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Citation for published version:

Digital Object Identifier (DOI):
10.3233/JAD-2011-110824

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Journal of Alzheimer's Disease

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The Role of Variation at AβPP, PSEN1, PSEN2, and MAPT in Late Onset Alzheimer’s Disease

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Accepted 5 September 2011
Abstract. Rare mutations in \(A\beta PP\), \(PSEN1\), and \(PSEN2\) cause uncommon early onset forms of Alzheimer’s disease (AD), and common variants in \(MAPT\) are associated with risk of other neurodegenerative disorders. We sought to establish whether common genetic variation in these genes confer risk to the common form of AD which occurs later in life (>65 years). We therefore tested single-nucleotide polymorphisms at these loci for association with late-onset AD (LOAD) in a large case-control sample consisting of 3,940 cases and 13,373 controls. Single-marker analysis did not identify any variants that reached genome-wide significance, a result which is supported by other recent genome-wide association studies. However, we did observe a significant association at the \(MAPT\) locus using a gene-wide approach \((p = 0.009)\). We also observed suggestive association between AD and the marker rs9468, which defines the H1 haplotype, an extended haplotype that spans the \(MAPT\) gene and has previously been implicated in other neurodegenerative disorders including Parkinson’s disease, progressive supranuclear palsy, and corticobasal degeneration. In summary common variants at \(A\beta PP\), \(PSEN1\), and \(PSEN2\) and \(MAPT\) are unlikely to make strong contributions to susceptibility for LOAD. However, the gene-wide effect observed at \(MAPT\) indicates a possible contribution to disease risk which requires further study.

Keywords: Alzheimer’s disease, amyloid-\(\beta\) protein precursor, genetics, human, \(MAPT\) protein, \(PSEN1\) protein, \(PSEN2\) protein

INTRODUCTION

The neuropathological hallmarks of late-onset Alzheimer’s disease (LOAD) are assumed to provide major clues to pathogenesis. These include extracellular plaques, which are predominantly made up of insoluble amyloid-\(\beta\) protein, and neurofibrillary tangles (NFTs), intracellular accumulations of paired helical filaments, which are comprised mainly of hyperphosphorylated forms of the microtubule associated protein, tau [1]. Genes involved in the amyloid pathway and the tau gene, \(MAPT\), have therefore long been considered as putative candidates for involvement in LOAD susceptibility.

Amyloid-\(\beta\) is formed from the cleavage of amyloid-\(\beta\) protein precursor (\(A\beta PP\)) by \(\beta\) - and \(\gamma\)-secretases. Mutations within \(A\beta PP\), plus presenilin 1 (\(PSEN1\)) and presenilin 2 (\(PSEN2\)), which encode part of the \(\gamma\)-secretase complex, can cause the autosomal dominant, predominantly early-onset forms of Alzheimer’s disease (EOAD) (Alzheimer Disease & Frontotemporal Dementia Mutation Database; http://www.molgen.ua.ac.be/admutations). These mutations increase cleavage of \(A\beta PP\) by \(\beta\)-secretase [4]. In addition, 185 \(PSEN1\) and 13 \(PSEN2\) pathogenic mutations have been observed in EOAD patients which increase \(\gamma\)-secretase cleavage of \(A\beta PP\) [4].

Genetic variation at the \(MAPT\) locus has been convincingly associated with an increased risk of the sporadic tauopathies progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [5]. The associations reported include several polymorphisms that span the \(MAPT\) locus and which are in high linkage disequilibrium (LD). These variants form two extended haplotypes H1 and H2, which have been shown to capture the common haplotypic variation across the gene. H1, the more common haplotype, consists of multiple sub-haplotypes. One of these, H1c has been found to capture the observed association between H1 and both PSP and CBD more effectively [6]. H2 is a less common, single, un-recombinating haplotype.

In addition a recent genome-wide association study (GWAS) identified association between \(MAPT\) and Parkinson’s disease (PD) [7], where three single nucleotide polymorphisms (SNPs) at the locus surpassed genome-wide significance. Simón-Sánchez and colleagues observed that the risk alleles at each SNP are in LD with the H1 haplotype, thus the findings are consistent with those from other neurodegenerative disorders.

While \(A\beta PP\), \(PSEN1\), and \(PSEN2\) are established contributors to rare forms of AD, as is \(MAPT\) to other neurodegenerative disorders including PD, PSP, and CBD, the question remains whether these genes are implicated in the common form of AD which occurs later in life (>65 years). Relatively recent studies testing these genes for association with LOAD have produced both positive [8–17] and negative results [18–24]. This includes analyses of the \(MAPT\) H1 and H1c haplotypes [8, 16, 17, 19, 21, 24]. However, these studies have been underpowered to detect common risk alleles of the effect sizes typically seen in common disorders. We therefore tested variants at the \(A\beta PP\), \(PSEN1\), \(PSEN2\), and \(MAPT\) loci for association with LOAD in an extended version of the Genetic and Environmental Risk in AD Consortium 1 (GERAD1)
case-control dataset, previously published by Harold and colleagues [25], consisting of 3,940 AD cases and 13,373 controls.

MATERIALS AND METHODS

SNPs within 20 kb of AβPP, PSEN1, PSEN2, and MAPT were analyzed for single-marker and gene-wide association to LOAD within the GERAD1 GWAS dataset (directly genotyped and imputed). Meta-analysis between GERAD1 and two publically available datasets was also performed for markers selected from the GERAD1 single-marker analysis. The details of all analyses are given below.

GERAD1 samples

The total sample analyzed in this study was comprised of 4,957 AD cases and 9,682 controls previously described in Harold and colleagues [25] plus an additional 5,529 controls. The sample included 4,113 cases and 1,602 elderly screened controls recruited by the Medical Research Council (MRC) Genetic Resource for AD (Cardiff University; Institute of Psychiatry, London; Cambridge University; Trinity College Dublin); the Alzheimer’s Research UK (ARUK) Collaboration (University of Nottingham; University of Manchester; University of Southampton; University of Bristol; Queen’s University Belfast; the Oxford Project to Investigate Memory and Ageing (OPTIMA), Oxford University); Washington University, St Louis, United States; MRC PRION Unit, University College London; London and the South East Region AD project (LASER-AD), University College London; Competence Network of Dementia (CND) and Department of Psychiatry, University of Bonn, Germany and the National Institute of Mental Health (NIMH) AD Genetics Initiative. In addition, 844 AD cases and 1,255 elderly screened controls were ascertained by the Mayo Clinic, Jacksonville, Florida; Mayo Clinic, Rochester, Minnesota; and the Mayo Brain Bank. All AD cases met criteria for either probable (NINCDS-ADRDA [26], DSM-IV) or definite (CERAD [27]) AD.

A total of 6,825 population controls were also included. These were drawn from large existing cohorts with available GWAS data, including the 1958 British Birth Cohort (1958BC) [http://www.b58cgene.ssgul.ac.uk/], the NINDS funded neurogenetics collection at Coriell Cell Repositories (Coriell) [http://ccc.coriell.org/], the KORA F4 Study [28], the Heinz Nixdorf Recall Study [29, 30], and amyotrophic lateral sclerosis controls [31]. Additional controls, not previously analyzed, included 1,456 elderly screened controls from the Lothian birth cohort, University of Edinburgh (http://www.lothianbirthcohort.ed.ac.uk/), plus 4,069 population controls from either the 1958BC (n = 1,596) or the National Blood Service [32] (n = 2,477). Additional genotypes were also made available for 1,068 1958BC controls previously included in the Harold and colleagues publications [25]. All individuals included in the analysis have provided informed consent to take part in genetic association studies and we obtained approval to perform a GWAS including 19,000 participants (MREC 04/09/030, Amendment 2 and 4, approved 27 July 2007).

Genome-wide analysis

The GWAS was performed as described by Harold and colleagues [25]. 5,715 samples were genotyped using the Illumina 610-quad chip; genotypes for the remaining subjects (n = 14,453) were made available either from population control datasets or through collaboration and were genotyped on the Illumina HumanHap 1.2M, 610, 550 or 300 BeadChips. Prior to association analysis, all samples and genotypes underwent stringent quality control (QC), which resulted in the elimination of 58,841 autosomal SNPs and 2,855 subjects. Thus, in Stage 1, we tested 528,747 autosomal SNPs for association in up to 17,313 subjects (3,940 AD cases and 13,373 controls, of whom 3,534 were elderly controls who were screened for cognitive decline or neuropathological signs of AD). The genomic control inflation factor \( \lambda \) [33] was 1.060 (\( \lambda_{1000} = 1.010 \)), suggesting little evidence for residual stratification. SNPs were tested for association with AD using logistic regression, assuming an additive model. Specific details of the logistic regression analysis and the covariates included are given elsewhere [25]. Genome-wide significance was defined as \( p \leq 5 \times 10^{-8} \) as suggested by Pe’er and colleagues [34].

GERAD1 imputation analysis

AD summary statistics were based on 3,940 cases and 13,373 controls from UK, USA, and Germany typed with the Illumina Chips 1.2M, 610, 550, and 300. Genotypes at the 201,228 SNPs common to each of the 4 chips were used as input for imputation. The imputation was performed using IMPUTE2 software [35] with two phased reference panels, the
1000 genomes (http://www.1000genomes.org) August 2009 release and Hapmap3, r. II. NCBI build 36 positions were used for all markers in this study. QC filters applied included a minor allele frequency (MAF) \( \geq 0.01 \) and an INFO score (representing imputation quality) \( \geq 0.8 \). After QC 4,685,506 markers remained. The AD case/control data were then analyzed using logistic regression including covariates accounting for country of data collection and the five principal components obtained with EIGENSTRAT [36] software based on individual genotypes for the GERAD1 study participants. The genomic control inflation factor \( \lambda \) for the imputed dataset was 1.11.

**Gene-wide analysis**

All SNPs located within A\(\beta\)PP, PSEN1, PSEN2, and MAPT that were either directly genotyped within the GERAD1 sample or imputed were identified. SNPs were assigned to a gene if they were located within \( \pm 20 \) kb of any transcript corresponding to that gene. \( p \)-values were calculated under an additive disease model and adjusted for genomic control (geno- typed \( \lambda = 1.06 \), imputed \( \lambda = 1.11 \)).

Gene-wide analysis was performed based on the Simes [37] method for conducting multiple tests of significance. The Simes method is less conservative than the Bonferroni method when the tests are not independent, and is thus better suited for analyzing multiple SNPs from the same gene (where the individual association tests are likely to be correlated due to linkage disequilibrium). If the \( p \)-values for the individual tests are ordered such that \( p(1) \leq p(2) \leq \ldots \leq p(n) \) then the null hypothesis of no association in the gene is rejected at significance level \( \alpha \) if \( p(j) \leq \alpha/n \) for any \( j = 1, \ldots, n \). The corrected \( p \)-value for the joint significance test of all SNPs in a gene using this method (denoted “Simes \( p \)-value”) is given by the minimum of \( p(j) \times n/j \).

**Meta-analysis with additional datasets**

Meta-analysis was performed on GERAD1 and two publically available GWAS datasets from the Translational Genomics (TGEN) Research Institute and the Alzheimer’s Disease Neuroimaging Initiative (ADNI). The TGEN sample, previously reported by Reiman and colleagues [23], is comprised of 861 cases and 550 controls. Imputation of this data set was performed using MACH software [38] with the August 2010 1000 genomes reference panel. SNPs were tested for association using logistic regression assuming an additive model. Sample population (USA or Netherlands) was included as a covariate.

The ADNI (http://www.loni.ucla.edu/ADNI) [39] GWAS data was subjected to QC-filtering prior to association analysis. This included retaining individuals with missing genotype rates \( < 0.01 \), with mean autosomal heterozygosity between 0.32 and 0.34, and with mean X-chromosome heterozygosity either \( < 0.02 \) for males, or between 0.25 and 0.40 for females. Following QC, 151 AD cases and 177 controls were analyzed in this study. Imputation was performed using IMPUTE2 software [35] and the August 2010 1000 genome data release. SNPs were tested for association with AD using logistic regression assuming an additive model.

Meta-analysis was performed by inverse variance weights (IVW) meta-analysis using summary data (i.e., odds ratios (OR) and standard errors). The standard error statistic included in the inverse variance weights meta-analysis accounts for variation in sample size between studies. The Cochran’s Q-test and the I\(^2\) heterogeneity index were used to assess heterogeneity between studies. Significant evidence of heterogeneity was determined by a Cochran’s Q-statistic \( p < 0.1 \) or \( I^2 > 50 \). In these instances a random effects meta-analysis was performed; alternatively, meta-analysis with a fixed effect model was used.

**RESULTS**

**Analysis of A\(\beta\)PP, PSEN1, PSEN2, and MAPT**

A summary of the results is given in Table 1. The most significant \( p \)-values for both genotyped and imputed SNPs. Single-marker analysis did not identify any variants within these four genes that reached genome-wide significance (\( p < 5 \times 10^{-8} \)) in either analysis. At the MAPT locus, rs11656151 shows the greatest evidence for association with AD (imputed \( p = 8.8 \times 10^{-8} \)). rs11656151 is located within intron 8 of MAPT isoform I-467 (NM_016835). The most significant SNP at the PSEN1 locus is a 1000 genomes marker at chr14:72745579 (NCBI36), imputed \( p = 1.9 \times 10^{-8} \) which is located within intron 8 of PSEN1 isoform 1 (NM_000021) and lies within a 4555 bp of a deletion which has been identified in two AD families. This deletion spans exon 9 of PSEN1 which results in an in-frame skipping of exon 9 and an amino acid change at the splice junction of exon 8 and 10 [40, 41]. At the A\(\beta\)PP locus, rs381743 shows the greatest evidence for association with AD (imputed \( p = 0.002 \)). It is located 15 kb 5’ to the A\(\beta\)PP gene. The most significant SNP within PSEN2 shows a borderline significant association with AD (rs12405469 imputed \( p = 0.041 \)). This SNP is located 7 kb 3’ to PSEN2.

**A. Gerrish et al. / Variation at A\(\beta\)PP, PSEN1, PSEN2, and MAPT in LOAD**
## Table 1
Analysis of AβPP, PSEN1, PSEN2, and MAPT in the GERAD1 dataset

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP ID</th>
<th>p Value</th>
<th>Simes p Value</th>
<th>Gene</th>
<th>SNP ID</th>
<th>p Value</th>
<th>Simes p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AβPP</td>
<td>rs2830088</td>
<td>0.04</td>
<td>0.362</td>
<td></td>
<td>rs381743</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>PSEN1</td>
<td>rs362350</td>
<td>0.90</td>
<td>0.240</td>
<td></td>
<td>chr14-72745579</td>
<td>0.80</td>
<td>1.37 × 10^-4</td>
</tr>
<tr>
<td>PSEN2</td>
<td>rs207349</td>
<td>0.96</td>
<td>0.611</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAPT</td>
<td>rs079125</td>
<td>1.10</td>
<td>0.034</td>
<td></td>
<td>rs1656151</td>
<td>0.84</td>
<td>0.009</td>
</tr>
</tbody>
</table>

The most significant results are shown for SNPs directly genotyped and those imputed in the dataset. Odds Ratios (OR) are based on the minor allele. Gene-wide analysis of AβPP, PSEN1, PSEN2, and MAPT in the GERAD1 dataset using the Simes method is also given.

## Table 2
Single-marker and meta-analysis results for the most significant SNPs within AβPP, PSEN1, PSEN2, and MAPT, plus the H1 haplotype tag SNP rs9468, within three independent LOAD GWAS samples (GERAD1, TGEN, and ADNI).

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP ID</th>
<th>GERAD1</th>
<th>TGEN</th>
<th>ADNI</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AβPP</td>
<td>rs381743</td>
<td>0.87</td>
<td>0.91</td>
<td>0.002</td>
<td>0.96</td>
</tr>
<tr>
<td>PSEN1</td>
<td>chr14-72745579</td>
<td>0.80</td>
<td>1.36</td>
<td>1.9 × 10^-4</td>
<td>0.71</td>
</tr>
<tr>
<td>PSEN2</td>
<td>rs12405469</td>
<td>0.81</td>
<td>0.94</td>
<td>0.041</td>
<td>0.99</td>
</tr>
<tr>
<td>MAPT</td>
<td>rs1656151</td>
<td>0.84</td>
<td>1.13</td>
<td>8.8 × 10^-3</td>
<td>0.89</td>
</tr>
<tr>
<td>MAPT</td>
<td>rs9468</td>
<td>0.87</td>
<td>0.89</td>
<td>7.8 × 10^-4</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Inverse variance weights (IVW) meta p-values were calculated from summary statistics. Odds ratios (OR) refer to the minor allele. Meta p-values given are based on a fixed effect model unless Q statistic p < 0.1 or I^2 > 50. In these instances a random effects model was used. N/A = Not available.
We attempted to impute these variants in two publicly available GWAS datasets [23, 39]. These results as well as the meta-analysis of all the datasets are given in Table 2. Meta-analysis of these variants did not produce any genome-wide significant variants. However, we observed a slight increase in significance of the association between the MAPT polymorphism rs11656151 \( (p = 4.7 \times 10^{-3}) \) and AD. While this SNP was not significant in the TGEN and ADNI datasets, both showed the same direction of effect as GERAD1 dataset for this variant.

In addition to single-marker analysis, we performed gene-wide analysis using all SNPs located within 20kbp of AβPP, PSEN1, PSEN2, and MAPT (Table 1). Gene-wide analysis may offer a number of possible advantages over single locus tests [42]. For example, if there is more than one independent association signal within a gene or set of markers, combining these into a single statistic may offer enhanced power over single SNP analysis [43]. We detected no significant association between AβPP, PSEN1, or PSEN2 and AD using this approach. However, MAPT shows significant gene-wide association (Simes \( p = 0.009 \)) which survives multiple testing correction for the four genes analyzed.

Further analysis of MAPT association

Previous studies of MAPT have reported association between the H1 haplotype and AD [16, 17] as well as other neurodegenerative disorders [6]. The marker rs9468 defines H1/H2 status [19]. In our imputed dataset rs9468 defines H1/H2 status [19]. In our imputed dataset rs9468 shows some evidence of association to AD \( (p = 7.8 \times 10^{-4}) \), with the risk allele (T) a proxy for the H1 haplotype. We imputed rs9468 in both the TGEN and ADNI datasets (Table 2). Meta-analysis of all three samples slightly increased the significance of this variant \( (p = 5.2 \times 10^{-3}) \). However, the H1 subhaplotypes including H1c could not be analyzed as only 5 out of the 6 markers, which define these haplotypes could be reliably imputed in the GERAD1 dataset.

**DISCUSSION**

AβPP, PSEN1, PSEN2, and MAPT are all implicated by AD pathology and been shown to have genetic effects on neurodegenerative disorders. In order to determine whether these genes cause susceptibility to LOAD, we analyzed AβPP, PSEN1, PSEN2, and MAPT in an imputed GWAS dataset of 3,940 cases and 13,373 controls. Association analysis of variants at each locus revealed no genome-wide significant SNPs. This observation is supported by other recent AD GWAS, which do not observe genome-wide significance at these loci [44–46]. Taken together this data suggests that common variation at these loci does not provide a strong contribution to LOAD susceptibility.

Conversely, we did observe a significant association between MAPT and AD using a gene-wide approach \( (p = 0.009) \), an analysis that has not been performed within the recent GWAS. A significant gene-wide result can be suggestive of multiple independent association signals within a gene. However, if genuine AD susceptibility variants exist at the MAPT loci, they are likely to be of weak effect. For example, rs11656151, the most significant single-marker at MAPT in our dataset, has an OR of 1.13. Meta-analysis of three GWAS datasets provided evidence of consistency between samples. However, the TGEN and ADNI datasets are relatively small and replication in much larger samples is needed.

The marker rs9468, tags the H1 haplotype which has been found to be overrepresented in both PSP and CBD cases [6]. Furthermore, the top hit in a recent PD GWAS of 3,361 cases and 4,573 controls \( (rs393152, p = 1.95 \times 10^{-16}) \) tags the H1 haplotype [7]. Marker rs9468 showed some evidence for association to LOAD in the GERAD1 dataset \( (p = 7.8 \times 10^{-4}) \). In addition, we observed the same direction of effect in the TGEN and ADNI datasets. However, as with rs11656151, this marker needs to be explored in larger datasets. Furthermore, as a result of insufficient data, we could not determine whether refining the H1 haplotype into a subhaplotype such as H1c, which has been found to be associated with neurodegenerative disorders CBD and PSP, would increase the significance of association observed.

While our results suggest that common variation at AβPP, PSEN1, PSEN2, and MAPT does not provide a strong contribution to AD risk, it is possible that these loci contain as yet undetected rare variants of larger effect. Genome-wide association studies are underpowered to detect these variants and sequencing of several thousand cases and controls would be required to detect rare variants at these loci.

In conclusion, it is unlikely that common variation at AβPP, PSEN1, PSEN2, and MAPT provide strong contributions to susceptibility for LOAD. However, the gene-wide effect observed at MAPT indicates a possible contribution to disease risk. Replication of this result is necessary although it is likely that large sample...
sizes will be required to achieve the power necessary to show a true effect.

ACKNOWLEDGMENTS

We thank the individuals and families who took part in this research. Cardiff University was supported by the Wellcome Trust, Medical Research Council (MRC, UK), Alzheimer’s Research UK (ARUK) and the Welsh Assembly Government. ARUK supported sample collections at the Institute of Psychiatry, the South West Dementia Bank and the Universities of Cambridge, Nottingham, Manchester and Belfast. The Belfast group acknowledges support from the Alzheimer’s Society, ARUK Ulster Garden Villages, Northern Ireland Research and Development Office and the Royal College of Physicians–Dunhill Medical Trust. They also acknowledge the‐American Federation for Aging Research for the Paul Beezen Career Development Awards in Aging Research Programme for the Island of Ireland. The MRC and Mercer’s Institute for Research on Ageing supported the Trinity College group. The South West Dementia Brain Bank acknowledges support from Bristol Research into Alzheimer’s and Care of the Elderly. The Charles Wolfson Charitable Trust supported the Oxford Project to Investigate Memory and Ageing group. A. Al-Chalabi and C. Shaw thank the Motor Neurone Disease Association and MRC for support. D.C.R. is a Wellcome Trust Senior Clinical Research Fellow. Washington University was funded by US National Institutes of Health (NIH) grants, the Barnes Jewish Foundation and the Charles and Joanne Knight Alzheimer’s Research Initiative. The Mayo GWAS was supported by NIH grants, the Robert and Clarice Smith and Abigail Van Buren AD Research Program, and the Palumbo Professorship in AD Research. Patient recruitment for the MRC Prion Unit/University College London Department of Neurodegenerative Disease collection was supported by the UCL Hospital/UCL Biomedical Centre. London and the South East Region (LASER)-AD was funded by Lundbeck SA. The Bonn group was supported by the German Federal Ministry of Education and Research (BMBF), Competence Network Dementia and Competence Network Degenerative Dementia, and by the Alfred Krupp von Bohlen und Halbach-Stiftung. The Cooperative gesundheitsforschung in der region Augsburg (KORA) F4 studies were financed by Helmholtz Zentrum München, the German Research Center for Environmental Health, BMBF, the German National Genome Research Network and the Munich Center of Health Sciences. The Heinz Nixdorf Recall cohort was funded by the Heinz Nixdorf Foundation (G. Schmidt, chairman) and BMBF: Corell Cell Repositories is supported by the US National Institute of Neurological Disorders and Stroke and the Intramural Research Program of the National Institute on Aging. We acknowledge use of DNA from the 1958 Birth Cohort collection and National Blood Service, funded by the MRC and the Wellcome Trust, which was genotyped by the Wellcome Trust Case Control Consortium and the Type-1 Diabetes Genetics Consortium, sponsored by the US National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, National Human Genome Research Institute, National Institute of Child Health and Human Development and Juvenile Diabetes Research Foundation International. Genotyping of the Lothian Birth Cohort (LBC) 1921 and 1936 was supported by the UK’s Biotechnology and Biological Sciences Research Council (BBSRC). Recruitment and genotype collection in the Lothian Birth Cohort 1921 was supported by the BBSRC. The Royal Society, and The Chief Scientist Office of the Scottish Government. Phenotype collection in the Lothian Birth Cohort 1936 was supported by Research Into Ageing (which continues as part of Age UK’s The Disconnected Mind project). The LBC work was undertaken in The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding from the BBSRC, EPSRC, ESRC and MRC is gratefully acknowledged. We thank R. Brown, J. Landers, D. Warden, D. Lehmann, N. Leigh, J. Uphill, J. Beck, T. Campbell, S. Klic, G. Adamson, J. Wyatt, M.I. Perez, T. Mettinger, P. Lichtner, G. Eckstein, N. Grafi-Radford, R. Petersen, D. Dickson, G. Fischer, H. Bickel, M. Hüll, H. Jahn, H. Kudukszewicz, C. Luckhaus, S. Riedel-Heller, S. Wolf, S. Weyerer, the Helmholtz Zentrum München genotyping staff and the NIMH AD Genetics Initiative. We thank Advanced Research Computing @Cardiff (ARCCA), which facilitated data analysis.

Authors’ disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1000).

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386  A. Grettë et al. / Variation at APOE, PSEN1, PSEN2, and MAPT in LOAD

473–477.

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