0091	0.0399	0.8201
rs9644032	G	T	NA	NA	-0.0159	0.0026	1.03E-09	0.0315	0.041	0.4426
rs9892297	G	A	NA	NA	-0.1366	0.0026	1.00E-200	0.0168	0.0438	0.7011

SNP, single nucleotide polymorphism; FTD, frontotemporal dementia; GWAS, genome-wide association studies; NA, not available.

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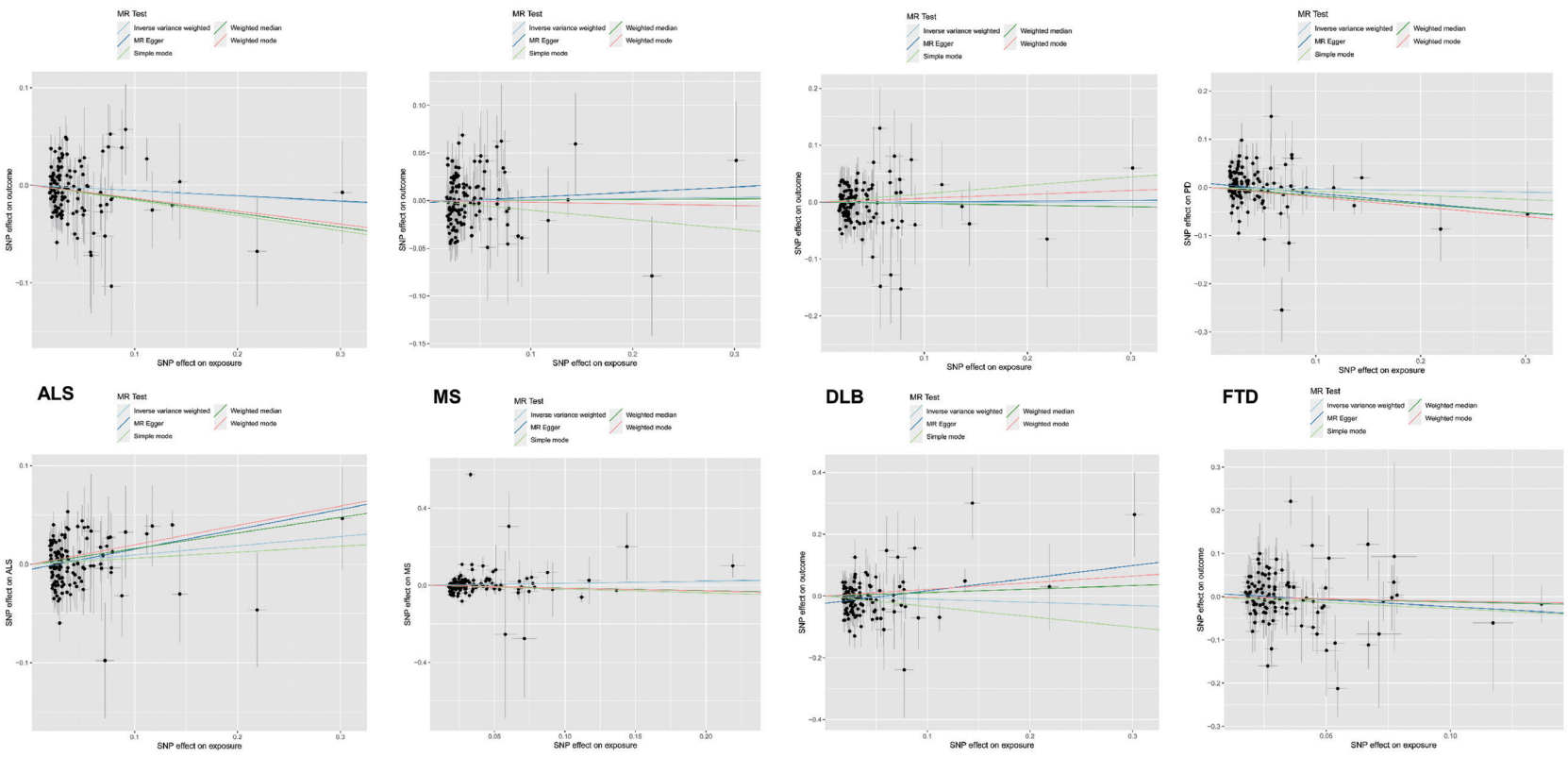

Figure S1 Scatter plots of serum SHBG level and neurodegenerative diseases (clump R^2=0.00001). Genome-wide significantly associated ($P<5\times10^{-8}$) independent (linkage disequilibrium R^2=0.00001, clumping distance =10,000 kb) SNPs were used as instruments. SHBG, sex-hormone binding globulin; MR, Mendelian randomization; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; DLB, Dementia with Lewy Bodies; FTD, frontotemporal dementia.

Outcome	Method	No. of SNPs	OR & 95% CI	P value
Late-onset AD	Inverse variance weighted	193	0.971 (0.889-1.062)	0.525
	MR Egger	193	0.889 (0.758-1.043)	0.151
	Weighted median	193	**0.871 (0.762-0.995)**	**0.042**
	Weighted mode	193	0.883 (0.768-1.016)	0.083
Maternal AD	Inverse variance weighted	193	1.029 (0.929-1.140)	0.587
	MR Egger	193	0.960 (0.798-1.155)	0.666
	Weighted median	193	1.006 (0.846-1.197)	0.944
	Weighted mode	193	0.992 (0.835-1.180)	0.931
Paternal AD	Inverse variance weighted	193	1.006 (0.889-1.139)	0.923
	MR Egger	193	1.000 (0.799-1.251)	0.999
	Weighted median	193	0.978 (0.784-1.218)	0.840
	Weighted mode	193	1.054 (0.832-1.335)	0.665
PD	Inverse variance weighted	193	0.988 (0.873-1.118)	0.848
	MR Egger	193	**0.795 (0.638-0.990)**	**0.042**
	Weighted median	193	0.861 (0.733-1.013)	0.071
	Weighted mode	193	**0.827 (0.700-0.977)**	**0.027**
ALS	Inverse variance weighted	194	1.071 (0.985-1.165)	0.109
	MR Egger	194	**1.181 (1.016-1.373)**	**0.032**
	Weighted median	194	**1.169 (1.039-1.315)**	**0.009**
	Weighted mode	194	**1.198 (1.048-1.370)**	**0.009**
MS	Inverse variance weighted	186	1.144 (0.916-1.429)	0.236
	MR Egger	186	1.065 (0.699-1.624)	0.769
	Weighted median	186	0.871 (0.739-1.027)	0.099
	Weighted mode	186	0.865 (0.728-1.026)	0.098
DLB	Inverse variance weighted	181	0.861 (0.706-1.050)	0.140
	MR Egger	181	1.380 (0.979-1.946)	0.067
	Weighted median	181	1.093 (0.788-1.514)	0.595
	Weighted mode	181	1.197 (0.828-1.731)	0.340
FTD	Inverse variance weighted	157	0.879 (0.688-1.124)	0.304
	MR Egger	157	0.789 (0.488-1.276)	0.335
	Weighted median	157	0.884 (0.564-1.387)	0.592
	Weighted mode	157	0.921 (0.590-1.436)	0.716

Figure S2 Mendelian randomization results of serum SHBG level and neurodegenerative diseases (clump R2=0.001). Genome-wide significantly associated ($P<5\times10^{-8}$) independent (linkage disequilibrium R^2=0.001, clumping distance =10,000 kb) SNPs were used as instruments. SHBG, Sex-hormone binding globulin; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; DLB, Dementia with Lewy Bodies; FTD, frontotemporal dementia.

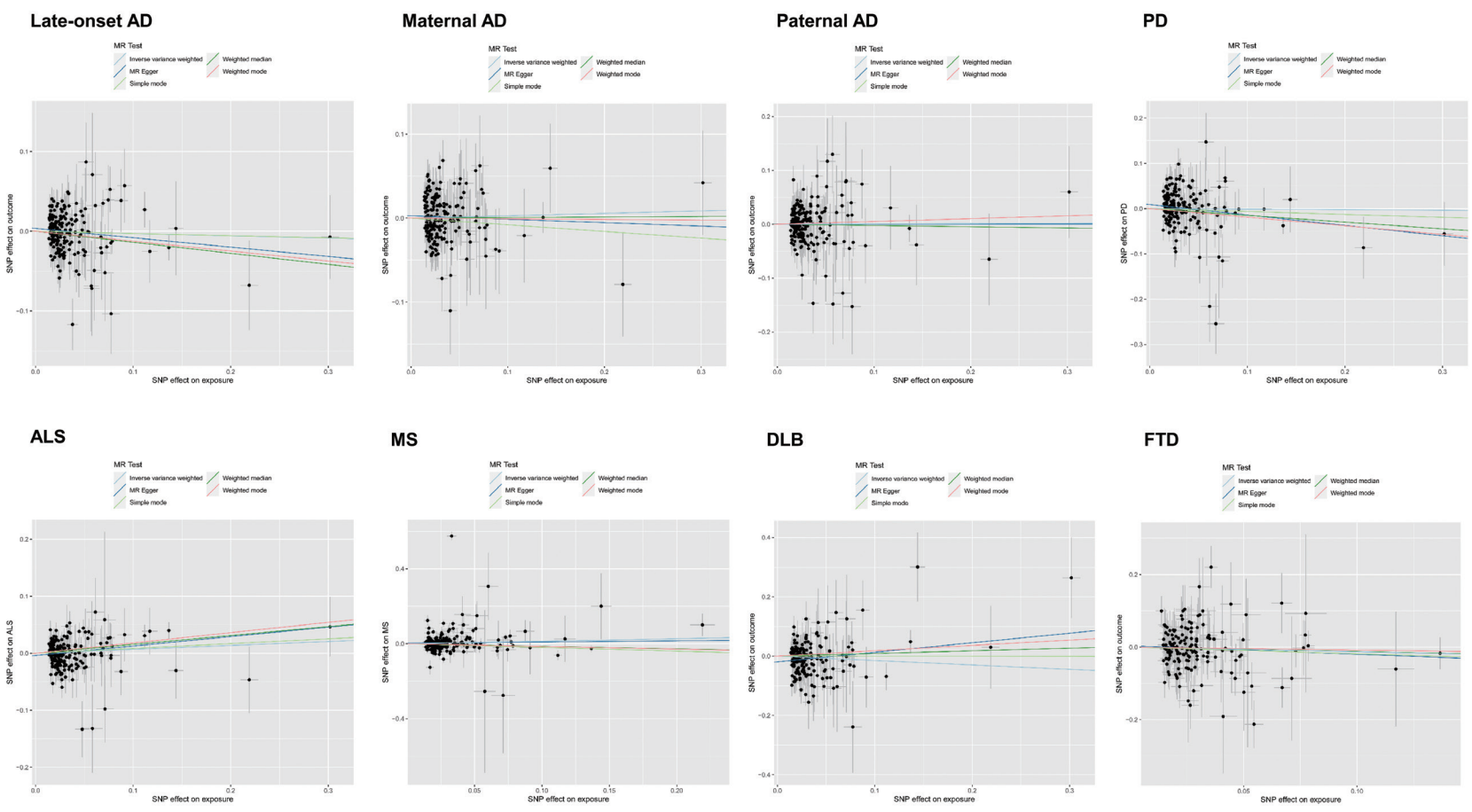

Figure S3 Scatter plots of SHBG and neurodegenerative diseases (clump R^2=0.001). Genome-wide significantly associated ($P<5\times10^{-8}$) independent (linkage disequilibrium R^2=0.001, clumping distance =10,000 kb) SNPs were used as instruments. SHBG, sex-hormone binding globulin; MR, Mendelian randomization; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; DLB, Dementia with Lewy Bodies; FTD frontotemporal dementia.

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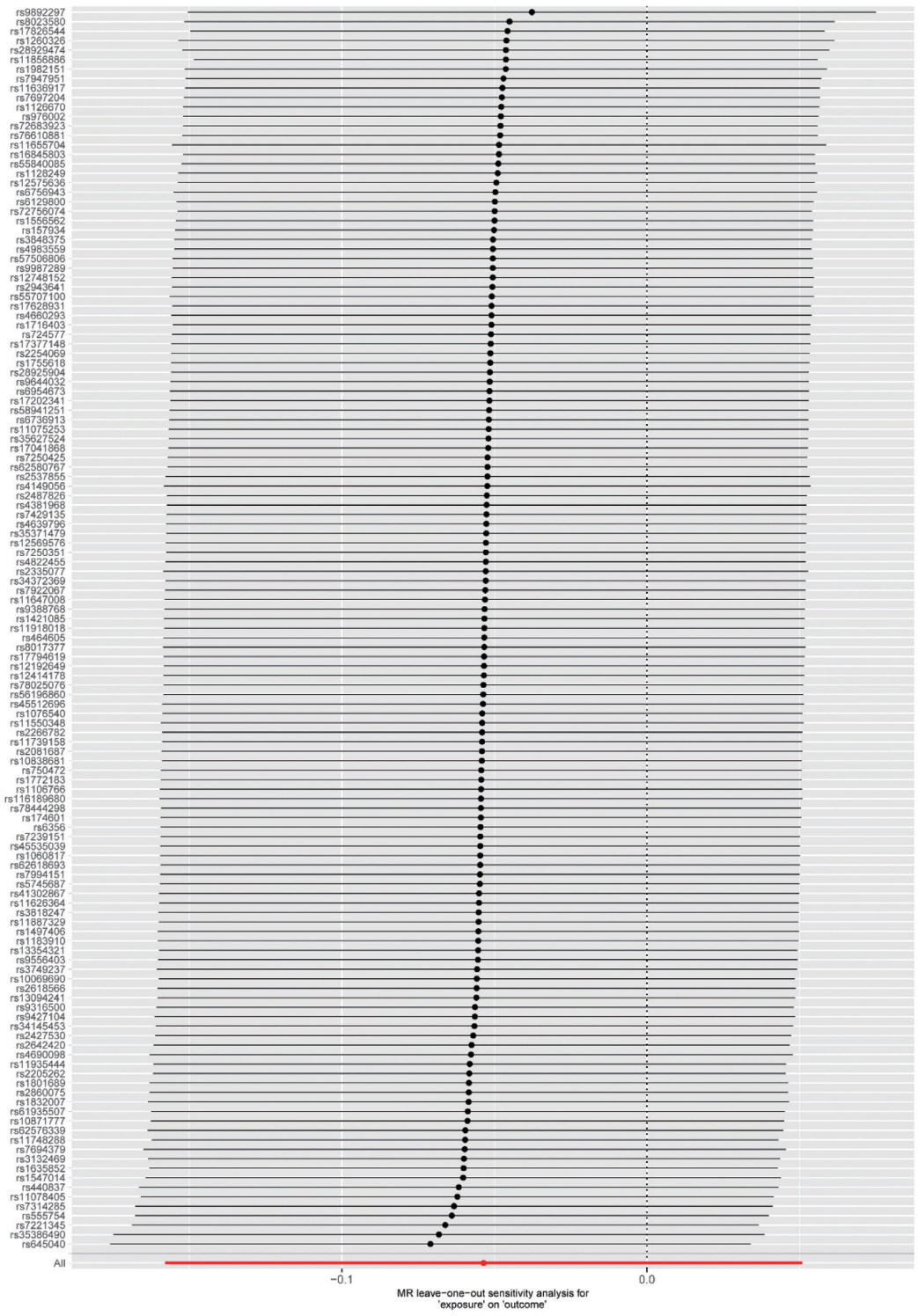

Figure S4 Leave-one-out and single-SNP analyses of late-onset AD.

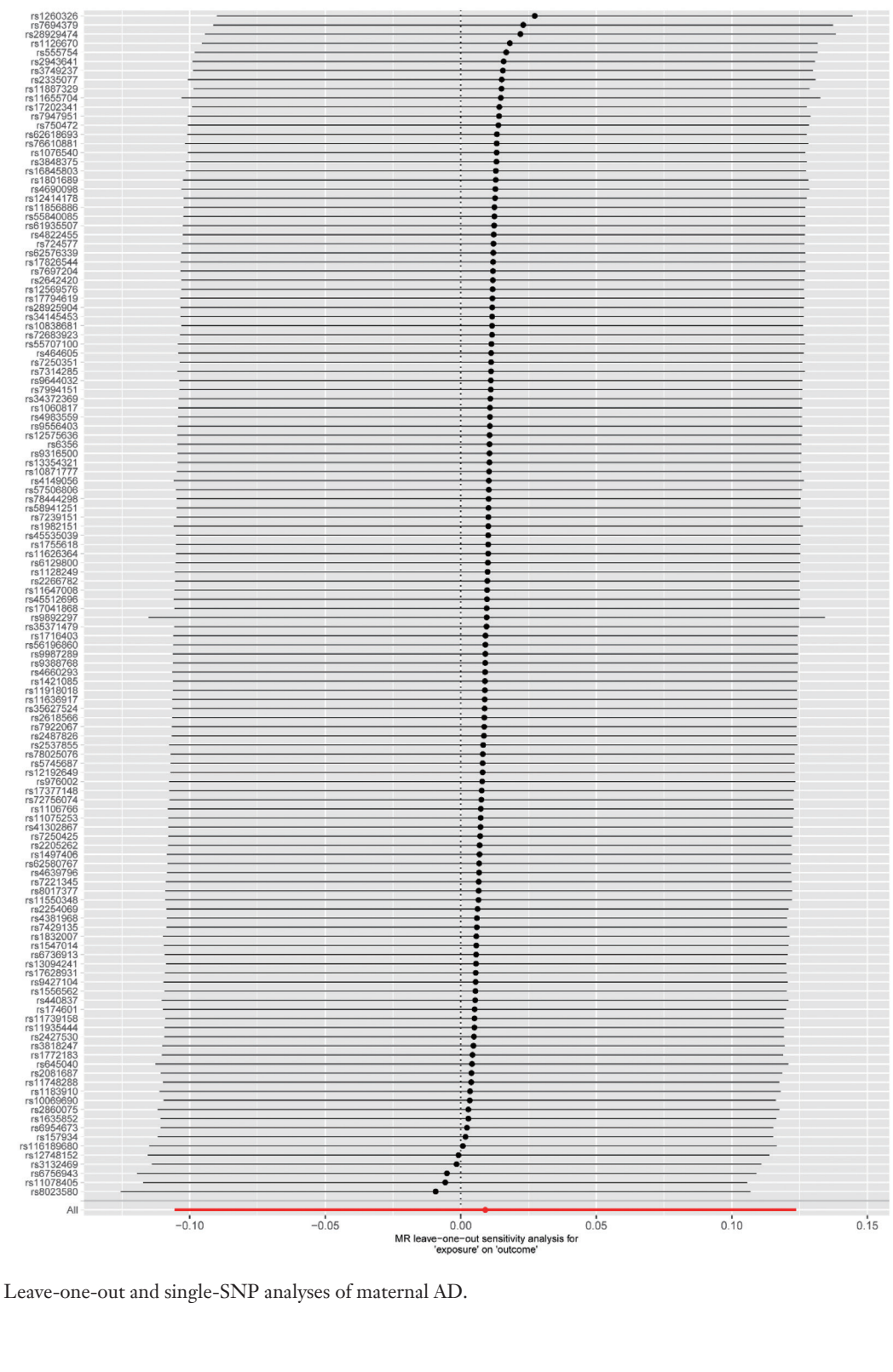

Figure S5 Leave-one-out and single-SNP analyses of maternal AD.

https://dx.doi.org/10.21037/atm-22-1156

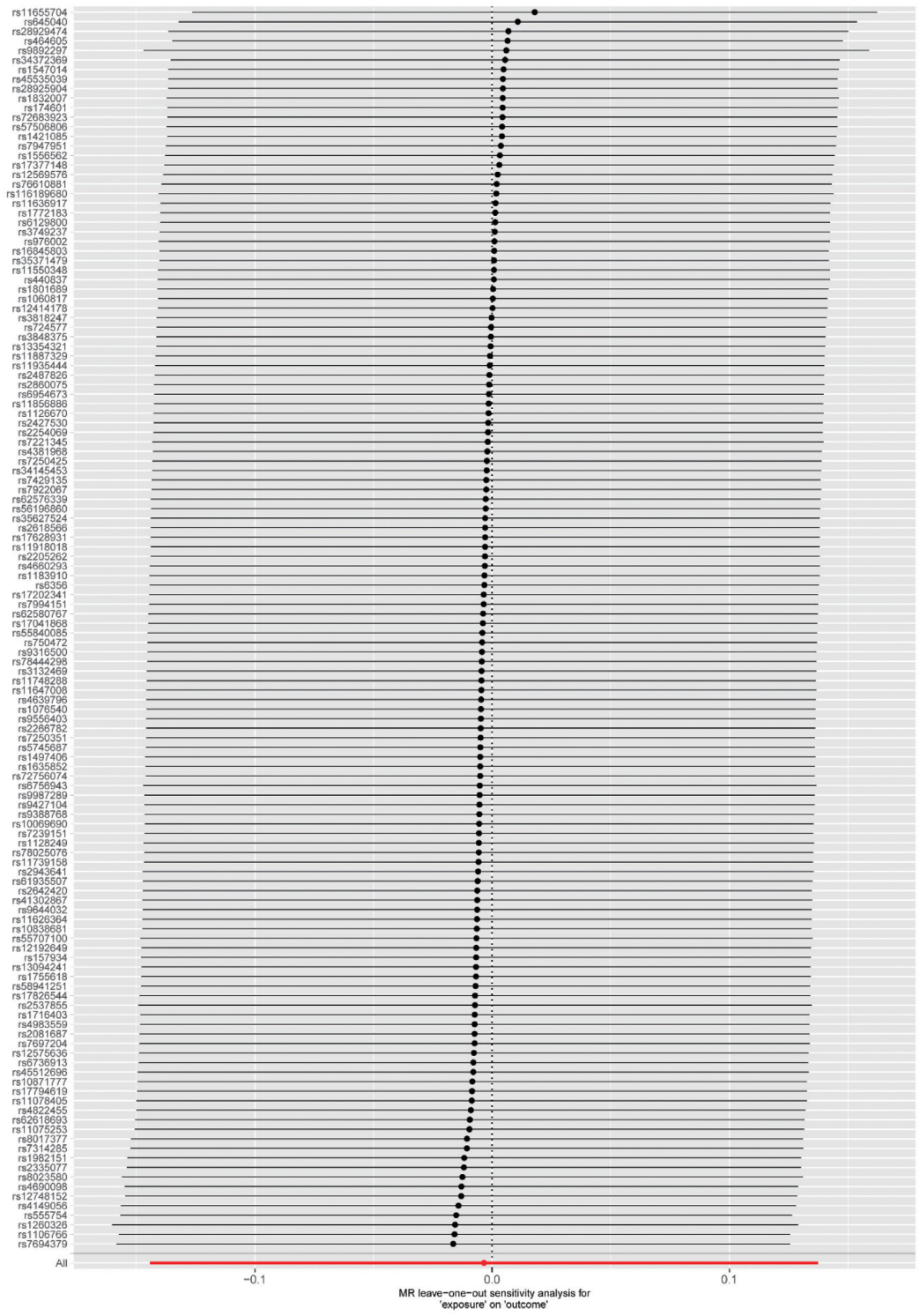

Figure S6 Leave-one-out and single-SNP analyses of paternal AD.

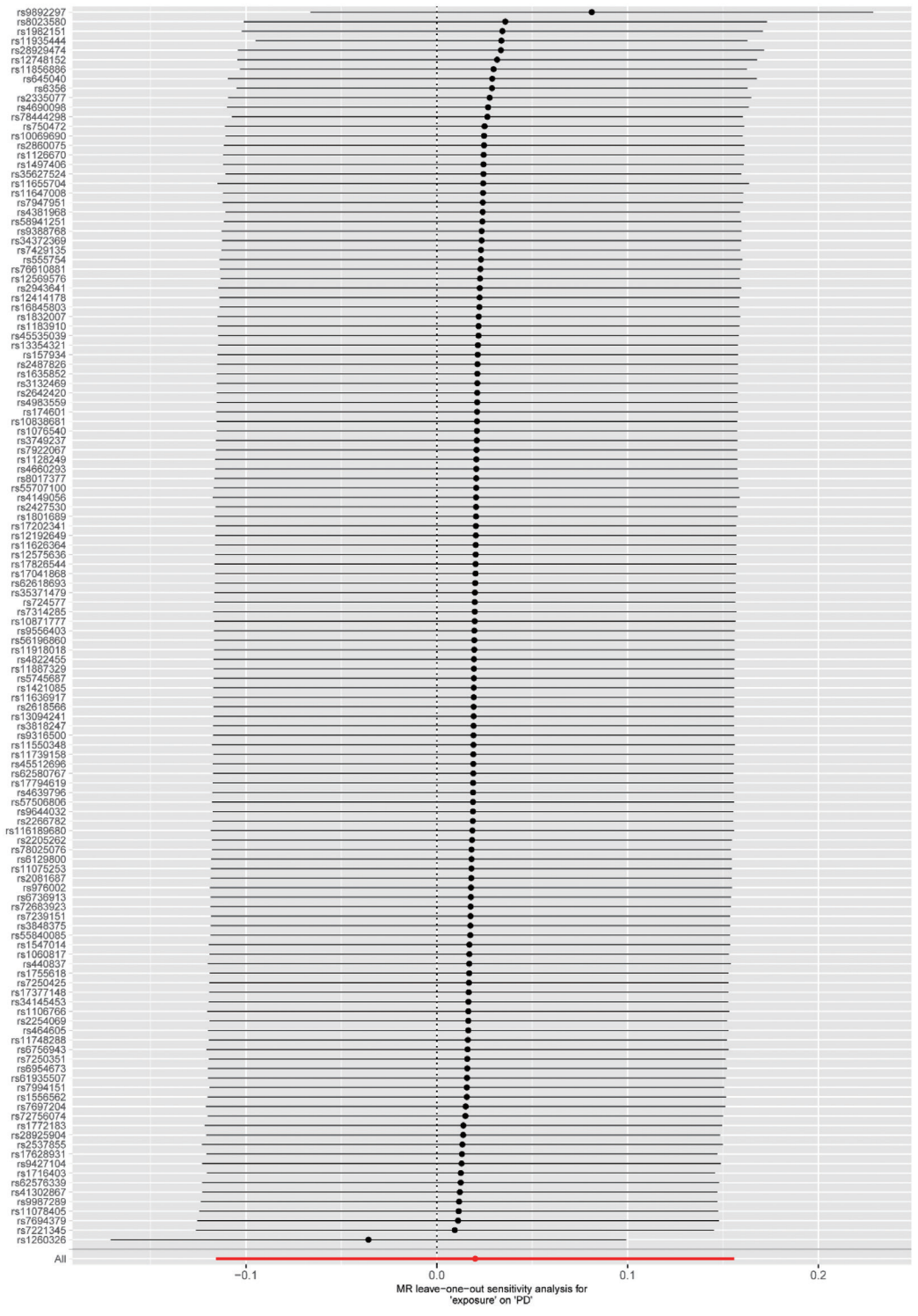

Figure S7 Leave-one-out and single-SNP analyses of PD.

https://dx.doi.org/10.21037/atm-22-1156

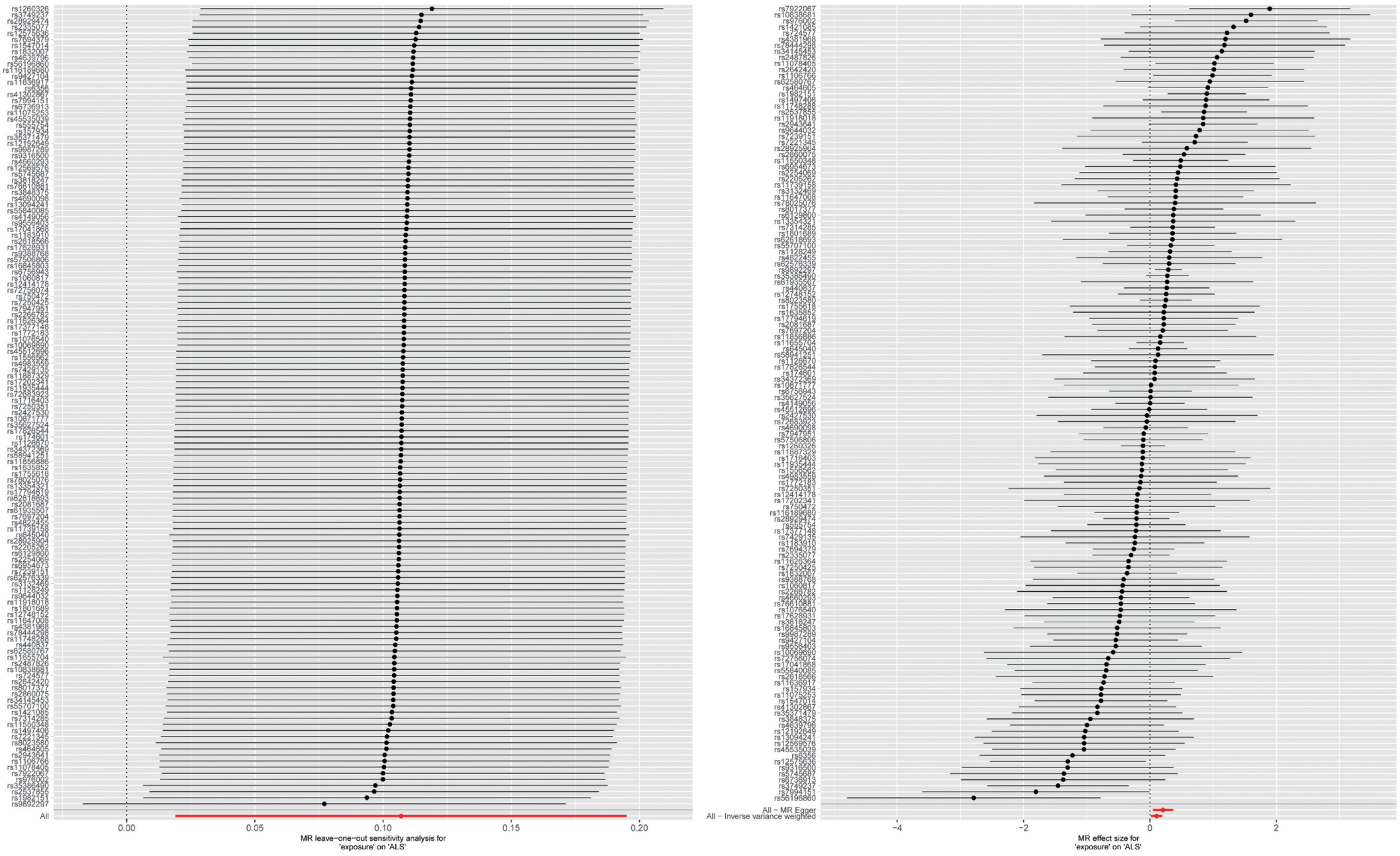

Figure S8 Leave-one-out and single-SNP analyses of ALS.

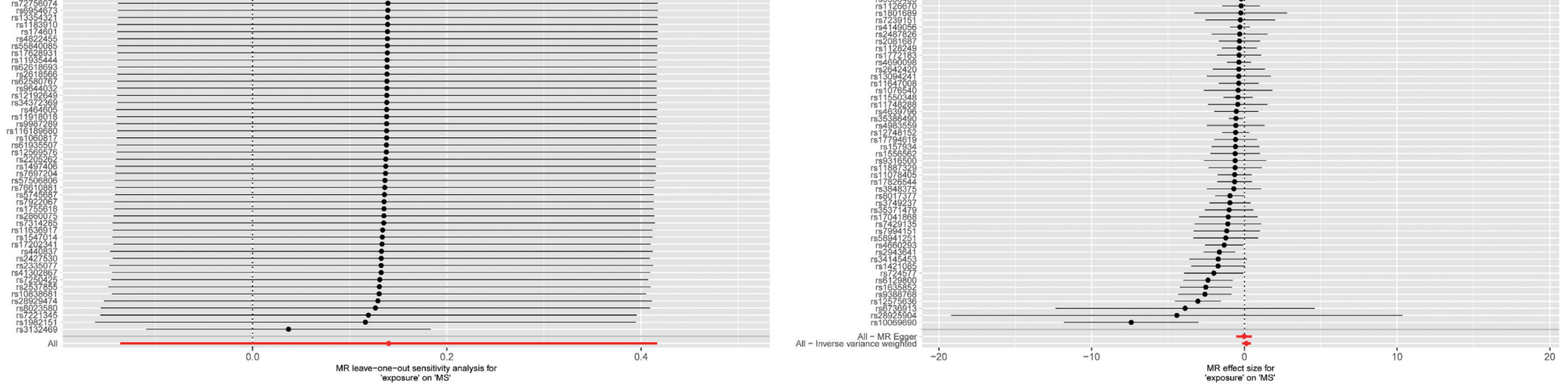

Figure S9 Leave-one-out and single-SNP analyses of MS.

https://dx.doi.org/10.21037/atm-22-1156

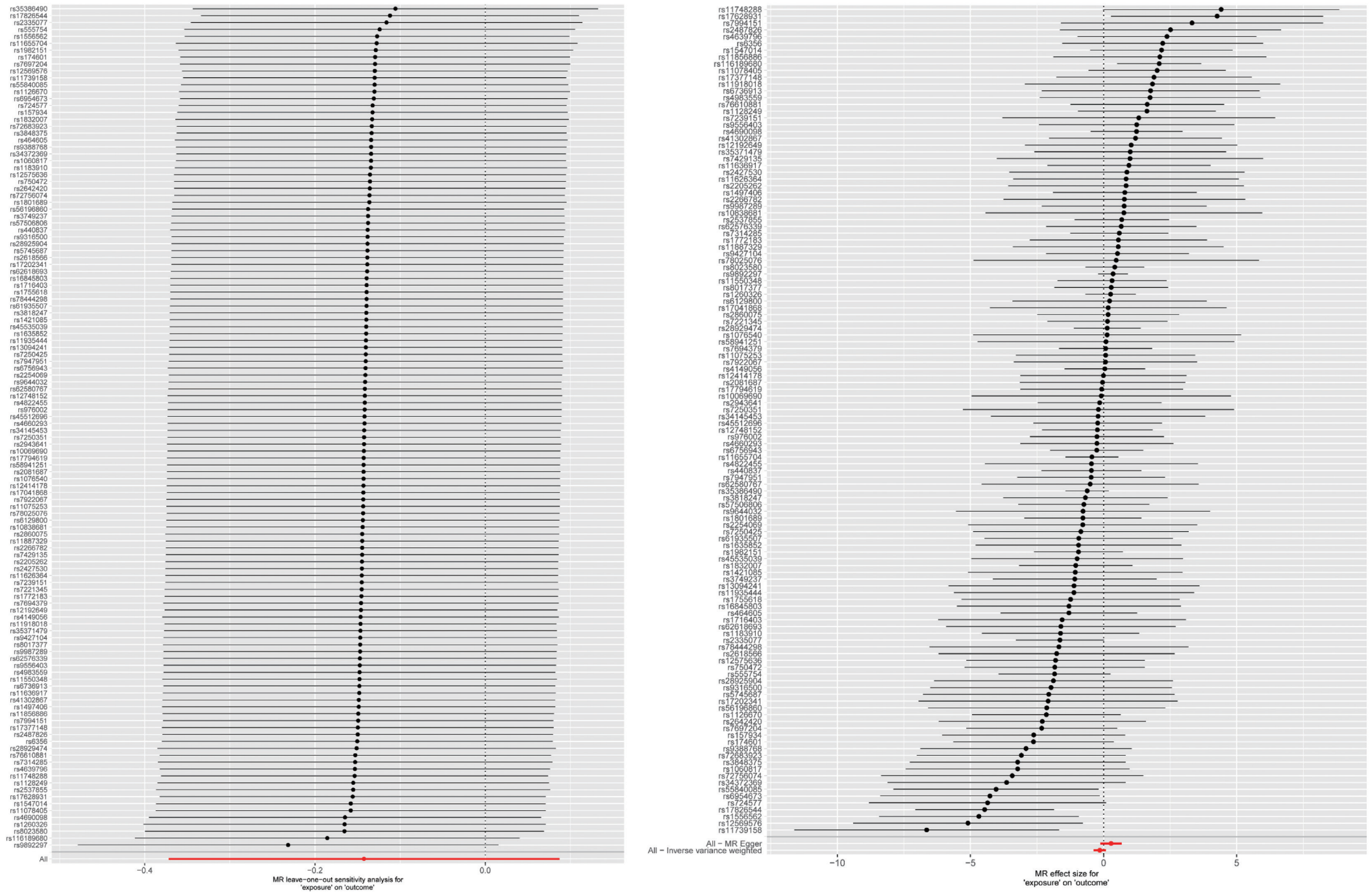

Figure 10 Leave-one-out and single-SNP analyses of DLB.

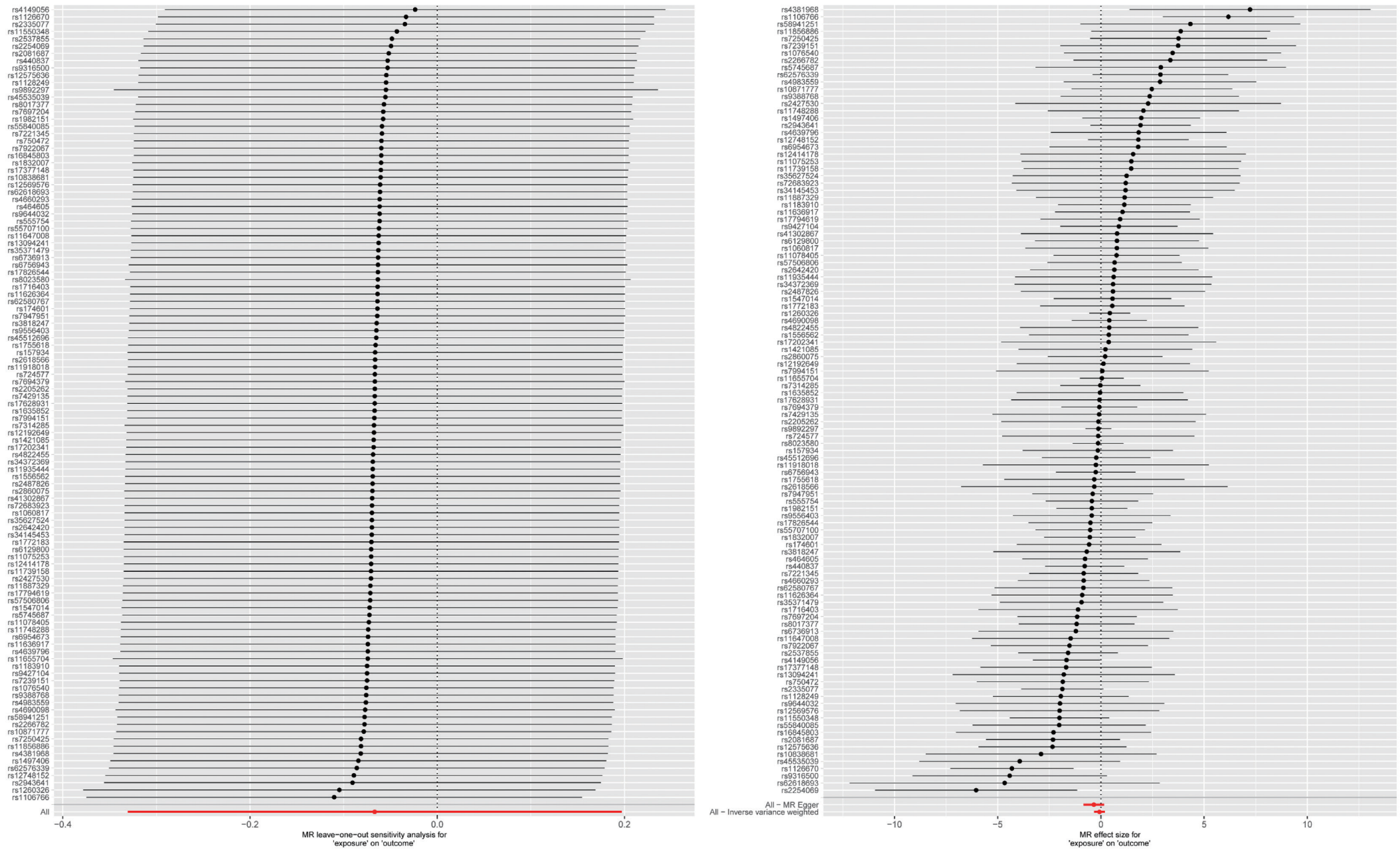

Figure S11 Leave-one-out and single-SNP analyses of FTD.

https://dx.doi.org/10.21037/atm-22-1156