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Transethnic genome-wide scan identifies novel Alzheimer disease loci

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Abstract

BACKGROUND—Genetic loci for Alzheimer disease (AD) have been identified in whites of European ancestry, but the genetic architecture of AD among other populations is less understood.

METHODS—We conducted a transethnic genome-wide association study (GWAS) for late-onset AD in Stage 1 sample including whites of European Ancestry, African Americans, Japanese, and Israeli-Arabs assembled by the Alzheimer's Disease Genetics Consortium (ADGC). Suggestive results from Stage 1 from novel loci were followed up using summarized results in the International Genomics Alzheimer's Project (IGAP) GWAS dataset.

RESULTS—Genome-wide significant (GWS) associations in SNP-based tests ($P<5\times10^{-8}$) were identified for SNPs in *PFDN1/HBEGF*, *USP6NL/ECHDC3*, and *BZRAP1-AS1*, and for the interaction of the *APOE* ε4 allele with *NFIC* SNP. We also obtained GWS evidence ($P<2.7\times10^{-6}$) for gene-based association in the total sample with a novel locus, *TPBG* ($P=1.8\times10^{-6}$).

DISCUSSION—Our findings highlight the value of transethnic studies for identifying novel AD susceptibility loci.

Keywords

transethnic; Alzheimer disease; genome-wide association; *APOE* interaction

1. Background

Alzheimer disease (AD) is the most prevalent neurodegenerative disease in persons aged 65 years and older and the sixth leading cause of death in the United States [1]. Total healthcare payments in 2014 for people aged 65 years and older with dementia are estimated at $214 billion [1]. By the middle of the century, the number of Americans with AD is projected at 13.8 million with one new case developing every 33 seconds or almost one million new

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Web Resources:
NIA Genetics of Alzheimer's Disease Data Storage Site: https://www.niagads.org/

cases per year. The global burden of AD or dementia in 2015 is more daunting with new cases of dementia in every 3 seconds, and the estimated worldwide costs of dementia are about $818 billion, rising to $2 trillion by 2030 [2]. The number of people living with dementia in 2015 is estimated to be 9.4 million in the Americas, 10.5 million in Europe, 4.0 million in Africa, and 22.9 million in Asia [2]. This is a tremendous global epidemic in elderly persons regardless of ethnic background.

AD with onset age after 65 years is highly heritable with an estimated 74% of the liability explained by genetic factors [3]. A major genetic risk factor for AD is *APOE* genotype [4] which accounts for approximately 35% of the genetic variance [5]. The three common *APOE* alleles (ε2, ε3 and ε4) are determined by combinations of polymorphic amino acid residues at Arg112 (rs429358) and Cys158 (rs7412) [6]. Among non-Hispanic whites of European Ancestry (EA), ε4 heterozygotes have a 2.5 to 3.0 fold increased risk and ε4 homozygotes have a 10-12 fold increased risk, compared to persons with the ε3/ε3 genotype [4]. The ε2 allele is protective [7] such that carriers of this allele have a 40% reduction in AD risk compared to ε3/ε3 individuals [4]. The effect of *APOE* genotype to AD risk is highly variable in other populations. The ε4 frequency is lower in Asians [8] and associated with higher AD risk among Japanese compared to EAs [9]. In contrast, the effect of ε4 on AD risk is much less in African Americans among whom the ε4 frequency is about 50% higher than in EAs [10]. It is noteworthy that the ε4 allele is virtually absent among Arabs living in northern Israeli community where the prevalence of dementia is roughly double than in EA populations [11].

More than 20 loci have been robustly associated with AD [12] and are enriched in immune response, regulation of endocytosis, cholesterol transport, and protein ubiquitination pathways [13]. A recent genome-wide association study (GWAS) identified significant association of AD with multiple single nucleotide polymorphisms (SNPs) in the *MAPT-KANSL1* region among EAs lacking an *APOE* ε4 allele [14]. Genetic studies in other populations have increased our understanding of the genetic architecture of AD. For example, the effect of the *APOE* ε4 allele is much greater in Japanese and substantially weaker in African American and some Hispanic groups, due in part to varying frequencies of this allele across populations [4]. Three loci (*SORL1, ABCA7*, and *ACE*) whose association with AD attained genome-wide significance in EAs [12] were found to have larger effects on AD risk in African Americans, (*ABCA7*) [15], Japanese (*SORL1*) [9], and Israeli-Arabs (*ACE*) [16]. Some loci including *PLXNA4* [17] and *SORL1* [18] demonstrate allelic heterogeneity among genetically diverse populations. In the current study, we leveraged genetic diversity across ethnic groups to increase discovery of additional AD risk loci by combining GWAS results obtained from samples of EAs, African Americans, Japanese and Israeli-Arabs.

2. Methods

2.1. Subjects, Genotyping, and Data Processing

Details of subject recruitment and genotyping for individual case-control and family-based datasets, genotype imputation, quality control, population substructure, and statistical methods for association analyses were reported previously for Alzheimer's Disease Genetics

Consortium (ADGC) datasets containing EAs [5], African Americans (AA) [15], Japanese (JPN) [9], and Israeli-Arab (IA) [11]. Characteristics of the 33,269 ADGC subjects (26,320 EA, 4,983 AA, 1,845 JPN, and 115 IA) used for discovery in Stage 1 were shown in **Supplementary Table 1.** Summarized results archived in the NIA Genetics of Alzheimer's Disease Data Storage Site (https://www.niagads.org/) that are from a previous GWAS of EAs conducted by the International Genomics Alzheimer's Project (IGAP) including 5,813 AD cases and 20,474 controls after excluding the ADGC datasets [12] were used in Stage 2 follow-up analyses (**Supplementary Table 1**).

2.2. Genome-wide Association Analysis in Stage 1

2.2.1. Design and Power Considerations—The primary analysis was a single GWAS including all discovery datasets. Analyses were performed separately for each dataset and the results were pooled sequentially, first within ethnic groups and then across ethnic groups. The minimum detectable genotype relative risk for EAs range from 1.16 for MAF=0.5 to 1.73 for MAF=0.01. The corresponding ranges for AAs and JPN are 1.40-2.69 and 1.74-3.78, respectively. GRRs of <5 are not detectable with 80% power in the small IA sample. However, the goal of this study was not for novel discovery within ethnic groups but rather in the total transethnic sample. Prompted by findings of previous studies [14], we also conducted separate GWAS in subgroups of subjects who have or lack an *APOE* ε4 allele. We also applied a complementary approach for assessing a differential effect of association by *APOE* genotype by evaluating association of AD with an interaction of SNP and ε4 status.

2.2.2. SNP-based association—Within each dataset, genome-wide association analyses were conducted using more than 7 million imputed SNPs in the total sample, as well as in subgroups of subjects with and without the *APOE* ε4 allele, using regression models including age, sex, the first three PCs. An additive effect of a SNP was included in the model as a quantitative estimate between 0 and 2 representing the probability score of the effect allele to incorporate the uncertainty of the imputation estimates. Models were evaluated using a logistic generalized linear model in case-control datasets and a logistic generalized estimating equation in family-based datasets. We also evaluated models including a term for the interaction of the SNP dosage with the *APOE* ε4 status and models among subgroups stratified by *APOE* ε4 status. Results for each model across datasets were combined by meta-analysis separately within each ethnic group using a fixed-effects, inverse-variance weighted meta-analysis in the METAL program [19]. SNPs with a minor allele frequency ≥1% and imputation quality≥0.4 that were available in at least 50% of the datasets were included in the meta-analysis. The meta-analysis *P*-value for association was estimated by the summarized test statistic, after applying genomic control within each individual study. Meta-analysis was also conducted using Han and Eskin's modified random effects model (RE-HE) that is optimized to detect associations under effect heterogeneity, as implemented in METASOFT [20]. This model has similar power to the fixed effects model when heterogeneity is modest, e.g., when the standard deviation of the different ethnicities log odds ratios is ≤0.5 times the mean log odds ratio, but has better power than the fixed effects model for substantial heterogeneity. Thus, we do not expect the RE-HE model to produce

substantially different results from the fixed effects model unless substantial heterogeneity among ethnicities exists.

2.2.3. Gene-based association—We conducted genome-wide gene-based tests using ethnic-specific association results from SNP-based tests. Intragenic SNPs and SNPs within 30 kilobases (kb) of transcription start and stop sites were included in each gene-based test. We used the GATES [21] method, which computes a gene-based P-value using SNP-based p values and SNP-SNP correlations by penalizing lack of association in correlated SNPs. Ethnic-specific gene-based results for EA, AA, JPN, and IA groups were combined using the sample-size weighted Z-score method in METAL assuming the same direction of effect.

2.3. Follow-Up Association Analysis

In Stage 2, we attempted to replicate Stage 1 top-ranked SNP-based ($P<10^{-5}$) results and validate gene-based ($P<10^{-4}$) results from each ethnic subgroup. Previously known AD genes were evaluated in Stage 2 only when both SNP-based and gene-based P values met threshold criteria for follow up. These analyses incorporated summarized results for the Stage 2 ADGC datasets and previously reported results for IGAP datasets excluding those from the ADGC that are described in **Supplementary Table 1**. The genome-wide significance threshold was set at $P<5\times10^{-8}$ for individual SNPs and $P<2\times10^{-6}$ for gene-based tests in the Stage 1+2 analyses.

3. Results

3.1. Findings with Individual SNPs

There was little evidence for genomic inflation in SNP-based GWA results in the total sample with main effect ($\lambda=1.02$) and interaction effect of a SNP with APOE ε4 status on AD risk ($\lambda=1.02$), as well as in APOE ε4+ subjects ($\lambda=0.99$) and APOE ε4− subjects ($\lambda=0.99$) (Supplementary Fig. 1). In the total sample, we confirmed genome-wide significant (GWS) association ($p<5\times10^{-8}$) with SNPs in several previously implicated AD loci including *CR1, BIN1, PTK2B, MS4A2/MS4A6A, PICALM* (**Supplementary Table 2, Supplementary Fig. 2**). GWS association was also observed with SNPs in *NFIC* and *PRKCE* through interaction with *APOE* (**Supplementary Fig. 2B**) and with SNPs between *USP6N* and *ECHDC3* among subjects lacking *APOE* ε4 (**Supplementary Fig. 2D**). Top-ranked SNPs in EA for *PICALM, SORL1,* and *ABCA7* had strong support for association in Japanese, whereas the top-ranked SNPs in *CR1, BIN1,* and *EPHA1* were consistently associated in EA and AA (**Supplementary Table 2**). In contrast, the effect direction was significantly opposite in EA versus AA for *NME8, ABCA7,* and *CASS4* SNPs (**Supplementary Table 2**). A total of 35 SNPs from nine novel loci met criteria for follow up in Stage 2 (**Supplementary Table 3**). Extensive evaluation of SNPs from the *APOE* region across the different ethnic groups demonstrated that only the *APOE* ε2 SNP (rs7412) remained genome-wide significant among *APOE* ε4− subjects (**Supplementary Table 4**), confirming our prior observation that *APOE* accounts for all association signals in this region [22]. SNPs in other loci showed suggestive evidence for association ($P<10^{-6}$) in EAs or AAs (**Supplementary Table 5**), but these results were much less significant in the transethnic meta-analyses. Analysis of models including an interaction term for each SNP

with *APOE* ε4 status identified a GWS significant interaction (interaction: P = 1.5×10^{-8}) for *NFIC* SNP rs9749589 (**Table 1**). This SNP appeared protective in ε4+ subjects (OR=0.83, P=6.4×10^{-6}) but slightly increased risk of AD in ε4− subjects (OR=1.11, P=6.0×10^{-3}) (**Supplementary Table 6**).

In the combined Stage 1+2 sample, GWS association was observed with SNPs in several previously established AD loci (*CR1, BIN1, PTK2B, MS4A4A,* and *PICALM*) (**Supplementary Fig. 3, Supplementary Fig. 4**). Follow-up of the 35 SNPs from novel loci in Stage 2 revealed nominally significant associations for nine SNPs in *PFDN1/HBEGF, USP6NL/ECHDC3,* and *BZRAP1-AS1* **(Supplementary Table 6**). In the combined Stage 1+2 sample, GWS association was attained with two intergenic SNPs between *PFDN1* and *HBEGF* (best SNP: rs11168036, P=7×10^{-9}), six intergenic SNPs between *USP6NL* and *ECHDC3* (best SNP: rs7920721, P=3×10^{-8}), *BZRAP1-AS1* SNP rs2632516 (P=4×10^{-8}) (**Table 1, Fig. 1, Supplementary Table 6**). Analyses of models that conditioned on the top SNP at the *PFDN1/HBEGF, USP6NL/ECHDC3*, and *BZRAP1-AS1* loci confirmed a single association signal in each region (**Supplementary Fig. 5**). The significant interaction between *NFIC* SNP rs9749589 and ε4 status in Stage 1 was not significant in Stage 2 (P=0.2), however the magnitude and direction of effect was the same and the interaction P value in the total sample was not diminished (**Table 1, Fig. 1**). These GWS associations, except for rs7920721, were supported by evidence in multiple ethnic groups (**Fig. 2**). Further evaluation of the Stage 1+2 findings revealed that the association with the *USP6NL/ ECHDC3* SNPs was exclusive to subjects lacking *APOE* ε4 (e.g., rs7920721: ε4+, P=0.07, OR=1.05; ε4−, P=2.7×10^{-9}, OR=1.14; interaction P = 0.01) and comparable in terms of effect size and direction in the non-European ancestry groups (**Supplementary Table 6** and **Supplementary Fig. 6**). All GWS findings were similar using the METASOFT Han and Eskin modified random effects model (**Supplementary Table 7**).

3.2. Gene-Based Test Findings

In Stage 1 analyses, there was strong evidence of association (gene-based P<10^{-4}) with previously established loci and novel loci in the total sample (**Supplementary Fig. 7** and **Supplementary Table 8**), but only seven known genes (*CR1, BIN1, PTK2B, CLU, MS4A4A, PICALM,* and *ABCA7*) and one novel one (*TPBG*) were GWS (P<2.7×10^{-6}) in the combined Stage 1+2 sample **(Table 2, Supplementary Table 8**). Both EAs and AAs contributed to the association with *TPBG*. No additional genes were identified as GWS in interaction models or *APOE* genotype subgroups.

4. Discussion

In this large transethnic genetic study of AD, we identified robust associations with several novel loci at the individual SNP level (*PFDN1/HBEGF, USP6NL/ECHDC3, BZRAP1-AS1* and *NFIC*) and gene level (*TPBG*) in a sample of AD subjects and cognitively normal elders in cohorts containing whites of European ancestry, African Americans, Japanese, and Israeli-Arabs. Most of these findings are supported by evidence in more than one ethnic group (Fig. 2 and Table 2). Previous GWAS using the EA discovery cohorts in this study did not detect genome-wide significant association with any of these loci, although there was

suggestive evidence of association (P>10-7) for the top SNPs in the *PFDN1/HBEGF* and *USP6NL/ECHDC3* regions in EAs [12, 14]. The other novel genes identified in this study were not previously reported to be associated with AD in any ethnic groups. The association with SNPs in the *USP6NL/ECHDC3* region was specific to persons lacking the *APOE* ε4 allele. Our study also showed that associations for several genes that have previously been robustly implicated in AD in Caucasians of European descent (*CR1, BIN1, PTK2B, MS4A4A*, and *PICALM*) were evident in other populations even at the SNP level.

HBEGF, heparin EGF like growth factor, has roles in wound healing, cardiac hypertrophy, and heart development [23]. Although the biological role for this gene in AD is not obvious, an *HBEGF* knock-out mouse that does not express *HBEGF* in cortex and hippocampus has psychiatric and cognitive dysfunctions that accompany down-regulated NMDA receptors [24]. Another study showed that rats exposed to the pesticide cypermethrin had a reduction of *HBEGF* expression leading to upregulation of GSK3b-dependent Aβ and phosphorylated tau [25].

A recent GWAS demonstrated pleiotrophic effects of SNPs in the *USP6NL/ECHDC3* (including rs7920721) and *BZRAP1-AS1* loci for AD and plasma C-reactive protein and lipid levels [26]. The pleiotropy at *USP6NL/ECHDC3* may be related to the association finding at this locus among persons lacking the *APOE* ε4 allele. *USP6NL*, ubiquitin specific peptidase 6 N-terminal like, has a role in the EGF receptor (EGFR) signaling pathway by acting as a GTPase-activating protein and inhibiting internalization of EGFR [27]. Insight for a role of *USP6NL* may be gained from information about USP6 which regulates ubiquitylation and trafficking of cargo protein by clathrin-independent endocytosis [28]. There is a growing body of evidence from studies in humans and mice supporting a role for clathrin-mediated endocytosis in AD [29-31] In addition, the association of the phosphatidylinositol binding clathrin assembly protein (*PICALM*) gene to AD is well established [12].

ECHDC3, enoyl CoA hydratase domain containing 3, is involved in fatty acid biosynthesis in mitochondria and its expression is increased in patients with acute myocardial infarction [32]. It has been observed that *ECHD3* expression is altered in brains from persons with AD compared to controls [26]. Although rs7920721 is closer to *ECHDC3* than *USP6NL*, it is located on *USP6NL* side of a recombination hotspot between these two genes (Fig. 1B). Therefore, we cannot rule out either of these genes, or even one not adjacent to rs7920721, as explaining the association signal in this region.

BZRAP1, benzodiazepine-associated protein 1 (renamed as TSPO associated protein 1, *TSPOAP1*), is a subunit of the benzodiazepine receptor complex in mitochondria and a marker of neuroinflammation [34]. A recent prospective cohort study of 8,240 individuals aged 65 years and older showed an increased risk of dementia with use of long half-life benzodiazepines [35], a drug often prescribed for treatment of anxiety. A TSPO ligand (Ro5-4864) has been shown to reverse β-amyloid accumulation and behavioral impairment in 3xTgAD mice [36]. A recent PET imaging study demonstrated that the change over time of TSPO binding to radioligand 11C-PBR28 is correlated with progression of AD [37].

The relationship of AD to the other novel loci identified in this study is less clear. *PFDN1*, a prefoldin subunit, is upregulated in colorectal cancer [33]. *NFIC* is a CCAAT-binding transcription factor. A study comparing brain gene expression profiles between HIV seropositive individuals with cognitive impairment and AD cases identified *NFIC* as having significant high co-expression connectivity in white matter [38]. Trophoblast glycoprotein (*TPBG*), also known as 5T4, regulates development of the olfactory bulb GABAgenic interneurons and its overexpression in newborns is associated with abnormal dendrites [39].

Our study highlights the benefit of combining results obtained from genetically diverse populations. The transethnic approach applied here identified three novel loci (*BZRAP1-AS1, NFIC,* and *TPBG*) and GWS association for the first time with two other loci (PFDN1/HBEGF and *USP6NL/ECHDC3*) noting that the size of the discovery sample in this study was less than 45% of the one included in a previous GWAS that contained more than 74,000 EA subjects. The improved power in our smaller sample can be ascribed to allele frequency differences and allelic heterogeneity among the ethnic groups. As an example highlighting the importance of these differences, the top SNPs from *BZRAP1-AS1* and *NFIC* had different minor allele frequencies across ethnic groups, but the effect sizes were similar and association signals were greater in fixed effect meta-analysis. In addition, gene-based tests, which consider association patterns with all SNPs in the locus, identified *TPBG*. Importantly, the most significant SNPs in these two regions differed among the ethnic groups. Gene-based tests also indicated potential allelic heterogeneity among ethnic groups for previously established AD genes including *TREM2* and *ABCA7*. The novel GWS SNP associations were robust in analyses allowing for heterogeneity across different ethnic groups, and the P-values for the RE-HE approach were slightly larger than for the fixed effect model, suggesting that the effect size heterogeneity across the groups is modest.

Our study also revealed that the effect direction for several SNPs vary across ethnic groups. For example, the top-ranked SNPs in *NME8, ABCA7,* and *CASS4* (**Supplementary Table 2)** were nominally significant in EAs and AAs, but the referent allele was associated with increased risk in one group and decreased risk in the other. One explanation for these differences is that the SNPs are tagging different functional variants across groups. This idea is consistent with our findings from gene-based tests showing that the constellation of variants contributing to the association with some genes was different across ethnic groups. Alternatively, when examining a large number of variants it is expected that a few will show nominal significance in opposite directions among groups.

There are several limitations associated with our study. The sample size imbalance between the EAs and the other populations weakened the opportunity to identify association patterns that may be unique to the non-EA groups. The small size of the non-EA groups also reduced power to detect novel gene associations if the functional variants (and the SNPs that tag them) differ among ethnic groups. An additional weakness is the lack of replication samples for the non-EA populations. Despite these limitations, our study highlights the importance of investigating the genetic architecture for AD in ethnically diverse populations.

Our findings warrant further replication in independent samples, deep sequencing and bioinformatics studies to identify the potentially functional variants, and experimental

validation. We expect that additional novel gene discoveries will emerge in future transethnic studies including larger samples from non-European ancestry populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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5. References

[1]. Association As. 2014 Alzheimer's disease facts and figures. Alzheimers Dement. 2014; 10:e47–92. [PubMed: 24818261]

[2]. International AsD. World Alzheimer Report 2015: The Global Impact of Dementia. Alzheimer's Disease International (ADI). 2015

[3]. Gatz M, Pedersen NL, Berg S, Johansson B, Johansson K, Mortimer JA, et al. Heritability for Alzheimer's disease: the study of dementia in Swedish twins. J Gerontol A Biol Sci Med Sci. 1997; 52:M117–25. [PubMed: 9060980]

[4]. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. Jama. 1997; 278:1349–56. [PubMed: 9343467]

[5]. Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buros J, et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet. 2011; 43:436–41. [PubMed: 21460841]

[6]. Yu L, Boyle PA, Leurgans S, Schneider JA, Bennett DA. Disentangling the effects of age and APOE on neuropathology and late life cognitive decline. Neurobiol Aging. 35:819–26.

[7]. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC Jr. et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet. 1994; 7:180–4. [PubMed: 7920638]

[8]. Singh PP, Singh M, Mastana SS. APOE distribution in world populations with new data from India and the UK. Ann Hum Biol. 2006; 33:279–308. [PubMed: 17092867]

[9]. Miyashita A, Koike A, Jun G, Wang LS, Takahashi S, Matsubara E, et al. SORL1 is genetically associated with late-onset Alzheimer's disease in Japanese, Koreans and Caucasians. PLoS One. 2013; 8:e58618. [PubMed: 23565137]

[10]. Graff-Radford NR, Green RC, Go RC, Hutton ML, Edeki T, Bachman D, et al. Association between apolipoprotein E genotype and Alzheimer disease in African American subjects. Arch Neurol. 2002; 59:594–600. [PubMed: 11939894]

[11]. Sherva R, Baldwin CT, Inzelberg R, Vardarajan B, Cupples LA, Lunetta K, et al. Identification of novel candidate genes for Alzheimer's disease by autozygosity mapping using genome wide SNP data. J Alzheimers Dis. 2011; 23:349–59. [PubMed: 21098978]

[12]. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013; 45:1452–8. [PubMed: 24162737]

[13]. IGAP. Convergent genetic and expression data implicate immunity in Alzheimer's disease. Alzheimers Dement. 2015; 11:658–71. [PubMed: 25533204]

[14]. Jun G, Ibrahim-Verbaas CA, Vronskaya M, Lambert JC, Chung J, Naj AC, et al. A novel Alzheimer disease locus located near the gene encoding tau protein. Mol Psychiatry. 2016; 21:108–17. [PubMed: 25778476]

[15]. Reitz C, Jun G, Naj A, Rajbhandary R, Vardarajan BN, Wang LS, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4,and the risk of late-onset Alzheimer disease in African Americans. JAMA. 2013; 309:1483–92. [PubMed: 23571587]

[16]. Meng Y, Baldwin CT, Bowirrat A, Waraska K, Inzelberg R, Friedland RP, et al. Association of polymorphisms in the Angiotensin-converting enzyme gene with Alzheimer disease in an Israeli Arab community. Am J Hum Genet. 2006; 78:871–7. [PubMed: 16642441]

[17]. Jun G, Asai H, Zeldich E, Drapeau E, Chen C, Chung J, et al. PLXNA4 is associated with Alzheimer disease and modulates tau phosphorylation. Ann Neurol. 2014; 76:379–92. [PubMed: 25043464]

[18]. Rogaeva E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, et al. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nat Genet. 2007; 39:168–77. [PubMed: 17220890]

[19]. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010; 26:2190–1. [PubMed: 20616382]

[20]. Han B, Eskin E. Random-effects model aimed at discovering associations in meta-analysis of genome-wide association studies. Am J Hum Genet. 2011; 88:586–98. [PubMed: 21565292]

[21]. Li MX, Gui HS, Kwan JS, Sham PC. GATES: a rapid and powerful gene-based association test using extended Simes procedure. Am J Hum Genet. 2011; 88:283–93. [PubMed: 21397060]

[22]. Jun G, Vardarajan BN, Buros J, Yu CE, Hawk MV, Dombroski BA, et al. Comprehensive Search for Alzheimer Disease Susceptibility Loci in the APOE Region. Arch Neurol. 2012:1–10.

[23]. Nanba D, Higashiyama S. Dual intracellular signaling by proteolytic cleavage of membrane-anchored heparin-binding EGF-like growth factor. Cytokine Growth Factor Rev. 2004; 15:13–9. [PubMed: 14746810]

[24]. Sasaki K, Omotuyi OI, Ueda M, Shinohara K, Ueda H. NMDA receptor agonists reverse impaired psychomotor and cognitive functions associated with hippocampal Hbegf-deficiency in mice. Mol Brain. 2015; 8:83. [PubMed: 26637193]

[25]. Maurya SK, Mishra J, Abbas S, Bandyopadhyay S. Cypermethrin Stimulates GSK3beta-Dependent Abeta and p-tau Proteins and Cognitive Loss in Young Rats: Reduced HB-EGF Signaling and Downstream Neuroinflammation as Critical Regulators. Mol Neurobiol. 2016; 53:968–82. [PubMed: 25575682]

[26]. Desikan RS, Schork AJ, Wang Y, Thompson WK, Dehghan A, Ridker PM, et al. Polygenic Overlap Between C-Reactive Protein, Plasma Lipids, and Alzheimer Disease. Circulation. 2015; 131:2061–9. [PubMed: 25862742]

[27]. Martinu L, Santiago-Walker A, Qi H, Chou MM. Endocytosis of epidermal growth factor receptor regulated by Grb2-mediated recruitment of the Rab5 GTPase-activating protein RN-tre. J Biol Chem. 2002; 277:50996–1002. [PubMed: 12399475]

[28]. Funakoshi Y, Chou MM, Kanaho Y, Donaldson JG. TRE17/USP6 regulates ubiquitylation and trafficking of cargo proteins that enter cells by clathrin-independent endocytosis. J Cell Sci. 2014; 127:4750–61. [PubMed: 25179595]

[29]. Logue MW, Schu M, Vardarajan BN, Farrell J, Lunetta KL, Jun G, et al. Search for age-related macular degeneration risk variants in Alzheimer disease genes and pathways. Neurobiol Aging. 2014; 35:1510. e7-18.

[30]. Thomas RS, Lelos MJ, Good MA, Kidd EJ. Clathrin-mediated endocytic proteins are upregulated in the cortex of the Tg2576 mouse model of Alzheimer's disease-like amyloid pathology. Biochem Biophys Res Commun. 2011; 415:656–61. [PubMed: 22079091]

[31]. Xiao Q, Gil SC, Yan P, Wang Y, Han S, Gonzales E, et al. Role of phosphatidylinositol clathrin assembly lymphoid-myeloid leukemia (PICALM) in intracellular amyloid precursor protein (APP) processing and amyloid plaque pathogenesis. J Biol Chem. 2012; 287:21279–89. [PubMed: 22539346]

[32]. Eicher JD, Wakabayashi Y, Vitseva O, Esa N, Yang Y, Zhu J, et al. Characterization of the platelet transcriptome by RNA sequencing in patients with acute myocardial infarction. Platelets. 2016; 27:230–9. [PubMed: 26367242]

[33]. Wang P, Zhao J, Yang X, Guan S, Feng H, Han D, et al. PFDN1, an indicator for colorectal cancer prognosis, enhances tumor cell proliferation and motility through cytoskeletal reorganization. Med Oncol. 2015; 32:264. [PubMed: 26553318]

[34]. Galiegue S, Jbilo O, Combes T, Bribes E, Carayon P, Le Fur G, et al. Cloning and characterization of PRAX-1. A new protein that specifically interacts with the peripheral benzodiazepine receptor. J Biol Chem. 1999; 274:2938–52. [PubMed: 9915832]

[35]. Shash D, Kurth T, Bertrand M, Dufouil C, Barberger-Gateau P, Berr C, et al. Benzodiazepine, psychotropic medication, and dementia: A population-based cohort study. Alzheimers Dement. 2016; 12:604–13. [PubMed: 26602630]

[36]. Barron AM, Garcia-Segura LM, Caruso D, Jayaraman A, Lee JW, Melcangi RC, et al. Ligand for translocator protein reverses pathology in a mouse model of Alzheimer's disease. J Neurosci. 2013; 33:8891–7. [PubMed: 23678130]

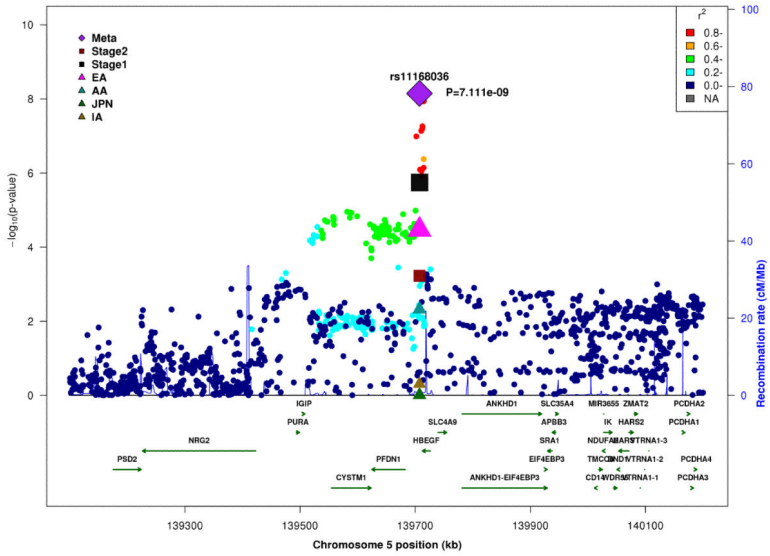
[37]. Kreisl WC, Lyoo CH, Liow JS, Wei M, Snow J, Page E, et al. (11)C-PBR28 binding to translocator protein increases with progression of Alzheimer's disease. Neurobiol Aging. 2016; 44:53–61. [PubMed: 27318133]

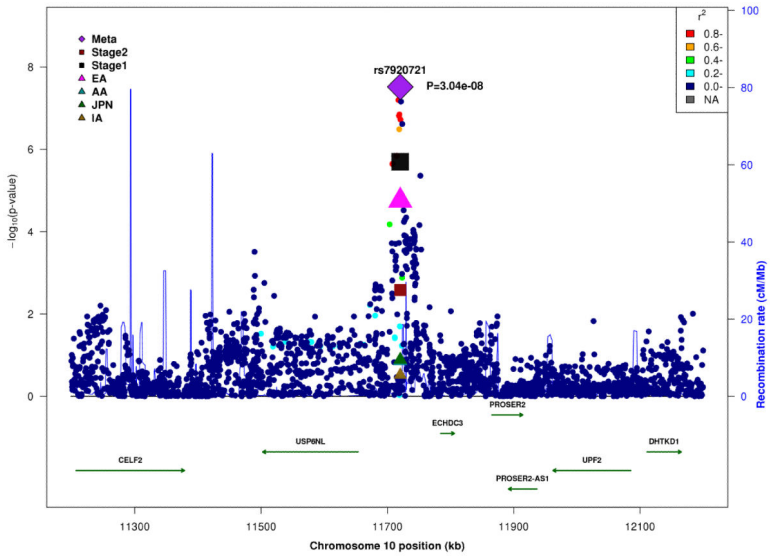
[38]. Levine AJ, Miller JA, Shapshak P, Gelman B, Singer EJ, Hinkin CH, et al. Systems analysis of human brain gene expression: mechanisms for HIV-associated neurocognitive impairment and common pathways with Alzheimer's disease. BMC Med Genomics. 2013; 6:4. [PubMed: 23406646]

[39]. Yoshihara S, Takahashi H, Nishimura N, Naritsuka H, Shirao T, Hirai H, et al. 5T4 glycoprotein regulates the sensory input-dependent development of a specific subtype of newborn interneurons in the mouse olfactory bulb. J Neurosci. 2012; 32:2217–26. [PubMed: 22323733]

Research in Context

1. **Systematic review**: We reviewed previously published genome-wide association studies (GWAS) for late onset Alzheimer disease (AD) including reports for non-white populations. Few GWAS have been conducted in populations of non-white European ancestry.
2. **Interpretation:** Transethnic meta-analysis of GWAS results for whites of European Ancestry, African Americans, Japanese, and Israeli-Arabs identified novel genome-wide significant associations with SNPs in *PFDN1/HBEGF, USP6NL/ECHDC3*, and *BZRAP1-AS1*, and with *TPBG* using a gene-based test. These findings further our understanding of the genetic basis of AD and provide insight about mechanisms leading to AD.
3. **Future directions**: These results should be confirmed in independent samples including subjects from the same ethnic populations and tested in populations of other genetic backgrounds. DNA sequencing studies are needed to identify the functional variants in these genes and their biological roles in AD should be determined experimentally.





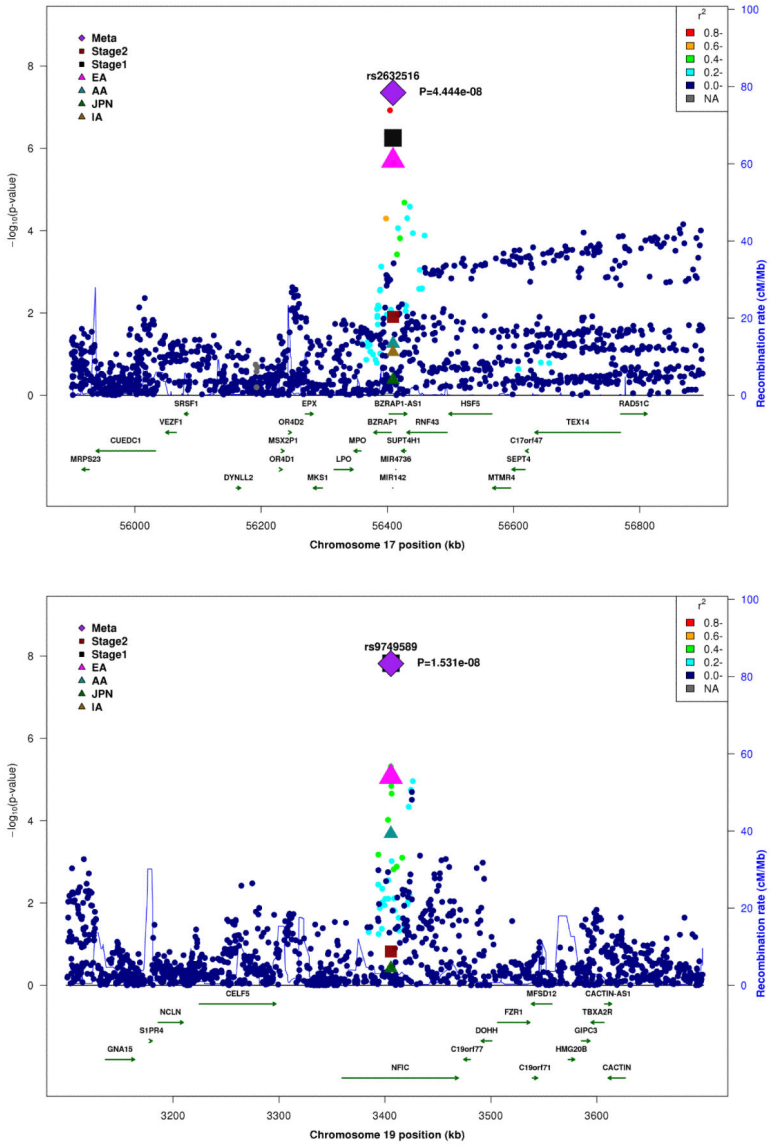
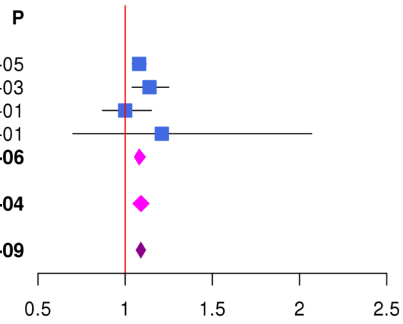


Figure 1.

Regional association plots in the combined stage 1 and stage 2 sample including main effects at **(A)** *PFDN1/HBEGF*, **(B)** *USP6NL/ECHDC3*, **(C)** *BZRAP1-AS1*, and **(D)** SNP*$APOE$ ε4 interaction near *NFIC*.

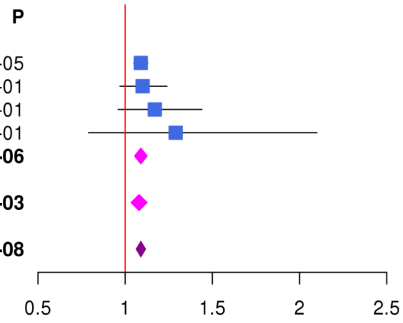
rs11168036

Study	MAF	OR	95%CI	P
EA	0.50	1.08	(1.04-1.12)	3.4e-05
AA	0.54	1.14	(1.04-1.25)	4.8e-03
JPN	0.53	1.00	(0.87-1.15)	9.8e-01
IA	0.60	1.21	(0.70-2.07)	4.9e-01
Stage1	**0.51**	**1.08**	**(1.05-1.12)**	**1.8e-06**
Stage2	**0.49**	**1.09**	**(1.04-1.14)**	**5.9e-04**
Stage1+2	**0.50**	**1.09**	**(1.06-1.12)**	**7.1e-09**



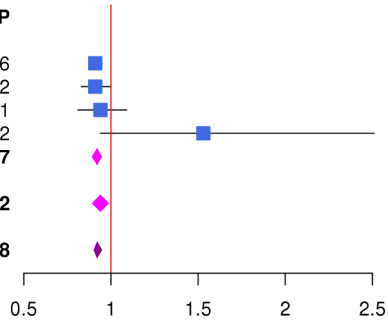
rs7920721

Study	MAF	OR	95%CI	P
EA	0.39	1.09	(1.05-1.13)	1.7e-05
AA	0.16	1.10	(0.97-1.24)	1.4e-01
JPN	0.16	1.17	(0.96-1.44)	1.3e-01
IA	0.38	1.29	(0.79-2.10)	3.0e-01
Stage1	**0.36**	**1.09**	**(1.05-1.13)**	**2.0e-06**
Stage2	**0.39**	**1.08**	**(1.03-1.13)**	**2.6e-03**
Stage1+2	**0.37**	**1.09**	**(1.06-1.12)**	**3.0e-08**



rs2632516

Study	MAF	OR	95%CI	P
EA	0.44	0.91	(0.88-0.95)	2.0e-06
AA	0.60	0.91	(0.83-1.00)	5.6e-02
JPN	0.51	0.94	(0.81-1.09)	4.2e-01
IA	0.44	1.53	(0.94-2.51)	8.9e-02
Stage1	**0.47**	**0.92**	**(0.89-0.95)**	**5.6e-07**
Stage2	**0.44**	**0.94**	**(0.89-0.99)**	**1.2e-02**
Stage1+2	**0.46**	**0.92**	**(0.90-0.95)**	**4.4e-08**



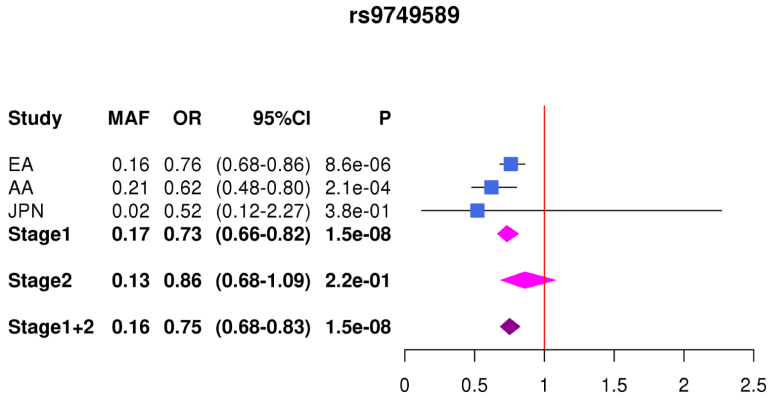


Figure 2.

Forest plots for by ethnicity and stage for **(A)** rs11168036 at*PFDN1/HBEGF*, **(B)** rs7920721 at *USP6NL/ECHDC3*, **(C)** rs2632516 at *BZRAP1-AS1,* **(D)** *NFIC* rs9749589* *APOE* ε4 interaction.

Table 1

Genome-wide significant results from individual SNP and SNP*_APOE_-ε4 interaction tests ($P<5\times10^{-8}$) in transethnic meta-analysis.

SNP	CH	Locus	EfA	EAF				Stage 1			Stage 2			Stages 1 + 2	
				EA	AA	JPN	IA	OR (95% CI)	P		OR (95% CI)	P		OR (95% CI)	P
SNP															
rs11168036	5	*PFDN1/ HBEGF*	T	0.5	0.5	0.5	0.6	1.08 (1.04-1.13)	1.8×10^{-6}		1.08 (1.04-1.13)	6.0×10^{-4}		1.08 (1.06-1.10)	7.1×10^{-9}
rs7920721	10	*USP6NL/ ECHDC3*	G	0.4	0.2	0.2	0.4	1.09 (1.05-1.14)	2.0×10^{-6}		1.07 (1.03-1.12)	2.6×10^{-3}		1.08 (1.04-1.13)	3.0×10^{-8}
rs2632516	17	*BZRAP1-AS1*	C	0.4	0.6	0.5	0.4	0.91 (0.88-0.95)	5.6×10^{-7}		0.94 (0.89-1.00)	0.01		0.92 (0.91-0.94)	4.4×10^{-8}
Interaction †															
rs9749589*ε4	19	*NFIC*	A	0.16	0.2	0.02	na	0.73 (0.66-0.81)	1.5×10^{-8}		0.86 (0.68-1.09)	0.22		0.76 (0.69-0.83)	1.5×10^{-8}
rs9749589								1.17 (1.04-1.20)	2.5×10^{-3}		1.04 (0.92-1.19)	0.50		1.10 (1.03-1.16)	3.3×10^{-3}

CH = chromosome; EfA = effect allele; EAF = effect allele frequency; EA = European Ancestry; AA = African American; JPN = Japanese; IA = Israeli-Arab; OR = odds ratio; CI = confidence interval; P = p-value;

† results for interaction term (*NFIC* rs9749589 * *APOE* ε4) and main effect of rs9749589

Table 2

Genome-wide significant results ($p<2.7\times10^{-6}$) from gene-based tests in Stage 1+2.

Gene	CH	Ethnic Specific P value in Stage1				Stage 1	Stage 2	Stage 1+2
		EA	AA	JPN	IA			
CR1	1	3.4×10^{-9}	0.84	0.35	0.10	4.8×10^{-9}	6.4×10^{-5}	1.4×10^{-12}
BIN1	2	1.4×10^{-14}	0.08	0.33	0.80	3.7×10^{-15}	2.5×10^{-9}	8.8×10^{-23}
TPBG	6	2.2×10^{-3}	3.5×10^{-3}	0.29	0.70	6.8×10^{-5}	8.2×10^{-3}	1.8×10^{-6}
PTK2B	8	4.7×10^{-6}	0.26	0.49	0.81	2.2×10^{-6}	1.9×10^{-3}	7.6×10^{-8}
CLU	8	7.0×10^{-6}	0.11	0.59	0.10	1.1×10^{-6}	1.1×10^{-9}	1.4×10^{-12}
MS4A4A	11	5.4×10^{-13}	0.18	0.03	0.95	3.6×10^{-14}	0.04	6.1×10^{-14}
PICALM	11	1.9×10^{-8}	0.71	1.8×10^{-3}	0.93	1.6×10^{-9}	3.6×10^{-3}	2.7×10^{-11}
ABCA7	19	2.3×10^{-4}	1.6×10^{-3}	0.07	0.02	6.6×10^{-7}	4.9×10^{-3}	1.1×10^{-8}

CH = chromosome; EA = European Ancestry; AA = African American; JPN = Japanese; IA = Israeli Arab; P = gene-based p value