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A candidate gene study of risk for dementia in older, post-menopausal women: Results from the Women's Health Initiative Memory Study

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Abstract

Objective: While a number of single nucleotide polymorphisms (SNPs) associated with Alzheimer's disease (AD) or cognitive impairment have been identified, independent replications remain the only way to validate proposed signals. We investigated SNPs in candidate genes associated with either cognitive impairment or AD pathogenesis and their relationships with probable dementia (PD) in the Women's Health Initiative Memory Study (WHIMS).

Methods: We analyzed 96 SNPs across five genes (*APOE/TOMM40*, *BDNF*, *COMT*, *SORL1*, and *KIBRA*) in 2857 women (ages 65) from the WHIMS randomized trials of hormone therapy using a custom Illumina GoldenGate assay; 19% of the sample were MCI (N=165) or PD (N=387), and the remaining 81% were free of cognitive impairment. SNP associations were

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evaluated for PD in non-Hispanic whites adjusting for age and HT using logistic regression under an additive genetic model.

Results: One SNP (rs157582), located in the *TOMM40* gene nearby *APOE*, was associated with the PD phenotype based on a *p*-value accounting for multiple comparisons. An additional 12 SNPs were associated with the PD phenotype at *p* 0.05 (*APOE*: rs405509, rs439401; *TOMM40*: rs8106922, and *KIBRA*: rs4320284, rs11740112, rs10040267, rs13171394, rs6555802, rs2241368, rs244904, rs6555805 and rs10475878). Results of the sensitivity analyses excluding MCI were similar, with addition of *COMT* rs737865 and *BDNF* rs1491850 (*p* 0.05).

Conclusions: Our results in older women provide supporting evidence that the *APOE/TOMM40* genes confer dementia risk and extend these findings to *COMT*, *BDNF* and *KIBRA*. Our findings may lead to a better understanding of the role these genes play in cognition and cognitive impairment.

Keywords

MCI; aging; hormone therapy; Alzheimer's disease; AD

INTRODUCTION

As our knowledge of the genetic and molecular basis of aging grows, the hope is that both common and divergent pathways for normal brain aging and neurodegeneration may be uncovered. Alzheimer's disease (AD), a progressive, age-related neurodegenerative disorder and the most common cause of dementia, remains one of the leading causes of death in the developed world (Alzheimer's Association 2017). As predictions indicate that 5 million Americans are living with AD and this number is expected to quadruple by 2050 (Heron 2016; Alzheimer's Association 2017), it is increasingly important to find effective preventative and therapeutic interventions. Progress is hindered, at least in part, by the similarities between normal age-associated and disease-related, pathological changes in cognition, especially in the early stages of disease.

Genes are considered good contenders as contributors to variation in a particular phenotype if they are functionally polymorphic and have some relevance to the trait under consideration (Glatt and Freimer 2002). These criteria guide our focus on five genes implicated in memory and other cognition functions, and possibly the neuropathology of AD, at the time of the study inception: (1) apolipoprotein E (*APOE*)/*TOMM40*, (2) sortilin-related receptor (*SORL1* or *SORLA*), (3) catechol-O-methyltransferase (*COMT*), (4) brain derived neurotrophic factor (*BDNF*), and (5) *KIBRA* (*KIAA0869* or *WWC1*) genes. Since, a number of large-scale GWAS have implicated novel AD genes and their variants, currently beyond our scope.

APOE presents a genetic polymorphism with three common alleles: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The $\epsilon 4$ allele, located on chromosome 19q13.2, is the most consistent genetic risk for late onset AD (Corder et al., 1993; Kehoe et al. 1999) and has been implicated in many biochemical AD disturbances, such as neuronal cell death, oxidative stress, synaptic plasticity and cholinergic signaling dysfunction (Cedazo-Minguez and Cowburn, 2001). At least some *APOE- $\epsilon 4$*

cognitive deficits are related to early AD pathology, with subtle differences between *APOE* genotypes in mid-adulthood, prior to the onset of the prodromal period (O'Donoghue et al. 2018). More recently, deep sequencing of the *APOE* region revealed a polymorphic poly-T repeat located in the intron of *TOMM40*, the longer lengths of which have been associated with a higher risk and earlier onset of AD in two independent clinical cohorts (Roses et al. 2010). A meta-analysis of GWASs of 31 cohorts suggests significant associations between general cognitive function and both *TOMM40* and *APOE* (Davies et al 2015).

The neuronal sortilin-related receptor (*SORL1*, also *SORLA* or *LR11*) is located on chromosome 11q23.2-q24.2 and encodes a 250-kD membrane protein expressed in neurons of the central and peripheral nervous system (Andersen et al. 2005) with known involvement in intracellular trafficking between the membrane and intracellular organelles (Annaert and De Strooper, 2002). Under-expression of *SORL1* leads to over-expression of amyloid- β (A β), which in turn is associated with an increased risk of AD (Reitz and Mayeux, 2009). Polymorphisms across *SORL1* have been associated with AD in several cohorts (Rogaeva et al. 2007; Webster et al. 2007)

Catechol-O-methyl Transferase (*COMT*) plays a pivotal role in the modulation of fronto-striatal network activity. A functional single nucleotide polymorphism (SNP) of *COMT* (val158met) located on chromosome 22q11 results in the substitution of valine (val) with methionine (met) at codon 158 of the protein sequence. The met allele produces an enzyme that is unstable and has only half the activity of the val-containing polypeptide Egan et al. 2001). Biologic and genetic findings suggests potential mechanisms for the role of *COMT* in the pathophysiology of dementia (Serretti and Olgiati, 2012); for example, *COMT* inhibitors improve executive memory in normal subjects and block beta-amyloid fibrils *in vitro*. Prior association studies of *COMT* and AD risk, however, have yielded inconsistent findings (Flirski et al., 2011; Perkovic et al 2018).

Brain Derived Neurotrophic Factor (*BDNF*) is a neurotrophin expressed throughout the brain, particularly in the prefrontal cortex and the hippocampus (Pezawas et al., 2004). The *BDNF* gene, composed of five or more exons, is located on chromosome 11p13. A frequent non-conservative SNP in the gene producing a val to met substitution at codon 66 (val66met) affects the activity dependent secretion of *BDNF* (Egan et al., 2003). While *BDNF* is involved in biologic mechanisms thought to underlie learning and memory (Figurov et al., 1996; Lee et al., 2004; Baquet et al., 2004; Gorski et al., 2003), the met allele is associated with worse memory and executive function (Savitz et al., 2006). Literature on whether *BDNF* genetic variations confer AD risk remains conflicting, although a meta-analysis reports a significant association between Val66Met and AD in women, but not in men (Fukumoto et al., 2010).

The first hypothesis free GWAS study in cognition revealed a previously unknown association of the *KIBRA* gene with episodic memory in 351, confirmed in a separate sample of 256, cognitively intact adults (ages 20–81; Papassotiropoulos et al., 2006). Rs17070145, a common T to C substitution within the ninth intron of *KIBRA* located on chromosome 5q34 encoding a neuronal protein was associated with memory (Papassotiropoulos et al., 2006; Schaper et al., 2007). While *KIBRA* seems to influence

episodic memory in later life, it does not seem to increase the MCI risk (Almeida et al., 2008) and the literature suggests a modest role in AD risk (Burgess et al., 2011).

Here we investigate the relationships of variations in the *APOE/TOMM40*, *BDNF*, *COMT*, *SORL1* and *KIBRA* genes with probable dementia within the randomized clinical trials of hormone therapy (HT) of the Women's Health Initiative Memory Study (WHIMS; Shumaker et al. 1998).

METHODS

Participants.

The current study is based on secondary analysis of existing data collected through the WHIMS (Shumaker et al. 1998) nested within the randomized HT clinical trials of the Women's Health Initiative (WHI), initiated in 1992. Blood specimens for DNA were collected in the WHI. Specimens selected for genotyping in the present study included all of the mild cognitive impairment (MCI) and probable dementia (PD) cases and a sample of unimpaired controls that were similar with respect to age from WHIMS. The phenotype and age were defined based on the last observation on or before a January 2014 data cutoff.

The primary aim of the WHI HT trials was to assess whether conjugated equine estrogen (CEE; 0.625 mg/day) alone or in combination with medroxyprogesterone acetate (CEE +MPA; 2.5mg/day) would reduce the risk of coronary heart disease; other cardiovascular diseases, cancers and hip and other fractures were secondary outcomes. Participants were randomly assigned with equal probability to therapy (CEE if prior hysterectomy; CEE+MPA if no prior hysterectomy) or matching placebos. The WHIMS added the additional outcomes of global cognitive function and cognitive impairment (WHIMS; 1998). The WHIMS clinical trial design, eligibility criteria, and recruitment procedures have been published (Shumaker et al. 1998). Race-ethnicity was collected by self-administered questionnaire at WHI baseline.

Ascertainment of Probable Dementia (PD) and MCI.

A detailed description of the WHIMS four-phase protocol for detecting PD and MCI has been published (Shumaker et al. 1998; Coker et al., 2010). Briefly, participants were screened annually with the Modified Mini Mental State exam (Teng, 1987) during in-clinic visits at 39 participating WHI sites in the U.S. For participants who scored below a pre-set score, the CERAD neurocognitive test battery was administered and a complete neuropsychiatric evaluation was conducted that optionally included a brain CT scan (without contrast) and standard blood assay panel. In addition, a friend or family member familiar with the participant's functional status was interviewed. All assessments were submitted to a central adjudication panel at the WHIMS Coordinating Center at Wake Forest University School of Medicine for classification as having MCI, PD, or no cognitive impairment based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (APA 1994). Clinic visits were terminated when WHI entered an extension study in 2008. WHIMS transitioned to a telephone-administered cognitive assessment and proxy interview with the

Dementia Questionnaire (Kawas et al). The neurocognitive battery was independently validated (Rapp et al., 2012) and centralized adjudication remained the same.

Gene and SNP Selection.

We analyzed SNPs in five genes chosen based on previously shown associations with either different aspects of cognition or AD pathogenesis. Haplotype tagging SNPs (tSNPs) were selected from the International Haplotype Map project (www.hapmap.org) using a bulk download of tag SNP data. To ensure robust haplotype tagging within the cohort, we selected SNPs based upon a pairwise r^2 of greater than 0.8 and a minor allele frequency of greater than 0.2, all based on CEPH Caucasian data typed as a part of the HapMap project. Five regions were studied; all exons of *BDNF*, *KIBRA*, *APOE* and *COMT* plus at least 20kb of 5' and 3' flanking sequence were selected for tSNP analysis producing a list of 75 SNPs required to tag the genes. The region on chromosome 19 was defined based on the *APOE* gene at the time of study design, however, *TOMM40*, located next to the *APOE* gene in a region of strong linkage disequilibrium (LD) has been identified since by deep sequencing (Roses et al., 2009). The SNPs that currently are considered to fall under *TOMM40* include: rs157580, rs157582, rs405697, and rs8106922. Although a majority of the SNPs were selected from the International Haplotype Map project (www.hapmap.org) to tag the genes; a few were missense SNPs with previously reported associations with related phenotypes (Supplementary Materials – Table 1). These include the SNPs that make up the common $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ *APOE* haplotypes (rs7412 and rs429358) and other well-established non-synonymous alterations in the five gene regions to produce a total of 96 SNPs to be assayed. The two variants that make up the *APOE* $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ haplotypes were included regardless of predicted quality control issues on Illumina custom chip and failed QC as expected.

Since, WHI GWAS was performed and genotype results from two SNPs, rs429358 and rs7412, based on imputation and harmonization of genetic data across WHI, were used to define *APOE* epsilon 2/3/4 genotypes for description in our study population and adjustment in regression models. The quality of this imputation was very high with $R^2 = 0.98$ for each SNP.

DNA and Genotyping.

DNA was extracted by the Specimen Processing Laboratory at the Fred Hutchinson Cancer Research Center using specimens collected at the time of WHI enrollment. All assays were performed in the Laboratory of Neurogenetics at the National Institute on Aging, using a custom Illumina GoldenGate assay. Custom assay design was initiated with Illumina; this process usually requires 2 iterations based on SNP genotyping likelihood scores generated for each chosen SNP. In our experience 80% of the initially selected SNPs are approved; the remaining 20% of SNPs are each replaced by one or more tagging SNPs that capture the necessary haplotype information and submitted for approval. This process occurs twice. The final genotyping panel included 96 SNPs. We used between 10–25 ng of DNA for each reaction.

Each GoldenGate assay required 250ng of genomic DNA and each assay was run in a 96-well plate format with each plate consisting of 92 study samples and 4 replicate samples

from CEPH families 1347 and 1331 to provide quality assurance of plate orientation and genotype reproducibility. Genotype calling was performed using the algorithms within BeadStudio (Illumina Inc, San Diego CA), and genotype cluster files were generated using a minimum of 1,000 individuals.

Genotyping Quality Control.

Genotyping was done on 96 SNPs and 3,005 samples. 2.3% (69) additional samples were genotyped as blind duplicates. 13 SNPs were flagged as having a call rate <0.90 : 5 SNPs had no calls (rs1862355, rs7412, rs4633, rs6267, rs165774), 5 additional SNPs had a call rate <0.85 (rs10074534, rs6887919, rs6555812, rs12285364, rs429358), and 3 SNPs had a call rate of 0.89 (rs2287703, rs11738934, rs668387). Heterozygote rates were flagged when >0.90 or <0.10 ; 144 individuals were flagged as having a call rate <0.80 : 17 had no calls, an additional 21 had call rate <0.70 , and 106 had a call rate from 0.70 to 0.80. Analysis of blind duplicates yielded 16 blind duplicate pairs with a concordance rate <0.95 , of which 13 were <0.82 . The overall concordance rate among blind duplicate samples was 91.7% (range 67.3–100%) among the 91 SNPs with calls. For each SNP association with $p = 0.05$, the control group's genotyping data was examined for a strong deviation ($p < 0.0001$) from Hardy-Weinberg equilibrium.

Statistical Analyses.

Two phenotypes were defined for analyses: 1) probable dementia (PD) versus all others; and 2) the sensitivity analyses excluding MCI. Initial analyses were performed in non-Hispanic whites only. This was followed up by sensitivity analyses excluding MCI, and inclusion of APOE or APOE+COMT as covariates. HT assignment was defined as CEE-alone, CEE-alone placebo, CEE+MPA, or CEE+MPA placebo. To evaluate the associations between phenotypes and single-SNP genotypes, multiple logistic regression analysis was performed, controlling for age and clinical trial arm (reference: CEE+MPA placebo). Associations were tested using a chi-squared statistic under an additive genetic model and expressed as adjusted odds ratios with corresponding 95% confidence intervals. For each regression model, all participants with complete data on phenotype and covariates, and with genotype data meeting quality control, were included. No covariate interaction terms were added. Uncorrected p values were reported together with a Bonferroni-corrected threshold to account for number of SNPs; no correction was calculated for the two related phenotypes. All analyses were conducted using S+ statistical software (TIBCO Spotfire S+ Version 8.2, TIBCO Software Inc., Palo Alto, CA).

RESULTS

Genotyping was done on 3005 individuals, including 69 blind duplicate samples. Genotyping quality control criteria were met on a total of 2857 individuals. This final sample was enriched, by design, for cases of cognitive impairment, with 19% ($N=552$) MCI ($N=165$) or PD ($N=387$); the remaining 81% ($N=2305$) had neither MCI nor dementia. Demographic information is presented in Table 1.

A summary of associations between SNPs that passed quality control in *APOE/TOMM40*, *SORL1*, *COMT*, *BDNF*, and *KIBRA* and PD (including and excluding MCI cases) is presented in Table 2. One SNP in the *APOE/TOMM40* (rs157582) gene was significantly associated with the PD phenotype, after correcting for multiple comparisons ($p = 0.0007$). An additional 12 SNPs (Figure 1) were associated with the PD phenotype at $p = 0.05$ (*APOE*: rs405509, rs439401; *TOMM40*: rs8106922; and *KIBRA*: rs4320284, rs11740112, rs10040267, rs13171394, rs6555802, rs2241368, rs244904, rs6555805 and rs10475878).

The results were similar when sensitivity analysis was performed excluding MCI; the *APOE/TOMM40* (rs157582) remained significant after correcting for multiple comparisons. An additional 7 SNPs were found to be associated with the PD phenotype at $p = 0.05$ (*APOE/TOMM40*: rs8106922; *COMT*: rs737865; *BDNF*: rs1491850; and *KIBRA*: rs4320284, rs2241368, and rs244904).

The results for the entire sample compared to non-Hispanic whites only were similar (data not shown). When we repeated the analysis adding *APOE* as a covariate, as there is a chance that signal in *APOE/TOMM40* may be in linkage disequilibrium with the two *APOE* ϵ -4 allele variants defining epsilon 2/3/4 genotypes (and alternately adding both *APOE* and *COMT* rs4680 to test for synergistic effects reported in the literature), the results were unchanged and no new SNPs were significant. Inferences were nearly identical for the sensitivity analysis (excluding MCI).

DISCUSSION

Our results in older women provide additional support for a role of *APOE/TOMM40* in dementia risk (Kehoe et al. 1999) and provide a validation for our general approach to investigation of GWAS signals related to cognitive impairment. The *APOE*- ϵ 4 allele is already known to be associated with cognition-related phenotypes in WHIMS (Cacciattolo et al. 2017; Goveas et al. 2016; Mozhui et al. 2017). Our results in older women are in line with and provide additional support for a role of *APOE/TOMM40* in dementia risk (Kehoe et al. 1999). A comprehensive search for AD susceptibility loci in the *APOE* region suggests that *APOE* alleles could essentially account for all the inherited AD risk and that other variants, including poly-T-track in *TOMM40*, do not seem to pose independent risks (Jun et al., 2012). In our sample, the results remained largely unchanged when *APOE* SNPs that define epsilon 2/3/4 genotypes were added to the analyses as covariates.

Although several studies have confirmed *SORL1* as a non-*APOE* genetic risk locus (Beecham et al., 2014; Chouraki & Seshadri, 2014; Jin et al., 2013; Karch and Goate, 2015), we did not observe significant associations of *SORL1* with cognitive impairment in our female sample. Our results suggest associations of *COMT* with PD. We did find associations for the loci in both *COMT* and *KIBRA* genes, although they did not survive the stringent Bonferroni correction. Our findings remain similar when sensitivity analyses were performed excluding MCI cases, with an additional significant signal in one of the *BDNF* SNPs (rs1491850), which also did not survive Bonferroni adjustment.

There is a general lack of understanding of the relationship between *COMT* and AD (but see Lin et al., 2012; Pereira et al., 2012), although there is a suggestion of a synergistic effect between *COMT*'s GG (Val/Val) and APOE ϵ -4 allele in increasing risk for MCI and AD that may be more pronounced in males (Lanni et al., 2012). Some have suggested that a combination of genetic polymorphisms involved in normal cognitive aging (such as *COMT*) and AD (such as *APOE*) may contribute to genetic heterogeneity in cognitive impairment (Dixon et al., 2014). In our sample, the results remained unchanged when both *APOE* and *COMT rs4680* were added to the analyses as covariates. Overall, we report an association for loci in the *KIBRA* gene with cognitive impairment, in agreement with the literature suggesting that *KIBRA* is modestly associated with predisposition for late-onset AD (Corneveaux et al., 2010; Burgess et al., 2011). Current literature also highlights the multifactorial complexity of *KIBRA*, given the evidence that the T-allele associations seem to be age-dependent, with an increased risk reported for very-late-onset (after age 86) (Rodriguez-Rodriguez et al., 2009). Nonetheless, our observations may provide novel insights into genetic risks for pathological age-related cognitive impairment, specifically in females.

A potential limitation of our study is that it is not a GWAS. Although GWAS can characterize a much larger number of SNPs, it does not obviate the need for the candidate gene approach which can aid in further exploration of the biological and clinical interactions related to genetic risk and serve to validate GWAS findings, which are not hypothesis driven. We fully acknowledge that most of the SNPs associated in our study likely are not causative. This study includes a SNP selection based on a Caucasian reference, given that most of the sample was predominantly non-Hispanic white. Also, the control group of non-demented individuals was similar in age but not age-matched, which could affect the results. Given the adjustment for age at the data analysis stage, we believe the end effect to be similar. The limitations, however, should not undermine many unique aspects of the study, including the large number of extensively screened and characterized community-dwelling, older women with detailed prospective follow-up and relatively short intervals between assessments.

CONCLUSION

A number of GWAS investigations of AD have been conducted since the inception of this study and novel genes and their variants have been implicated in the pathogenesis of AD, which are currently beyond the scope of the current study. Follow-up studies are needed to address the newly identified risk genes. There is also a need for endophenotype strategies to further explore phenotypes related to dementia and age-related cognitive impairment. Candidate gene approaches may not only aid in the discovery of novel pathways involved in structural and functional brain aging, but also lead to better understanding of individual variations in brain structure and function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

- A number of large-scale GWAS investigations of AD have been conducted and novel genes and their variants have been implicated in the pathogenesis of AD.
- Candidate gene approaches may aid in the discovery of novel pathways involved in structural and functional brain aging.
- Our findings may lead to a better understanding of the role these candidate genes play in cognition and cognitive impairment.

Figure 1.
Associations between SNPs in *APOE/TOMM40*, *BDNF*, *COMT*, *SORL1*, and *KIBRA* and PD phenotype.

Table 1.Characteristics of women by cognitive status [mean $\pm$ SD or count (column percent)]

Characteristic	Control Group (N = 2305)	MCI Cases (N = 165)	PD Cases (N = 387)	Overall P Value*
Age (years) at last cognitive assessment, mean $\pm$ SD	81.4 $\pm$ 5.1	81.7 $\pm$ 5.7	81.7 $\pm$ 4.9	0.45
Education, n (%)				0.15
High school or less	660 (28.7)	57 (34.6)	128 (33.2)	
Some college	943 (41.0)	66 (40.0)	140 (36.3)	
College graduate	700 (30.4)	42 (25.5)	118 (30.6)	
Race-ethnicity n (%)				<0.001
African American	164 (7.1)	25 (15.2)	42 (10.9)	
Hispanic	41 (1.8)	8 (4.9)	11 (2.8)	
Non-Hispanic white	2033 (88.2)	128 (77.6)	323 (83.5)	
Other/unknown	67 (2.9)	4 (2.4)	11 (2.8)	
WHI HT assignment, n (%)				0.054
Hormone therapy	1134 (49.2)	75 (45.5)	213 (55.0)	
Placebo	1171 (50.8)	90 (54.6)	174 (45.0)	
BMI (kg/m ²), mean $\pm$ SD	28.7 $\pm$ 5.8	28.4 $\pm$ 5.8	27.8 $\pm$ 5.5	0.023
Diabetes, n (%)	179 (7.8)	16 (9.8)	43 (11.1)	0.068
Hypertension, n (%)	1113 (48.3)	96 (58.2)	220 (56.9)	<0.001
Stroke n (%)	29 (1.3)	8 (4.9)	10 (2.6)	<0.001
MI, n (%)	72 (3.1)	7 (4.2)	20 (5.2)	0.11
Coronary revascularization, n (%)	60 (2.6)	3 (1.9)	18 (4.8)	0.055
Smoking history, n (%)				0.74
Current	130 (5.7)	11 (6.8)	21 (5.6)	
Former	892 (39.1)	61 (37.4)	135 (35.8)	
Never	1258 (55.2)	91 (55.8)	221 (58.6)	
Alcohol intake, n (%)				0.0036
Never	286 (12.5)	24 (14.6)	59 (15.5)	
Past	438 (19.1)	32 (19.4)	92 (24.2)	
< 1 drink/week	745 (32.5)	71 (43.0)	112 (29.4)	
1 to <7 drinks/week	550 (24.0)	23 (13.9)	79 (20.7)	
7 drinks/week	272 (11.9)	15 (9.1)	39 (10.2)	
APOE genotype (imputed), n (%) [†]				<0.001 [‡]
e2/e2	11 (0.6)	0 (0.0)	1 (0.3)	
e2/e3	244 (12.9)	14 (12.4)	26 (8.7)	
e2/e4	50 (2.7)	2 (1.8)	7 (2.4)	
e3/e3	1201 (63.5)	61 (54.0)	132 (44.3)	
e3/e4	354 (18.7)	32 (28.3)	114 (38.3)	

Characteristic	Control Group (N = 2305)	MCI Cases (N = 165)	PD Cases (N = 387)	Overall P Value *
e4/e4	30 (1.6)	4 (3.5)	18 (6.0)	

MCI = Mild Cognitive Impairment; PD = probable dementia; SD = standard deviation; HT = hormone therapy; BMI = body mass index; MI = myocardial infarction; APOE = Apolipoprotein E

* P values were calculated for comparison of characteristics across the three cognitive impairment groups based on 1) means and Analysis of Variance (ANOVA), or 2) distribution of counts and chi-square for data cross-classified by nominal variables into contingency tables (r rows x c columns)

[†]Non-Hispanic whites only

[‡]P value for comparison between high risk as defined by (e3/e4 or e4/e4) and low risk (e2/e2, e2/e3, or e3/e3)

Table 2.

Adjusted SNP associations with the PD phenotype in non-Hispanic whites (with and without MCI); p 0.05 only.

	Gene Region	SNP	Alleles [*]	Allele Frequency [†]	Odds Ratio [‡]	95% CI [‡]	P Value [‡]
PD	KIBRA	rs6555802	A/C	0.35	1.19	(1.02, 1.39)	2.8×10^{-2}
		rs11740112	A/G	0.57	0.850	(0.731, 0.988)	3.4×10^{-2}
		rs10475878	A/G	0.29	1.22	(1.04, 1.43)	1.4×10^{-2}
		rs6555805	C/T	0.75	1.19	(1.00, 1.41)	5.0×10^{-2}
		rs13171394	A/G	0.57	1.19	(1.02, 1.38)	2.7×10^{-2}
		rs4320284	G/T	0.42	1.25	(1.07, 1.45)	4.0×10^{-3}
		rs2241368	C/T	0.24	1.23	(1.04, 1.46)	1.5×10^{-2}
		rs10040267	A/G	0.41	0.843	(0.720, 0.988)	3.5×10^{-2}
		rs244904	A/G	0.48	0.827	(0.710, 0.962)	1.4×10^{-2}
	TOMM40	rs157582	A/G	0.20	1.64	(1.38, 1.94)	2.4×10^{-8}
		rs8106922	A/G	0.59	1.31	(1.12, 1.52)	7.8×10^{-4}
	APOE	rs405509	A/C	0.48	1.28	(1.10, 1.49)	1.6×10^{-3}
MCI excluded		rs439401	C/T	0.63	1.21	(1.03, 1.42)	2.1×10^{-2}
	KIBRA	rs4320284	G/T	0.42	1.21	(1.02, 1.44)	2.8×10^{-2}
		rs2241368	C/T	0.24	1.35	(1.12, 1.64)	1.9×10^{-3}
		rs244904	A/G	0.48	0.809	(0.679, 0.963)	1.7×10^{-2}
	BDNF	rs1491850	C/T	0.44	0.810	(0.681, 0.962)	1.6×10^{-2}
	TOMM40	rs157582	A/G	0.20	1.80	(1.48, 2.18)	2.1×10^{-9}
		rs8106922	A/G	0.59	1.43	(1.20, 1.72)	9.0×10^{-5}
	APOE	rs405509	A/C	0.48	1.41	(1.19, 1.68)	1.1×10^{-4}
	COMT	rs737865	C/T	0.27	0.762	(0.622, 0.933)	8.7×10^{-3}

CI = confidence interval; HT = hormone therapy; MCI = Mild Cognitive Impairment; PD = probable dementia

^{*} Alleles are ordered as effect allele/ other allele. The effect allele is the first of the two alleles after alphabetizing. The direction of odds ratio reflects the "effect" of this allele.

[†] Overall observed frequency for the effect allele

[‡] Odds ratio measures of SNP association, 95% CI, and p value results are based on multiple logistic regression models with covariates age at last observation, WHI HT assignment status (CEE-alone, CEE-alone placebo, CEE+MPA, and CEE+MPA placebo), and one SNP in each model; the Bonferroni-corrected threshold for SNP association p values is 7×10^{-4} .

*** The results with inclusion of all race-ethnic groups were similar (results not shown).