



Published in final edited form as:

*J Alzheimers Dis.* 2012 ; 28(2): 377–387. doi:10.3233/JAD-2011-110824.

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

A full list of authors and affiliations appears at the end of the article.

### Abstract

Rare mutations in *AβPP*, *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 *AβPP*, *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-β 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-β 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.

© 2012 – IOS Press and the authors. All rights reserved

\*Correspondence to: Julie Williams, MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, Henry Wellcome Building, Heath Park, Cardiff, CF14 4XN, UK. Tel.: +44 (0)2920 687067; Fax: +44 (0)2920 687068; WilliamsJ@cardiff.ac.uk.

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

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 [2, 3]. To date, 32 pathogenic *A $\beta$ PP* mutations have been identified in patients with early-onset 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-recombining 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 *A $\beta$ PP*, *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.sgu.ac.uk>), the NINDS funded neurogenetics collection at Coriell Cell Repositories (Coriell) (<http://ccr.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 publication [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  $p < 5 \times 10^{-8}$  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) 0.01 and an INFO score (representing imputation quality) 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 *AβPP*, *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 (genotyped  $\lambda = 1.06$ , 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  $p(1) \leq p(2) \leq \dots \leq p(n)$  then the null hypothesis of no association in the gene is rejected at significance level  $\alpha$  if  $p(j) \leq j\alpha/n$  for any  $j = 1, \dots, n$ . 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 dataset 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 are shown 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  $p = 8.8 \times 10^{-5}$ ). 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  $p = 1.9 \times 10^{-4}$ ) 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*.

We attempted to impute these variants in two publically available GWAS datasets [23, 39]. These results as well as the meta-analysis of all three 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 ( $p = 4.7 \times 10^{-5}$ ) 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 20 kb of *A $\beta$ PP*, *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 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 rs9486 in both the TGEN and ADNI datasets (Table 2). Meta-analysis of all three samples slightly increased the significance of this variant ( $p = 5.2 \times 10^{-4}$ ). However, the H1 sub-haplotypes 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.

## Authors

Amy Gerrish<sup>1</sup>, Giancarlo Russo<sup>1</sup>, Alexander Richards<sup>1</sup>, Valentina Moskvina<sup>1</sup>, Dobril Ivanov<sup>1</sup>, Denise Harold<sup>1</sup>, Rebecca Sims<sup>1</sup>, Richard Abraham<sup>1</sup>, Paul Hollingworth<sup>1</sup>, Jade Chapman<sup>1</sup>, Marian Hamshere<sup>1</sup>, Jaspreet Singh Pahwa<sup>1</sup>, Kimberley Dowzell<sup>1</sup>, Amy Williams<sup>1</sup>, Nicola Jones<sup>1</sup>, Charlene Thomas<sup>1</sup>, Alexandra Stretton<sup>1</sup>, Angharad R. Morgan<sup>1</sup>, Simon Lovestone<sup>2</sup>, John Powell<sup>3</sup>, Petroula Proitsi<sup>3</sup>, Michelle K. Lupton<sup>3</sup>, Carol Brayne<sup>4</sup>, David C. Rubinsztein<sup>5</sup>, Michael Gill<sup>6</sup>, Brian Lawlor<sup>6</sup>, Aoibhinn Lynch<sup>6</sup>, Kevin Morgan<sup>7</sup>, Kristelle S. Brown<sup>7</sup>, Peter A. Passmore<sup>8</sup>, David Craig<sup>8</sup>, Bernadette McGuinness<sup>8</sup>, Stephen Todd<sup>8</sup>, Janet A. Johnston<sup>8</sup>, Clive Holmes<sup>9</sup>, David Mann<sup>10</sup>, A. David Smith<sup>11</sup>, Seth Love<sup>12</sup>, Patrick G. Kehoe<sup>12</sup>, John Hardy<sup>13</sup>, Simon Mead<sup>14</sup>, Nick Fox<sup>15</sup>, Martin Rossor<sup>15</sup>, John Collinge<sup>14</sup>, Wolfgang Maier<sup>16</sup>, Frank Jessen<sup>16</sup>, Heike Kölsch<sup>16</sup>, Reinhard Heun<sup>16,17</sup>, Britta Schürmann<sup>16</sup>, Hendrik van den Bussche<sup>18</sup>, Isabella Heuser<sup>19</sup>, Johannes Kornhuber<sup>20</sup>, Jens Wiltfang<sup>21</sup>, Martin Dichgans<sup>22,23</sup>, Lutz Frölich<sup>24</sup>, Harald Hampel<sup>25</sup>, Michael Hüll<sup>26</sup>, Dan Rujescu<sup>26</sup>, Alison M. Goate<sup>27</sup>, John S. K. Kauwe<sup>28</sup>, Carlos Cruchaga<sup>27</sup>, Petra Nowotny<sup>27</sup>, John C. Morris<sup>27</sup>, Kevin Mayo<sup>27</sup>, Gill Livingston<sup>29</sup>, Nicholas J. Bass<sup>29</sup>, Hugh Gurling<sup>29</sup>, Andrew McQuillin<sup>29</sup>, Rhian Gwilliam<sup>30</sup>, Panagiotis Deloukas<sup>30</sup>, Gail Davies<sup>31,32</sup>, Sarah E. Harris<sup>31,33</sup>, John M. Starr<sup>31,34</sup>, Ian J. Deary<sup>31,32</sup>, Ammar Al-Chalabi<sup>35</sup>, Christopher E. Shaw<sup>35</sup>, Magda Tsolaki<sup>36</sup>, Andrew B. Singleton<sup>37</sup>, Rita Guerreiro<sup>37</sup>, Thomas W. Mühleisen<sup>38,39</sup>, Markus M. Nöthen<sup>38,39</sup>, Susanne Moebus<sup>40</sup>, Karl-Heinz Jöckel<sup>40</sup>, Norman Klopp<sup>41</sup>, H-Erich Wichmann<sup>41,42,43</sup>, Minerva M Carrasquillo<sup>44</sup>, V Shane Pankratz<sup>45</sup>, Steven G. Younkin<sup>44</sup>, Lesley Jones<sup>1</sup>, Peter A. Holmans<sup>1</sup>, Michael C. O'Donovan<sup>1</sup>, Michael J. Owen<sup>1</sup>, and Julie Williams<sup>1,\*</sup>

## Affiliations

<sup>1</sup>MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, School of Medicine, Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, UK <sup>2</sup>King's College London, Institute of Psychiatry, Kings College, London, UK <sup>3</sup>Department of Neuroscience, Institute of Psychiatry, Kings College, London, UK <sup>4</sup>Institute of Public Health, University of Cambridge, Cambridge, UK <sup>5</sup>Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK <sup>6</sup>Mercer's Institute for Research

on Aging, St. James Hospital and Trinity College, Dublin, Ireland <sup>7</sup>Human Genetics Group, School of Molecular Medical Sciences, Queen's Medical Centre, University of Nottingham, UK <sup>8</sup>Ageing Group, Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, UK <sup>9</sup>Division of Clinical Neurosciences, School of Medicine, University of Southampton, Southampton, UK <sup>10</sup>Neurodegeneration and Mental Health Research Group, School of Community Based Medicine, University of Manchester, Salford, UK <sup>11</sup>Oxford Project to Investigate Memory and Ageing, University of Oxford, John Radcliffe Hospital, Oxford, UK <sup>12</sup>Dementia Research Group, University of Bristol Institute of Clinical Neurosciences, Frenchay Hospital, Bristol, UK <sup>13</sup>Department of Molecular Neuroscience and Reta Lilla Weston Laboratories, Institute of Neurology, London, UK <sup>14</sup>MRC Prion Unit and Department of Neurodegenerative Disease, Institute of Neurology, University College London <sup>15</sup>Dementia Research Centre, Department of Neurodegenerative Diseases, UCL Institute of Neurology, London, UK <sup>16</sup>Department of Psychiatry, University of Bonn, Bonn, Germany <sup>17</sup>Radbourne Unit, Royal Derby Hospital, Derby, UK <sup>18</sup>Institute of Primary Medical Care, University Medical Center Hamburg-Eppendorf, Germany <sup>19</sup>Department of Psychiatry, Charité Berlin, Berlin, Germany <sup>20</sup>Department of Psychiatry and Psychotherapy, University of Erlangen-Nuremberg, Germany <sup>21</sup>LVR-Hospital Essen, Department of Psychiatry and Psychotherapy, University Duisburg-Essen, Germany <sup>22</sup>Institute for Stroke and Dementia Research, Klinikum der Universität München, Munich, Germany <sup>23</sup>Department of Neurology, Klinikum der Universität München, Munich, Germany <sup>24</sup>Department of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany <sup>25</sup>Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Goethe University, Frankfurt, Germany <sup>26</sup>Ludwig-Maximilians-University, Department of Psychiatry, Munich, Germany <sup>27</sup>Departments of Psychiatry, Neurology and Genetics, Washington University School of Medicine, St. Louis, Missouri, USA <sup>28</sup>Department of Biology, Brigham Young University, Provo, Utah, USA <sup>29</sup>Mental Health Unit, UCL, London, UK <sup>30</sup>The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK <sup>31</sup>Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK <sup>32</sup>Department of Psychology, University of Edinburgh, Edinburgh, UK <sup>33</sup>Medical Genetics, Molecular Medicine Centre, University of Edinburgh, Edinburgh, UK <sup>34</sup>Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK <sup>35</sup>MRC Centre for Neurodegeneration Research, King's College London, Institute of Psychiatry, Department of Clinical Neuroscience, London, UK <sup>36</sup>Third Department of Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece <sup>37</sup>Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA <sup>38</sup>Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany <sup>39</sup>Institute of Human Genetics, University of Bonn, Bonn, Germany <sup>40</sup>Institute for Medical Informatics, Biometry and Epidemiology, University Hospital of Essen, University Duisburg-Essen, Essen, Germany <sup>41</sup>Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for



Environmental Health, Neuherberg, Germany <sup>42</sup>Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany <sup>43</sup>Klinikum Grosshadern, Munich, Germany <sup>44</sup>Department of Neuroscience, Mayo Clinic College of Medicine, Jacksonville, Florida, USA <sup>45</sup>Division of Biomedical Statistics and Informatics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

## 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 Beeson 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 Alfried Krupp von Bohlen und Halbach-Stiftung. The Kooperative 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. Coriell 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 phenotype 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. Klier, G. Adamson, J. Wyatt, M.L. Perez, T. Meitinger, P. Lichtner, G. Eckstein, N. Graff-Radford, R. Petersen, D. Dickson, G. Fischer, H. Bickel, M. Hüll, H. Jahn, H. Kaduszkiewicz, 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.

## References

1. Dickson TC, Vickers JC. The morphological phenotype of beta-amyloid plaques and associated neuritic changes in Alzheimer's disease. *Neuroscience*. 2001; 105:99–107. [PubMed: 11483304]
2. Ertekin-Taner N. Genetics of Alzheimer's disease: A centennial review. *Neurol Clin*. 2007; 25:611–667. [PubMed: 17659183]

3. Zetzsche T, Rujescu D, Hardy J, Hampel H. Advances and perspectives from genetic research: Development of biological markers in Alzheimer's disease. *Expert Rev Mol Diagn.* 2010; 10:667–690. [PubMed: 20629514]
4. Selkoe DJ. Alzheimer's disease: Genes, proteins, and therapy. *Physiol Rev.* 2001; 81:741–766. [PubMed: 11274343]
5. Houlden H, Baker M, Morris HR, MacDonald N, Pickering-Brown S, Adamson J, Lees AJ, Rossor MN, Quinn NP, Kertesz A, Khan MN, Hardy J, Lantos PL, St George-Hyslop P, Munoz DG, Mann D, Lang AE, Bergeron C, Bigio EH, Litvan I, Bhatia KP, Dickson D, Wood NW, Hutton M. Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. *Neurology.* 2001; 56:1702–1706. [PubMed: 11425937]
6. Pittman AM, Myers AJ, Abou-Sleiman P, Fung HC, Kaleem M, Marlowe L, Duckworth J, Leung D, Williams D, Kilford L, Thomas N, Morris CM, Dickson D, Wood NW, Hardy J, Lees AJ, de Silva R. Linkage disequilibrium fine mapping and haplotype association analysis of the tau gene in progressive supranuclear palsy and corticobasal degeneration. *J Med Genet.* 2005; 42:837–846. [PubMed: 15792962]
7. Simon-Sanchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, Paisan-Ruiz C, Lichtner P, Scholz SW, Hernandez DG, Kruger R, Federoff M, Klein C, Goate A, Perlmutter J, Bonin M, Nalls MA, Illig T, Gieger C, Houlden H, Steffens M, Okun MS, Racette BA, Cookson MR, Foote KD, Fernandez HH, Traynor BJ, Schreiber S, Arepalli S, Zonozzi R, Gwinn K, van der Brug M, Lopez G, Chanock SJ, Schatzkin A, Park Y, Hollenbeck A, Gao J, Huang X, Wood NW, Lorenz D, Deuschl G, Chen H, Riess O, Hardy JA, Singleton AB, Gasser T. Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet.* 2009; 41:1308–1312. [PubMed: 19915575]
8. Zhang N, Yu JT, Yang Y, Yang J, Zhang W, Tan L. Association analysis of GSK3B and MAPT polymorphisms with Alzheimer's disease in Han Chinese. *Brain Res.* 2011; 1391:147–153. [PubMed: 21443865]
9. Belbin O, Beaumont H, Warden D, Smith AD, Kalsheker N, Morgan K. PSEN1 polymorphisms alter the rate of cognitive decline in sporadic Alzheimer's disease patients. *Neurobiol Aging.* 2009; 30:1992–1999. [PubMed: 18403054]
10. Feulner TM, Laws SM, Friedrich P, Wagenpfeil S, Wurst SH, Riehle C, Kuhn KA, Krawczak M, Schreiber S, Nikolaus S, Forstl H, Kurz A, Riemenschneider M. Examination of the current top candidate genes for AD in a genome-wide association study. *Mol Psychiatry.* 2010; 15:756–766. [PubMed: 19125160]
11. Guyant-Marechal L, Rovelet-Lecrux A, Goumidi L, Cousin E, Hannequin D, Raux G, Penet C, Ricard S, Mace S, Amouyel P, Deleuze JF, Frebourg T, Brice A, Lambert JC, Campion D. Variations in the APP gene promoter region and risk of Alzheimer disease. *Neurology.* 2007; 68:684–687. [PubMed: 17325276]
12. Kwok JB, Loy CT, Hamilton G, Lau E, Hallupp M, Williams J, Owen MJ, Broe GA, Tang N, Lam L, Powell JF, Lovestone S, Schofield PR. Glycogen synthase kinase-3beta and tau genes interact in Alzheimer's disease. *Ann Neurol.* 2008; 64:446–454. [PubMed: 18991351]
13. Laws SM, Friedrich P, Diehl-Schmid J, Muller J, Eisele T, Bauml J, Forstl H, Kurz A, Riemenschneider M. Fine mapping of the MAPT locus using quantitative trait analysis identifies possible causal variants in Alzheimer's disease. *Mol Psychiatry.* 2007; 12:510–517. [PubMed: 17179995]
14. Liu Z, Jia J. The association of the regulatory region of the presenilin-2 gene with Alzheimer's disease in the Northern Han Chinese population. *J Neurol Sci.* 2008; 264:38–42. [PubMed: 17727891]
15. Martinez-Garcia A, Aldudo J, Recuero M, Sastre I, Vilella-Cuadrada E, Rosich-Estrago M, Frank A, Valdivieso F, Bullido MJ. Presenilin 1 polymorphism associated with Alzheimer's disease in apolipoprotein E4 carriers. *Dement Geriatr Cogn Disord.* 2008; 26:440–444. [PubMed: 18957849]
16. Bullido MJ, Aldudo J, Frank A, Coria F, Avila J, Valdivieso F. A polymorphism in the tau gene associated with risk for Alzheimer's disease. *Neurosci Lett.* 2000; 278:49–52. [PubMed: 10643798]
17. Myers AJ, Kaleem M, Marlowe L, Pittman AM, Lees AJ, Fung HC, Duckworth J, Leung D, Gibson A, Morris CM, de Silva R, Hardy J. The H1c haplotype at the MAPT locus is associated with Alzheimer's disease. *Hum Mol Genet.* 2005; 14:2399–2404. [PubMed: 16000317]

18. Seto-Salvia N, Clarimon J, Pagonabarraga J, Pascual-Sedano B, Campolongo A, Combarros O, Mateo JI, Regana D, Martinez-Corral M, Marquie M, Alcolea D, Suarez-Calvet M, Molina-Porcel L, Dols O, Gomez-Isla T, Blesa R, Lleo A, Kulisevsky J. Dementia risk in Parkinson disease: Disentangling the role of MAPT haplotypes. *Arch Neurol*. 2011; 68:359–364. [PubMed: 21403021]
19. Abraham R, Sims R, Carroll L, Hollingworth P, O'Donovan MC, Williams J, Owen MJ. An association study of common variation at the MAPT locus with late-onset Alzheimer's disease. *Am J Med Genet B Neuropsychiatr Genet*. 2009; 150B:1152–1155. [PubMed: 19308965]
20. Cousin E, Mace S, Rocher C, Dib C, Muzard G, Hannequin D, Pradier L, Deleuze JF, Genin E, Brice A, Campion D. No replication of genetic association between candidate polymorphisms and Alzheimer's disease. *Neurobiol Aging*. 2011; 32:1443–1451. [PubMed: 19889475]
21. Mukherjee O, Kauwe JS, Mayo K, Morris JC, Goate AM. Haplotype-based association analysis of the MAPT locus in late onset Alzheimer's disease. *BMC Gene*. 2007; 8:3.
22. Nowotny P, Simcock X, Bertelsen S, Hinrichs AL, Kauwe JS, Mayo K, Smemo S, Morris JC, Goate A. Association studies testing for risk for late-onset Alzheimer's disease with common variants in the beta-amyloid precursor protein (APP). *Am J Med Genet B Neuropsychiatr Genet*. 2007; 144B:469–474. [PubMed: 17427190]
23. Reiman EM, Webster JA, Myers AJ, Hardy J, Dunckley T, Zismann VL, Joshipura KD, Pearson JV, Hu-Lince D, Huentelman MJ, Craig DW, Coon KD, Liang WS, Herbert RH, Beach T, Rohrer KC, Zhao AS, Leung D, Bryden L, Marlowe L, Kaleem M, Mastroeni D, Grover A, Heward CB, Ravid R, Rogers J, Hutton ML, Melquist S, Petersen RC, Alexander GE, Caselli RJ, Kukull W, Papassotiropoulos A, Stephan DA. GAB2 alleles modify Alzheimer's risk in APOE epsilon4 carriers. *Neuron*. 2007; 54:713–720. [PubMed: 17553421]
24. Kwon JM, Nowotny P, Shah PK, Chakraverty S, Norton J, Morris JC, Goate AM. Tau polymorphisms are not associated with Alzheimer's disease. *Neurosci Lett*. 2000; 284:77–80. [PubMed: 10771166]
25. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskva V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schurmann B, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frolich L, Hampel H, Hull M, Rujescu D, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jockel KH, Klopp N, Wichmann HE, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ, Williams J. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet*. 2009; 41:1088–1093. [PubMed: 19734902]
26. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–944. [PubMed: 6610841]
27. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van Belle G, Berg L. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology*. 1991; 41:479–486. [PubMed: 2011243]
28. Wichmann HE, Gieger C, Illig T. KORA-gen—resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen*. 2005; 67(Suppl 1):S26–S30. [PubMed: 16032514]
29. Birnbaum S, Ludwig KU, Reutter H, Herms S, Steffens M, Rubini M, Baluardo C, Ferriani M, Almeida de Assis N, Alblas MA, Barth S, Freudenberg J, Lauster C, Schmidt G, Scheer M, Braumann B, Berge SJ, Reich RH, Schiefke F, Hemprich A, Potzsch S, Steegers-Theunissen RP, Potzsch B, Moebus S, Horsthemke B, Kramer FJ, Wienker TF, Mossey PA, Propping P, Cichon S, Hoffmann P, Knapp M, Nothen MM, Mangold E. Key susceptibility locus for nonsyndromic cleft

- lip with or without cleft palate on chromosome 8q24. *Nat Genet.* 2009; 41:473–477. [PubMed: 19270707]
30. Hillmer AM, Brockschmidt FF, Hanneken S, Eigelshoven S, Steffens M, Flaquer A, Herms S, Becker T, Kortum AK, Nyholt DR, Zhao ZZ, Montgomery GW, Martin NG, Muhleisen TW, Alblas MA, Moebus S, Jockel KH, Bocker-Preuss M, Erbel R, Reinartz R, Betz RC, Cichon S, Propping P, Baur MP, Wienker TF, Kruse R, Nothen MM. Susceptibility variants for male-pattern baldness on chromosome 20p11. *Nat Genet.* 2008; 40:1279–1281. [PubMed: 18849994]
  31. Landers JE, Melki J, Meininger V, Glass JD, van den Berg LH, van Es MA, Sapp PC, van Vught PW, McKenna-Yasek DM, Blauw HM, Cho TJ, Polak M, Shi L, Wills AM, Broom WJ, Ticozzi N, Silani V, Ozoguz A, Rodriguez-Leyva I, Veldink JH, Ivinson AJ, Saris CG, Hosler BA, Barnes-Nessa A, Couture N, Wokke JH, Kwiatkowski TJ Jr, Ophoff RA, Cronin S, Hardiman O, Diekstra FP, Leigh PN, Shaw CE, Simpson CL, Hansen VK, Powell JF, Corcia P, Salachas F, Heath S, Galan P, Georges F, Horvitz HR, Lathrop M, Purcell S, Al-Chalabi A, Brown RH Jr. Reduced expression of the Kinesin-Associated Protein 3 (KIFAP3) gene increases survival in sporadic amyotrophic lateral sclerosis. *Proc Natl Acad Sci U S A.* 2009; 106:9004–9009. [PubMed: 19451621]
  32. Craddock N, Hurles ME, Cardin N, Pearson RD, Plagnol V, Robson S, Vukcevic D, Barnes C, Conrad DF, Giannoulatou E, Holmes C, Marchini JL, Stirrups K, Tobin MD, Wain LV, Yau C, Aerts J, Ahmad T, Andrews TD, Arbury H, Attwood A, Auton A, Ball SG, Balmforth AJ, Barrett JC, Barroso I, Barton A, Bennett AJ, Bhaskar S, Blaszczyk K, Bowes J, Brand OJ, Braund PS, Bredin F, Breen G, Brown MJ, Bruce IN, Bull J, Burren OS, Burton J, Byrnes J, Caesar S, Clee CM, Coffey AJ, Connell JM, Cooper JD, Dominiczak AF, Downes K, Drummond HE, Dudakia D, Dunham A, Ebbs B, Eccles D, Edkins S, Edwards C, Elliot A, Emery P, Evans DM, Evans G, Eyre S, Farmer A, Ferrier IN, Feuk L, Fitzgerald T, Flynn E, Forbes A, Forty L, Franklyn JA, Freathy RM, Gibbs P, Gilbert P, Gokumen O, Gordon-Smith K, Gray E, Green E, Groves CJ, Grozeva D, Gwilliam R, Hall A, Hammond N, Hardy M, Harrison P, Hassanali N, Hebaishi H, Hines S, Hinks A, Hitman GA, Hocking L, Howard E, Howard P, Howson JM, Hughes D, Hunt S, Isaacs JD, Jain M, Jewell DP, Johnson T, Jolley JD, Jones IR, Jones LA, Kirov G, Langford CF, Lango-Allen H, Lathrop GM, Lee J, Lee KL, Lees C, Lewis K, Lindgren CM, Maisuria-Armer M, Maller J, Mansfield J, Martin P, Massey DC, McArdle WL, McGuffin P, McLay KE, Mentzer A, Mimmack ML, Morgan AE, Morris AP, Mowat C, Myers S, Newman W, Nimmo ER, O'Donovan MC, Onipinla A, Onyiah I, Ovington NR, Owen MJ, Palin K, Parnell K, Pernet D, Perry JR, Phillips A, Pinto D, Prescott NJ, Prokopenko I, Quail MA, Rafelt S, Rayner NW, Redon R, Reid DM, Renwick, Ring SM, Robertson N, Russell E, St Clair D, Sambrook JG, Sanderson JD, Schuilenburg H, Scott CE, Scott R, Seal S, Shaw-Hawkins S, Shields BM, Simmonds MJ, Smyth DJ, Somaskantharajah E, Spanova K, Steer S, Stephens J, Stevens HE, Stone MA, Su Z, Symmons DP, Thompson JR, Thomson W, Travers ME, Turnbull C, Valsesia A, Walker M, Walker NM, Wallace C, Warren-Perry M, Watkins NA, Webster J, Weedon MN, Wilson AG, Woodburn M, Wordworth BP, Young AH, Zeggini E, Carter NP, Frayling TM, Lee C, McVean G, Munroe PB, Palotie A, Sawcer SJ, Scherer SW, Strachan DP, Tyler-Smith C, Brown MA, Burton PR, Caulfield MJ, Compston A, Farrall M, Gough SC, Hall AS, Hattersley AT, Hill AV, Mathew CG, Pembrey M, Satsangi J, Stratton MR, Worthington J, Deloukas P, Duncanson A, Kwiatkowski DP, McCarthy MI, Ouwehand W, Parkes M, Rahman N, Todd JA, Samani NJ, Donnelly P. Genome-wide association study of CNVs in 16,000 cases of eight common diseases and 3,000 shared controls. *Nature.* 2010; 464:713–720. [PubMed: 20360734]
  33. Devlin B, Roeder K. Genomic control for association studies. *Biometrics.* 1999; 55:997–1004. [PubMed: 11315092]
  34. Pe'er I, Yelensky R, Altshuler D, Daly MJ. Estimation of the multiple testing burden for genome-wide association studies of nearly all common variants. *Genet Epidemiol.* 2008; 32:381–385. [PubMed: 18348202]
  35. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet.* 2009; 5:e1000529. [PubMed: 19543373]
  36. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet.* 2006; 38:904–909. [PubMed: 16862161]

37. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. *Biometrika*. 1986; 73:751–754.
38. Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: Using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genet Epidemiol*. 2010; 34:816–834. [PubMed: 21058334]
39. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, Jack CR Jr, Jagust WJ, Shaw LM, Toga AW, Trojanowski JQ, Weiner MW. Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. *Neurology*. 2010; 74:201–209. [PubMed: 20042704]
40. Hiltunen M, Helisalmi S, Mannermaa A, Alafuzoff I, Koivisto AM, Lehtovirta M, Pirskanen M, Sulkava R, Verkkoniemi A, Soininen H. Identification of a novel 4.6-kb genomic deletion in presenilin-1 gene which results in exclusion of exon 9 in a Finnish early onset Alzheimer's disease family: An Alu core sequence-stimulated recombination? *Eur J Hum Genet*. 2000; 8:259–266. [PubMed: 10854108]
41. Prihar G, Verkkoniemi A, Perez-Tur J, Crook R, Lincoln S, Houlden H, Somer M, Paetau A, Kalimo H, Grover A, Myllykangas L, Hutton M, Hardy J, Haltia M. Alzheimer disease PS-1 exon 9 deletion defined. *Nat Me*. 1999; 5:1090.
42. Neale BM, Sham PC. The future of association studies: Gene-based analysis and replication. *Am J Hum Genet*. 2004; 75:353–362. [PubMed: 15272419]
43. Moskva V, Craddock N, Holmans P, Nikolov I, Pahwa JS, Green E, Owen MJ, O'Donovan MC. Gene-wide analyses of genome-wide association data sets: Evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk. *Mol Psychiatry*. 2009; 14:252–260. [PubMed: 19065143]
44. Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fievet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossu P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanche H, Dartigues JF, Tzourio C, Gut I, Van Broeckhoven C, Alperovitch A, Lathrop M, Amouyel P. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet*. 2009; 41:1094–1099. [PubMed: 19734903]
45. Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buross J, Gallins PJ, Buxbaum JD, Jarvik GP, Crane PK, Larson EB, Bird TD, Boeve BF, Graff-Radford NR, De Jager PL, Evans D, Schneider JA, Carrasquillo MM, Ertekin-Taner N, Younkin SG, Cruchaga C, Kauwe JS, Nowotny P, Kramer P, Hardy J, Huentelman MJ, Myers AJ, Barmada MM, Demirci FY, Baldwin CT, Green RC, Rogava E, St George-Hyslop P, Arnold SE, Barber R, Beach T, Bigio EH, Bowen JD, Boxer A, Burke JR, Cairns NJ, Carlson CS, Carney RM, Carroll SL, Chui HC, Clark DG, Corneveaux J, Cotman CW, Cummings JL, DeCarli C, DeKosky ST, Diaz-Arrastia R, Dick M, Dickson DW, Ellis WG, Faber KM, Fallon KB, Farlow MR, Ferris S, Frosch MP, Galasko DR, Ganguli M, Gearing M, Geschwind DH, Ghetti B, Gilbert JR, Gilman S, Giordani B, Glass JD, Growdon JH, Hamilton RL, Harrell LE, Head E, Honig LS, Hulette CM, Hyman BT, Jicha GA, Jin LW, Johnson N, Karlawish J, Karydas A, Kaye JA, Kim R, Koo EH, Kowall NW, Lah JJ, Levey AI, Lieberman AP, Lopez OL, Mack WJ, Marson DC, Martiniuk F, Mash DC, Masliah E, McCormick WC, McCurry SM, McDavid AN, McKee AC, Mesulam M, Miller BL, Miller CA, Miller JW, Parisi JE, Perl DP, Peskind E, Petersen RC, Poon WW, Quinn JF, Rajbhandary RA, Raskind M, Reisberg B, Ringman JM, Roberson ED, Rosenberg RN, Sano M, Schneider LS, Seeley W, Shelanski ML, Slifer MA, Smith CD, Sonnen JA, Spina S, Stern RA, Tanzi RE, Trojanowski JQ, Troncoso JC, Van Deerlin VM, Vinters HV, Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Williamson J, Woltjer RL, Cantwell LB, Dombroski BA, Beekly D, Lunetta KL, Martin ER, Kamboh MI, Saykin AJ, Reiman EM, Bennett DA, Morris JC, Montine TJ, Goate AM, Blacker D, Tsuang DW, Hakonarson H, Kukull WA, Foroud TM, Haines JL, Mayeux R, Pericak-Vance MA, Farrer LA, Schellenberg GD. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat Genet*. 2011; 43:436–441. [PubMed: 21460841]
46. Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carassquillo MM, Lambert JC, Harold D, Schrijvers EM, Ramirez-Lorca R, Debette S, Longstreth

WT Jr, Janssens AC, Pankratz VS, Dartigues JF, Hollingworth P, Aspelund T, Hernandez I, Beiser A, Kuller LH, Koudstaal PJ, Dickson DW, Tzourio C, Abraham R, Antunez C, Du Y, Rotter JI, Aulchenko YS, Harris TB, Petersen RC, Berr C, Owen MJ, Lopez-Arrieta J, Varadarajan BN, Becker JT, Rivadeneira F, Nalls MA, Graff-Radford NR, Campion D, Auerbach S, Rice K, Hofman A, Jonsson PV, Schmidt H, Lathrop M, Mosley TH, Au R, Psaty BM, Uitterlinden AG, Farrer LA, Lumley T, Ruiz A, Williams J, Amouyel P, Younkin SG, Wolf PA, Launer LJ, Lopez OL, van Duijn CM, Breteler MM. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA*. 2010; 303:1832–1840. [PubMed: 20460622]

Table 1

Analysis of *AβPP*, *PSENI*, *PSEN2*, and *MAPT* in the GERAD1 dataset

Gene	Gene position ± 20 KB (NCBI36)	GWAS results				Imputed Results				
		Single-marker analysis		Gene-wide analysis		Single-marker analysis		Gene-wide analysis		
		SNP ID	OR	p value	Simes p value	SNP ID	Info	OR	P value	Simes p value
<i>AβPP</i>	chr21 : 26,154,732-26,485,003	rs2830088	0.94	0.010	0.362	rs381743	0.87	0.92	0.002	0.420
<i>PSENI</i>	chr14 : 72,652,932-72,776,862	rs362350	0.90	0.020	0.240	chr14-72745579	0.80	1.37	$1.9 \times 10^{-4}$	0.077
<i>PSEN2</i>	chr1 : 225,104,896-225,170,427	rs2073489	0.96	0.136	0.611	rs12405469	0.81	0.94	0.041	0.784
<i>MAPT</i>	chr17 : 41,307,544-41,481,546	rs8079215	1.10	0.001	0.034	rs11656151	0.84	1.13	$8.8 \times 10^{-5}$	0.009

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*, *PSENI*, *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 (GERADI, TGEN, and ADNI)

Gene	SNP ID	GERADI			TGEN			ADNI			Meta-analysis			
		Info	OR	p value	RSQR	OR	p value	Info	OR	p value	OR	p value	Q-statistic	I <sup>2</sup>
AβPP	rs381743	0.87	0.91	0.002	0.96	0.97	0.789	N/A	N/A	N/A	0.92	0.003	0.586	0
PSEN1	chr14-72745579	0.80	1.36	$1.9 \times 10^{-4}$	0.71	0.75	0.378	N/A	N/A	N/A	1.10	0.743	0.071	69
PSEN2	rs12405469	0.81	0.94	0.041	0.99	1.06	0.573	N/A	N/A	N/A	0.95	0.072	0.264	20
MAPT	rs11656151	0.84	1.13	$8.8 \times 10^{-5}$	0.89	1.08	0.538	0.95	1.21	0.283	1.13	$4.7 \times 10^{-5}$	0.855	0
MAPT	rs9468	0.87	0.89	$7.8 \times 10^{-4}$	0.95	0.96	0.725	0.98	0.83	0.289	0.89	$5.2 \times 10^{-4}$	0.786	0

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<sup>2</sup> > 50. In these instances a random effects model was used.

N/A = Not available.