Original Investigation

Common Genetic Variants on 6q24 Associated With Exceptional Episodic Memory Performance in the Elderly

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IMPORTANCE There are genetic influences on memory ability as we age, but no specific genes have been identified.

OBJECTIVE To use a cognitive endophenotype, exceptional episodic memory (EEM) performance, derived from nondemented offspring from the Long Life Family Study (LLFS) to identify genetic variants that may be responsible for the high cognitive performance of LLFS participants and further replicate these variants using an additional 4006 nondemented individuals from 4 independent elderly cohorts.

DESIGN, SETTING, AND PARTICIPANTS A total of 467 LLFS participants from 18 families with 2 or more offspring that exhibited exceptional memory performance were used for genome-wide linkage analysis. Adjusted multivariate linear analyses in the 40-megabase region encompassing the linkage peak were conducted using 4 independent replication data sets that included 4006 nondemented elderly individuals. Results of the individual replication cohorts were combined by meta-analysis.

MAIN OUTCOME MEASURE Episodic memory scores computed as the mean of the 2 standardized measures of Logical Memory IA and IIA.

RESULTS Heritability estimates indicated a significant genetic component for EEM (h^2 = 0.21; SE = 0.09). Genome-wide linkage analysis revealed that EEM was linked to the 6q24 region (maximum logarithm of odds score, 3.64). Association analysis in LLFS families identified single-nucleotide polymorphisms (SNPs) nominally associated with EEM in the 40-megabase window encompassing the linkage peak. Replication in one cohort identified a set of 26 SNPs associated with episodic memory ($P \leq .05$). Meta-analysis of the 26 SNPs using the 4 independent replication cohorts found SNPs rs9321334 and rs6902875 to be nominally significantly associated with episodic memory ($P = .009$ and $P = .013$, respectively). With meta-analysis restricted to individuals lacking an *APOE* ε4 allele, SNP rs6902875 became statistically significant (meta-analysis, $P = 6.7 \times 10^{-5}$). Haplotype analysis incorporating the 2 SNPs flanking rs6902875 (rs9321334 and rs4897574) revealed that the A-A-C haplotype was significantly associated with episodic memory performance ($P = 2.4 \times 10^{-5}$). This genomic region harbors monooxygenase dopamine β-hydroxylase-like 1 gene (*MOXD1*), implicated in the biosynthesis of norepinephrine, which is prominently involved in cognitive functions.

CONCLUSIONS AND RELEVANCE The results provide strong evidence for potential candidate genes related to EEM on 6q24. Identifying the genes will help in understanding the biological basis of memory performance and allow interventions for enhancement of cognitive function.

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The origin of the differences in human cognitive abilities is not fully understood. There is a substantial genetic contribution to the variability observed in different cognitive tasks, evidenced by heritability estimates for episodic memory ranging between 30% and 60%.[1]

Why some individuals demonstrate better memory performance than others in late life remains unknown. Results from the limited number of studies[2] that have investigated the underlying factors of this exceptionality showed a strong genetic component; however, no specific genes have been identified. As has been seen for other cognitive endophenotypes, genetic contributions for memory most likely involve multiple quantitative trait loci and environmental factors with relatively small effect sizes.

The Long Life Family Study[1] (LLFS) has previously defined a cognitive endophenotype based on exceptional episodic memory (EEM) performance and demonstrated that there is a familial aggregation of EEM in families from that study. We present the results of a genome-wide linkage analysis of long-lived families selected on the basis of their EEM and the follow-up single-nucleotide polymorphism (SNP) association analysis with episodic memory in 4 independent cohorts of elderly individuals without dementia.

Methods

Ethics Statement

Ethics approval was obtained for each institution involved. Written informed consent for the study was obtained from all participants and/or their authorized representatives and study partners. The participants did not receive financial compensation. Institutional review boards were constituted according to applicable state and federal requirements for each study. The LLFS, National Institute on Aging Late-Onset Alzheimer Disease (NIA-LOAD), and Washington Heights Aging Project (WHICAP) studies were approved by the institutional review board of the New York State Psychiatric Institute; the Alzheimer Disease Neuroimaging Initiative (ADNI) and Alzheimer Disease Genetic Consortium (ADGC) studies were approved by the institutional review board of the University of Pennsylvania.

The study was designed to identify common genetic variants that influence episodic memory performance. We identified an extreme phenotype, EEM, by using a threshold of 1.5 SDs above the demographically adjusted mean episodic memory in the offspring generation of the LLFS, which was designed to use families to characterize exceptional health well beyond what is expected in the general population.[1] Among the total of 554 LLFS families who were genotyped (Omni 2.5-million SNPs platform; Illumina),[4] 18 families (467 participants) had 2 or more offspring who exhibited EEM and were selected to perform linkage analysis.

To obtain an unbiased estimate of the genetic effect size, we used the entire distribution of episodic memory scores in 4 independent cohorts of unrelated elderly individuals without dementia: NIA-LOAD, ADNI, ADGC, and WHICAP. The replication in these samples was designed to represent the general population to ensure sufficient power and unbiased estimates of the effect sizes.[5]

Replication Cohort 1: The NIA-LOAD

The NIA-LOAD Family Study has been described elsewhere.[6] A total of 508 unrelated healthy individuals were included. Episodic memory scores at the last cognitive assessment were computed as the mean of the 2 standardized measures of Logical Memory IA and IIA.[7] Genome-wide genotyping was performed (Human610Quadv1_B BeadChip; Illumina).[6]

Replication Cohort 2: The ADNI

The ADNI is a longitudinal study consisting of 819 participants aged 55 to 90 years; of these, 355 individuals without dementia were selected for analysis. Episodic memory scores at the last cognitive assessment were computed as the mean of the 2 standardized measures of Logical Memory IA and IIA.[7] Genome-wide genotyping was obtained (Human610-Quad BeadChip; Illumina).[8]

Replication Cohort 3: The ADGC

The ADGC cohort consists of cognitively normal elderly individuals ascertained by the NIA-funded Alzheimer Disease Centers.[9] A sample of 1841 participants was used in the present analysis. Episodic memory scores at the last cognitive assessment were computed as the mean of the 2 standardized measures of Logical Memory IA and IIA.[7] Genome-wide genotyping was performed using various genotyping arrays.[9]

Replication Cohort 4: The WHICAP

The WHICAP is a population-based study of elderly individuals residing in New York City.[10] A total of 1302 individuals from 3 ethnic groups (Hispanic, 42%; white, 35%; and African American, 23%) were used for the analysis. The memory domain included the total and delayed recall of the Selective Reminding Test[11] and the recognition component of the Benton Visual Retention Test.[12] The composite measure of memory was computed as the mean of the standardized individual memory tests from the last cognitive assessment.[13] Genome-wide genotyping was done using differing platforms for the Caribbean Hispanic sample (HumanHap 650Y; Illumina) and the white and African American samples (OmniExpress; Illumina). The 3 WHICAP ethnic groups were used in the analysis.

Statistical Analysis

Heritability of the EEM Phenotype

Heritability of the EEM phenotype using the 18 LLFS families was obtained after adjustment for covariates (sex, age, educational level, and dementia status) using Solar, version 4.0.6 software.[14] Multipoint identity-by-descent (IBD) allele-sharing probabilities were estimated using Loki software, version 2.3.[15] The multipoint IBD estimates were calculated with 500 000 iterations run, using every 10th iteration to compute the estimate. The meiotic map used was constructed by linear interpolation onto the deCODE map by using sequence base pair (bp) positions of the SNPs on the deCODE map. The SNPs for use in IBD estimation were selected as follows. First, each chromosome was divided into 0.5-cM bins, and SNPs meet-

ing our screening criteria were identified in each bin. The screening criteria used were minimum allele frequency greater than 10%, no Mendel errors, and an index of mean within-family variance of greater than 0.10. Not all bins had SNPs, but in those that did, the first SNP in each bin was used. If a bin had no SNP, we checked to see whether any SNP was available. These SNPs constitute a 0.5-cM framework that was used in the IBD estimates.

Multipoint Linkage Analysis

Multipoint linkage analysis of the 18 LLFS families harboring EEM was performed using the multipoint IBD matrices and variance components model in Solar. Chromosomal regions with logarithm of odds (LOD) scores of 3.6 or greater were considered as genome-wide significant evidence of linkage.[16]

SNP Quantitative Tests of Association

To narrow the linkage region in the 18 families with the EEM phenotype, we performed association tests in the 112- to 164-megabase (Mb) region encompassing the linkage signal, using generalized equation estimates models to adjust for the relatedness of the LLFS participants by treating family membership as a cluster and adjusting for sex, age, and educational level. Regression models adjusted for sex, age, and educational level were conducted in 4 replication data sets (N = 4006) using PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml). For replication cohorts ADGC and WHICAP_Hispanic, additional adjustment for population stratification was conducted. In the ADGC cohort, loadings for the first 10 principal components derived using EIGENSTRAT[17] were used as covariates in the analysis. In the WHICAP_Hispanic cohort, analyses were performed using identity-by-state-based clusters calculated with PLINK as covariates.[18] Assessment of population structure within the NIA-LOAD, ADNI, WHICAP_white, and WHICAP_African American cohorts, using the whole-genome SNP data in a clustering algorithm implemented in PLINK software,[19] showed that all cohorts were genetically homogeneous (≥97% of the individuals clustered in the same subpopulation group within each of the cohorts).

In each of the replication cohorts, interaction between SNP marker rs6902875 and *APOE* locus (coded as 0 or 1 based on the presence or absence of the *APOE* ε4 allele) was performed using linear regression analyses that modeled the main effect of both loci, an interaction term, and covariates (sex, age, educational level, and population stratification).

Haplotype Analysis

Linear regression haplotype-based association analysis of episodic memory within each of the cohorts was performed using PLINK.[19] The SNP markers flanking the SNPs with the strongest association that also showed significant association with memory performance in the *APOE* non-ε4 carriers were considered for haplotype analysis.

Statistical Significance

Multiple testing correction was computed to adjust for multiple testing in the follow-up SNP association analyses performed in the 112- to 164-Mb linkage region encompassing the linkage peak. Statistically significant adjusted genome-wide threshold ($P \leq 10^{-5}$) was computed using the genetic type I error calculator tool.[20] Combined *P* values across the replication cohorts were computed using the Fisher exact test (http://www.jurgott.org/linkage/util.htm).

Meta-analysis

Significance levels across the 4 independent replication cohorts were combined by meta-analysis, taking into account study-specific sample size and direction of the effect using Meta-analysis Helper.[21] Results obtained from rs6902875-*APOE* interaction models within each cohort were also meta-analyzed.

Because of the known association of *APOE* ε4 with impaired cognitive performance[10] and the significant interaction between SNP rs6902875 and *APOE* locus found in the meta-analysis of the replication cohorts (meta-analysis $P = .004$), we stratified our analysis by *APOE* classifying the cohort's participants as carriers of 1, 2, or no copies of the *APOE* ε4 allele.

Results

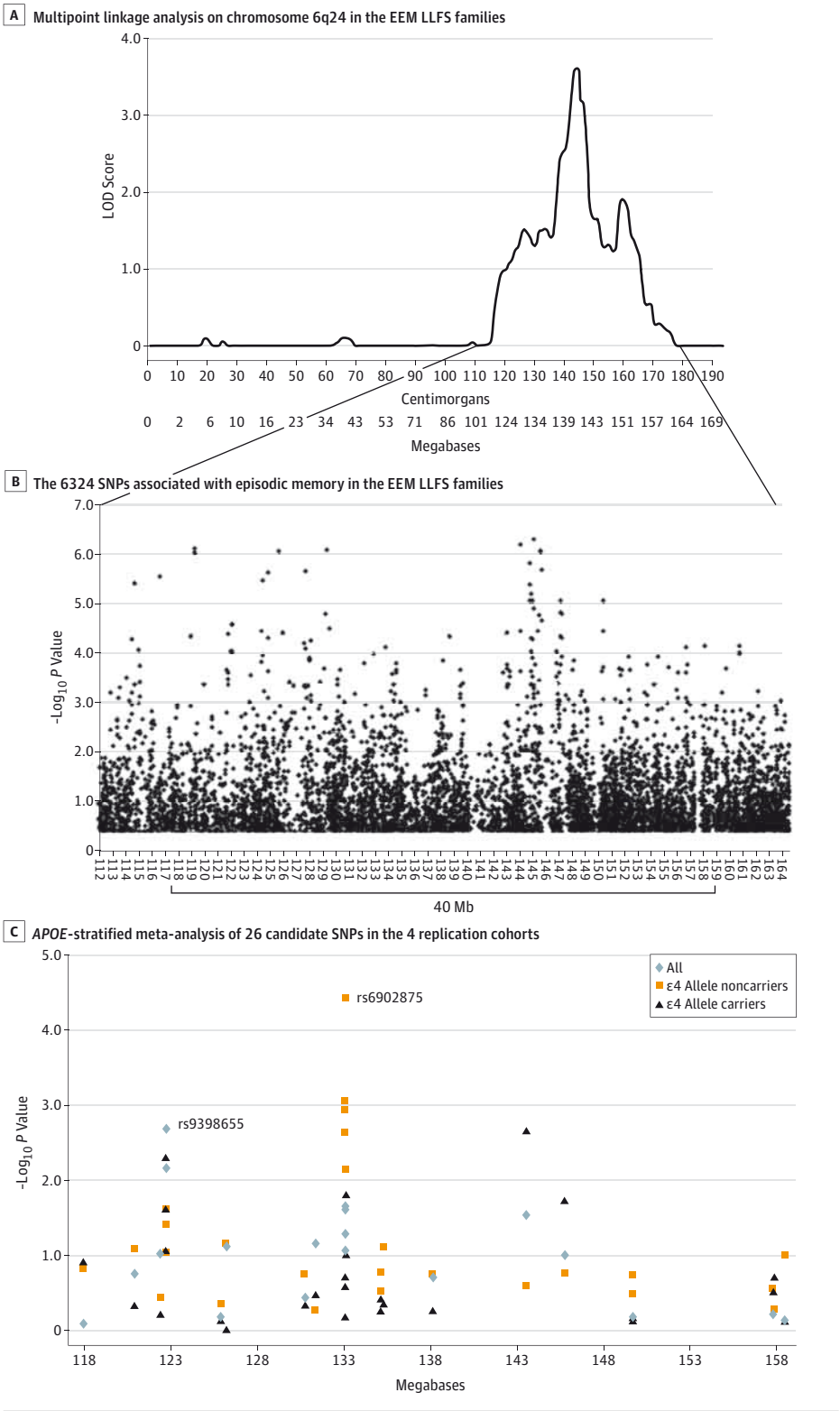
Demographic characteristics of the study cohorts are provided in eTable 1 in the Supplement. The minimum allele frequencies and the number of individuals within each of the 3 genotype categories within each study cohort for each of the 26 SNPs that appeared to be associated in the NIA-LOAD replication data set were used in the meta-analysis of the replication cohorts (eTable 2 in the Supplement); eTable 3 in the Supplement shows the distribution of *APOE* ε4 allele carriers and noncarriers within each study cohort.

Heritability estimation, adjusting for sex, age, educational level, and ascertainment bias, in the 18 LLFS families indicated a significant genetic component for EEM ($h^2 = 0.21$; SE = 0.09; $P < .001$). Results from the multipoint linkage analysis revealed that EEM was linked to the 6q24 region with a maximum genome-wide LOD score of 3.64 at 145 cM (**Figure**, A).

A linear regression analysis, adjusted for sex, age, and educational level, in these LLFS families identified 1025 SNPs nominally associated with EEM in the 40-Mb window encompassing the linkage peak. The strongest association with EEM was for SNP rs9398655 ($\beta = 0.98$; SE = 0.24; $P = 3.3 \times 10^{-5}$). Replication in the NIA-LOAD cohort yielded a set of 26 SNPs associated with episodic memory ($P \leq .05$) with effects in the same direction. The association between episodic memory performance and SNP rs9398655 was confirmed ($P = .009$), as were nominal associations for 2 flanking SNPs: rs4401702 and rs1554438 ($P = .005$ and $P = .004$, respectively; eTable 4 in the Supplement).

Two SNPs (rs9321334 and rs6902875), located 50 kilobases apart and 1.5 Mb upstream of the linkage peak, showed the strongest nominal association with episodic memory ($P = .009$ and $P = .013$, respectively) in a meta-analysis of the 26 SNPs associated with episodic memory using the 4 independent replication cohorts (NIA-LOAD, ADNI, ADGC, and WHICAP; 4006 individuals) (Figure, B and eTable 4 in the Supplement). Because

Figure. Linkage Analysis and Follow-up Single-Nucleotide Polymorphism (SNP) Association Analyses



A, Multipoint linkage analyses on chromosome 6q24 in 18 Long Life Family Study (LLFS) families. Logarithm of odds (LOD) scores are plotted against the genetic distance in centimorgans. The maximum LOD score of 3.62 is located at 145 cM (139 011 233 base pairs [bp]). Follow-up SNP association analyses evaluated the 112- to 164-megabase region encompassing the linkage peak. B, Plot of the 6324 SNPs associated with exceptional memory in the LLFS families. C, *APOE*-stratified meta-analysis of 26 candidate SNPs in all 4 replication cohorts (National Institute on Aging Late-Onset Alzheimer Disease, Alzheimer Disease Neuroimaging Initiative, Alzheimer Disease Genetic Consortium, and Washington Heights Aging Project). SNP marker rs6902875, which had the strongest association with episodic memory performance, is located downstream from a potential candidate gene, *MOXD1* (123 bp).

of the significant interaction of rs6902875 and *APOE* locus in the meta-analysis (meta-analysis $P = .004$) (eTable 5 in the Supplement) and the frequency and known deleterious effect of *APOE* ε4 on memory,[10] we repeated the analysis stratifying by *APOE ε4* allele (eTable 6 and eTable 7 in the Supplement). These analyses revealed that, among individuals lacking an

APOE ε4 allele, SNP rs6902875 had the strongest association with episodic memory in all replication cohorts (meta-analysis $P = 6.7 \times 10^{-5}$; eTable 6 in the Supplement), reaching experiment-wise significance after adjusting for multiple testing (Bonferroni-adjusted $P \leq .002$).

Subsequent haplotype analysis in the 4 replication data sets incorporating the 2 SNPs flanking rs6902875 that were also significant in meta-analysis (rs9321334 and rs4897574; $P = .001$ and $P = .001$, respectively) revealed that the A-A-C haplotype was significantly associated with episodic memory performance after adjustment for multiple testing (combined Fisher exact test, $P = 2.4 \times 10^{-5}$).

Discussion

We conducted a genome-wide linkage analysis in a set of long-lived families whose EEM abilities appeared to have a significant genetic influence. We detected linkage to a derived phenotype, EEM, with a region on chromosome 6q24, possessing a LOD score of 3.64 ($P = 2.1 \times 10^{-5}$). To follow up the 6q24 linkage signal, we tested the association between episodic memory performance and SNPs in the linkage region in 4 independent replication data sets and identified a region including SNP rs6902875 to be significantly associated with episodic memory, especially among individuals lacking an *APOE* ε4 allele. Subsequent haplotype analysis confirmed our findings.

The region on chromosome 6q24 associated with episodic memory contains biological candidate genes. The strongest SNP, rs6902875, is located 372 bp downstream of the *MOXD1* (OMIM 609000) gene, a dopamine β-hydroxylase-like gene that is involved in the biosynthesis of norepinephrine, a neurotransmitter expressed in brain areas involved in cognitive performance. Additional candidate genes include *HSF2* (OMIM 140581); heat-shock factor protein 2, a gene that contributes to neural plate induction in early mammalian central nervous system and brain development[22]; and *NKAIN2* (OMIM 609758), the sodium/potassium-transporting adenosine triphosphatase subunit beta-1-interacting protein gene that is part of a transmembrane protein family neuronally expressed in mouse brains and associated with human neurologic phenotypes.[23] Identifying genes responsible for EEM provides insights into biological pathways associated with memory performance and possible interventions for enhancement of cognitive function.

We cannot exclude the possibility that rare variants other than the common SNPs represented in the present study might explain additional portions of the heritability of EEM as well as episodic memory. Although episodic memory performance was adjusted for educational level, we did not include environmental measures as part of our study. Thus, we cannot discard the role of environmental factors on episodic memory observed in these families or in the replication data sets. By selecting LLFS families demonstrating EEM, we were able to identify relevant quantitative trait loci in the 6q24 chromosomal region and demonstrated that these common genetic variants can be extended to a related phenotype in the general population.

Conclusions

Our results provide strong evidence that the 6q24 region may harbor common genetic variants that influence memory ability. Identifying the genes will help in understanding the biological basis of memory performance and allow interventions for enhancement of cognitive function.

ARTICLE INFORMATION

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REFERENCES

1. Barral S, Cosentino S, Costa R, et al; Long Life Family Study. Exceptional memory performance in the Long Life Family Study. *Neurobiol Aging*. 2013; 34(11):2445-2448.

2. Haworth CM, Wright MJ, Martin NW, et al. A twin study of the genetics of high cognitive ability selected from 11,000 twin pairs in six studies from four countries. *Behav Genet*. 2009;39(4):359-370.

3. Sebastiani P, Hadley EC, Province M, et al. A family longevity selection score: ranking sibships by their longevity, size, and availability for study. *Am J Epidemiol*. 2009;170(12):1555-1562.

4. Bae HT, Sebastiani P, Sun JX, et al. Genome-wide association study of personality traits in the Long Life Family Study. *Front Genet*. 2013;4:65. doi:10 .3389/fgene.2013.00065.

5. Guey LT, Kravic J, Melander O, et al. Power in the phenotypic extremes: a simulation study of power in discovery and replication of rare variants. *Genet Epidemiol*. 2011;(Feb):9. doi:10.1002/gepi.20572.

6. Wijsman EM, Pankratz ND, Choi Y, et al; NIA-LOAD/NCRAD Family Study Group. Genome-wide association of familial late-onset Alzheimer's disease replicates *BIN1* and *CLU* and nominates *CUGBP2* in interaction with *APOE*. *PLoS Genet*. 2011;7(2):e1001308. doi:10.1371/journal .pgen.1001308.

7. Wechsler D. *The Wechsler Memory Scale–Revised*. San Antonio, TX: Psychological Corp; 1987.

8. Saykin AJ, Shen L, Foroud TM, et al; Alzheimer's Disease Neuroimaging Initiative. Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: genetics core aims, progress, and plans. *Alzheimers Dement*. 2010;6(3):265-273.

9. Naj AC, Jun G, Beecham GW, et al. Common variants at *MS4A4/MS4A6E*, *CD2AP*, *CD33* and *EPHA1* are associated with late-onset Alzheimer's disease. *Nat Genet*. 2011;43(5):436-441.

10. Mayeux R, Small SA, Tang M, Tycko B, Stern Y. Memory performance in healthy elderly without Alzheimer's disease: effects of time and apolipoprotein-E. *Neurobiol Aging*. 2001;22(4): 683-689.

11. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*. 1974;24(11):1019-1025.

12. Benton A. *The Visual Retention Test*. New York, NY: Psychological Corp; 1955.

13. Siedlecki KL, Honig LS, Stern Y. Exploring the structure of a neuropsychological battery across healthy elders and those with questionable dementia and Alzheimer's disease. *Neuropsychology*. 2008;22 (3):400-411.

14. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet*. 1998;62(5):1198-1211.

15. Heath SC. Markov chain Monte Carlo segregation and linkage analysis for oligogenic models. *Am J Hum Genet*. 1997;61(3):748-760.

16. Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet*. 1995;11(3):241-247.

17. Reitz C, Jun G, Naj A, et al; Alzheimer Disease Genetics Consortium. Variants in the ATP-binding cassette transporter (*ABCA7*), apolipoprotein E ε4, and the risk of late-onset Alzheimer disease in African Americans. *JAMA*. 2013;309(14):1483-1492.

18. Lee JH, Cheng R, Barral S, et al. Identification of novel loci for Alzheimer disease and replication of *CLU*, *PICALM*, and *BIN1* in Caribbean Hispanic individuals. *Arch Neurol*. 2011;68(3):320-328.

19. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81(3):559-575.

20. Li MX, Yeung JM, Cherny SS, Sham PC. Evaluating the effective numbers of independent tests and significant *P*-value thresholds in commercial genotyping arrays and public imputation reference datasets. *Hum Genet*. 2012;131(5):747-756.

21. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010;26(17):2190-2191.

22. Walsh D, Li Z, Wu Y, Nagata K. Heat shock and the role of the HSPs during neural plate induction in early mammalian CNS and brain development. *Cell Mol Life Sci*. 1997;53(2):198-211.

23. Yue Y, Stout K, Grossmann B, et al. Disruption of *TCBA1* associated with a de novo t(1;6)(q32.2;q22.3) presenting in a child with developmental delay and recurrent infections. *J Med Genet*. 2006;43(2):143-147.