Genetic risk factors for the posterior cortical atrophy variant of Alzheimer’s disease

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HAL Id: hal-01289466
http://hal.upmc.fr/hal-01289466
Submitted on 16 Mar 2016

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Featured Article

Genetic risk factors for the posterior cortical atrophy variant of Alzheimer’s disease

Jonathan M. Schott a,*, Sebastian J. Crutch a, Minerva M. Carrasquillo b, James Uphill c, Tim J. Shakespeare a, Natalie S. Ryan a, Keir X. X. Yong a, Manja Lehmann a, Nilufer Ertekin-Taner b, Neil R. Graff-Radford d, Bradley F. Boeve e, Melissa E. Murray b, Qurat ul Ain Khan b, Ronald C. Petersen e, Dennis W. Dickson b, David S. Knopman e, Gil D. Rabinovici f, Bruce L. Miller f, Aida Suarez Gonzalez a,g, Eulogio Gil-Néciga g, Julie S. Snowden h, Jenny Harris h, Stuart M. Pickering-Brown h, Eva Louwersheimer i, Wiesje M. van der Flier i, Philip Scheltens i, Yolande A. Pijnenburg i, Douglas Galasko j,k, Marie Sarazin l, Bruno Dubois m, Eloi Magnin n, Daniela Galimberti o, Elio Scarpini o, Stefano F. Cappa p, John R. Hodges q, John Collinge c, Maria C. Carrillo r, Jose T. Bras s, John Hardy s, Martin N. Rossor a, Nick C. Fox a, Simon Mead c

aDepartment of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, UK
bDepartment of Neuroscience, Mayo Clinic, Jacksonville, FL, USA
cDepartment of Neurodegenerative Disease, MRC Prion Unit, UCL Institute of Neurology, UK
dDepartment of Neurology, Mayo Clinic, Jacksonville, FL, USA
eDepartment of Neurology, Mayo Clinic, Rochester, MN, USA
fUCSF, San Francisco, CA, USA
geUniversity Hospital Virgen del Rocío, Seville, Spain
hInstitute of Brain, Behaviour and Mental Health, University of Manchester, UK
iAlzheimer center, Department of Neurology, VU University Medical Center, Neuroscience Campus, Amsterdam, Netherlands
jDepartment of Epidemiology & biostatistics, VU University Medical Center, Amsterdam, The Netherlands
kUC San Diego/VA San Diego Healthcare System, San Diego, CA, USA
lINSERM U610, Hôpital de la Salpêtrière, Paris, France
mCentre des Maladies Cognitives et Comportementales, IM2A, ICM, Paris 6 University, France
nRegional Memory Centre (CMRR), CHU Besançon, Besançon, France
oUniversity of Milan, Fondazione Ca Granda, IRCCS Ospedale Policlinico, Italy
pVita-Salute San Raffaele University, Milan, Italy
qUniversity of New South Wales, Sydney, Australia
rAlzheimer’s Association, Chicago, IL, USA
sDepartment of Molecular Neurosciences, UCL Institute of Neurology, UK

Abstract

Introduction: The genetics underlying posterior cortical atrophy (PCA), typically a rare variant of Alzheimer’s disease (AD), remain uncertain.

Methods: We genotyped 302 PCA patients from 11 centers, calculated risk at 24 loci for AD/DLB and performed an exploratory genome-wide association study.

Results: We confirm that variation in/near APOE/TOMM40 (P = 6 × 10^{-14}) alters PCA risk, but with smaller effect than for typical AD (PCA: odds ratio [OR] = 2.03, typical AD: OR = 2.83, P = .0007). We found evidence for risk in/near CR1 (P = 7 × 10^{-4}), ABCA7 (P = .02) and BIN1 (P = .04). ORs at variants near INPP5D and NME8 did not overlap between PCA and typical AD.

*Corresponding author. Tel.: +1 020 3448 3011; Fax: —.
E-mail address: j.schott@ucl.ac.uk

http://dx.doi.org/10.1016/j.jalz.2016.01.010
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Exploratory genome-wide association studies confirmed APOE and identified three novel loci: rs76854344 near CNTNAP5 (P = 8 × 10^{-10} OR = 1.9 [1.5–2.3]); rs72907046 near FAM46A (P = 1 × 10^{-9} OR = 3.2 [2.1–4.9]); and rs2525776 near SEMA3C (P = 1 × 10^{-8} OR = 3.3 [2.1–5.1]).

Discussion: We provide evidence for genetic risk factors specifically related to PCA. We identify three candidate loci that, if replicated, may provide insights into selective vulnerability and phenotypic diversity in AD.

Keywords: Posterior cortical atrophy; Alzheimer’s disease; Genetics; GWAS; Selective vulnerability; ApoE

1. Introduction

Posterior cortical atrophy (PCA) is a rare neurodegenerative syndrome, typically a variant of Alzheimer’s disease (AD), although occasionally due to other pathologies including dementia with Lewy bodies, corticobasal degeneration, and prion disease [1]. Patients with PCA present with combinations of cognitive problems attributable to posterior cortical dysfunction and in particular difficulties with higher level visual processing including simultanagnosia, optic apraxia, optic ataxia, and visual disorientation; other features may include dyslexia, dyscalculia, dysgraphia, and limb dyspraxia. In contrast with typical, amnestic AD, memory is relatively spared until the disease becomes advanced. MR brain imaging in PCA typically shows parieto-occipital lobe atrophy with relative preservation of medial temporal lobe structures [2]; fluoro-deoxyglucose positron emission tomography (PET) shows prominent posterior cortical hypometabolism [3]; and in a single case study using the AV1451 tau PET tracer, posterior cortical tau deposition [4]. By contrast, PET imaging using amyloid-binding ligands typically shows global amyloid deposition [3]. Aside from the imaging and cognitive differences, patients with PCA are typically younger than those with typical amnestic late-onset AD, usually with disease onset in the sixth or seventh decade [1]. PCA is almost invariably a sporadic disorder, and the risk factors for developing the syndrome are unknown.

Understanding the genetic architecture of the PCA variant of AD may provide insights both into factors predisposing to young onset AD, as well as mechanisms underlying regional vulnerability in AD.

To date, only a few, single-center studies have addressed genetic risk for PCA [5–10], and due to the rarity of the syndrome all have been relatively small, the largest being a maximum of 81 cases [9]. Some, but not all, of these studies have suggested that despite their early-disease onset, patients with PCA may be less likely than expected to have an APOE E4 allele, the commonest risk factor for late-onset AD. Other studies have suggested that there may be differences in some of the more recently identified genetic risks for AD in patients with PCA [9]. Recognizing the rarity of this AD variant, we formed an international consortium comprising eleven centers, using clinical diagnostic criteria to define cases of PCA, with the principal aim of determining whether APOE E4 and genetic risks from recent genome-wide association studies (GWAS) of AD and dementia with Lewy bodies (DLB, see below) are the risk factors for the PCA variant of AD. In a second, exploratory analysis, we performed a pilot GWAS analysis to identify novel putative genetic risk factors for PCA.

2. Methods

2.1. PCA patients and controls

After an inaugural multidisciplinary meeting of PCA researchers [11], latterly formalized as the Alzheimer’s Association’s International Society to Advance Alzheimer’s Research and Treatment (ISTAART) Professional Interest Area in Atypical AD and Associated Syndromes, an international collaborative group was established to assess genetic risk factors for PCA. Researchers identified individuals with PCA, in whom a deoxyribo nucleic acid (DNA) sample was available. Patients who the referring physician had diagnosed with AD, had multidomain cognitive impairment fulfilling criteria for AD dementia, and had one or both of two published criteria for PCA, as proposed by Tang-Wai [5] and Mendez [12] (Table 1) were included. Additional data collected included gender, age at disease onset, age at death (where applicable), and whether there was molecular (cerebrospinal fluid or amyloid PET using locally defined ranges) evidence or pathologic confirmation of underlying AD pathology. Each site had appropriate local ethical approvals in place, and all participants gave informed written consent. Controls were from UK, USA, and Germany (see below).

2.2. Genetic and statistical analyses

DNA samples were analyzed at the MRc Prion Unit, Department of Neurodegenerative Disease, Institute of Neurology, UCL. PCA samples were genotyped on Illumina 660 arrays (n = 54, UCL cohort only) and OmniExpress arrays (n = 239, all cohorts); in total, 293 passed sample quality control, implemented using PLINK. Controls were genotyped on Illumina 550 (n = 809, KORA F4 German, PMID: 16032514), OmniExpress (n = 1185, Geisinger US
Table 1

<table>
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<tbody>
<tr>
<td><strong>Core features</strong></td>
<td><strong>Core diagnostic features (all must be present)</strong></td>
</tr>
<tr>
<td>Insidious onset and gradual progression</td>
<td>Insidious onset and gradual progression</td>
</tr>
<tr>
<td>Presentation of visual complaints in the absence of significant primary ocular disease</td>
<td>Presentation of visual complaints with intact primary visual functions</td>
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<tr>
<td>Relative preservation of anterograde memory and insight early in the disorder</td>
<td>Evidence of predominant complex visual disorder on examination</td>
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<tr>
<td>Disabling visual impairment throughout the disorder</td>
<td>Elements of Balint’s syndrome</td>
</tr>
<tr>
<td>Absence of stroke or tumor</td>
<td>Visual agnosia</td>
</tr>
<tr>
<td>Absence of early parkinsonism and hallucinations</td>
<td>Dressing apraxia</td>
</tr>
<tr>
<td>Any of the following findings</td>
<td>Environmental disorder</td>
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<tr>
<td>Simultanagnosia with or without optic ataxia or ocular apraxia</td>
<td>Proportionally less impaired deficits in memory and verbal fluency</td>
</tr>
<tr>
<td>Constructional dyspraxia</td>
<td>Relatively preserved insight with or without depression</td>
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<tr>
<td>Visual field defect</td>
<td></td>
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<tr>
<td>Environmental disorientation</td>
<td></td>
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<tr>
<td>Any of the elements of Gerstmann syndrome</td>
<td></td>
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<tr>
<td><strong>Supportive features</strong></td>
<td><strong>Supportive diagnostic features</strong></td>
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<td>Alexia</td>
<td>Presenile onset</td>
</tr>
<tr>
<td>Presence on or dressing apraxia</td>
<td>Elements of Gerstmann’s syndrome</td>
</tr>
<tr>
<td>Prosopagnosia</td>
<td>Idiomeotor apraxia</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td><strong>Physical examination within normal limits</strong></td>
</tr>
<tr>
<td>Neuropsychological deficits referable to parietal and/or occipital regions</td>
<td>Physical examination within normal limits</td>
</tr>
<tr>
<td>Focal or asymmetric atrophy in parietal and/or occipital regions on structural imaging</td>
<td></td>
</tr>
<tr>
<td>Focal or asymmetric hypoperfusion/hypometabolism in parietal and/or occipital regions on functional imaging</td>
<td></td>
</tr>
</tbody>
</table>

http://www.geisinger.org), Illumina 2.5 M (n = 1882, KORA F3 German), Illumina 5M (n = 1651, Framingham US, see acknowledgments), and Illumina 1.2 M (n = 5020, WTCCC2 UK, see acknowledgments) arrays. Physical locations refer to the Feb 2009 (GRCh37/hg19) assembly. We excluded SNPs with a minor allele frequency (MAF) < 1% (n = 70,042 from OmniExpress case arrays); genotyping rate <99% (n = 85,086 from OmniExpress case arrays); or Hardy-Weinberg Equilibrium (HWE) exact test P < 10^{-3} in controls. Cases with call rate <98% (n = 6) as well as ethnic outliers (n = 2) were excluded after visualization of multidimensional scaling plots. Related and duplicate cases were removed by IBS/IBD calculation (n = 1) and re-examination of patient data, as they became available post genotyping (n = 2). A Pi-Hat (proportion identity by descent) threshold of >0.1875 was used, which should exclude first and second degree relatives. Two duplicates were removed due to later availability of patient data were also included within the six cases removed for low call rate thus bringing the total number of cases removed to nine. Owing to the multitude of different genotyping platforms, control comparisons were carried out sequentially and exclusions removed at each stage. A total of 840 KORAF4 German controls were originally genotyped; 17 with call rate <98%, six with Pi-Hat > 0.1875 and eight MDS outliers were removed. A total of 1950 KORAF3 German controls were originally downloaded; three with call rate <98%, 57 with Pi-Hat > 0.1875, and eight MDS outliers were removed. A total of 1264 Geisinger US controls were originally downloaded; two with call rate <98%, 69 with Pi-Hat > 0.1875, and eight MDS outliers were removed. 2467 FHS US controls were originally downloaded; 16 with call rate <98%, 793 with Pi-Hat > 0.1875 and seven MDS outliers were removed. 5050 WTCCC2 UK controls were generated from available raw IDAT files; 26 with call rate <98%, four with Pi-Hat > 0.1875, and zero MDS outliers were removed (see Supplementary Table 1). All remaining cases and controls were finally visualized on an MDS plot (see Supplementary Fig. 1), outlier detection was performed using PLINK v1.07, and no further outliers were detected. IBS/IBD estimation of the final cases and controls also lead to no further exclusions based on relatedness. Shapeit2 was used, in conjunction with the 1000 Genomes Phase 1 Integrated variant set (b37 March 2012 release), to align all data relative to the positive strand [13]. To avoid potential downstream cross platform confusion, however, we removed any A/T or G/C transversions to phase each chromosome from each platform separately before imputation using Impute2 (v2.3.0). GTOOL (v0.6.6) was used to extract and collate samples into their respective cohorts for association testing [14]. Association testing was performed using SNPtest_v2.5-beta4 employing the frequentist (additive model) score method which involves weighting by the likelihood of each imputed genotype [15]. Four population
covariates derived from IBS/IBD analysis in PLINK were used in the association analysis [16,17]. The case-control association test statistic inflation factor was 1.06 (Supplementary Fig. 2). Any association statistics mentioned in the results section are shown with standard genomic control ($P_{GC}$) corrected and uncorrected $P$ values.

Post association-testing QC excluded markers with a MAF <1% and departure from HWE, in both combined and any single control cohort $P < 10^{-4}$. We also excluded markers with SNPtestv2 derived “info metric” and “add info metric” below 0.9. The final autosomal analysis thus included 5.9 M markers.

We assessed whether the genetic risks for typical AD and PCA were different by comparing odds ratios (OR) between our study and those published in typical AD [18]. We employed a Wald-type test, first calculating the standard error of the difference in log (OR) from the reported CIs. We then divided the empirical difference in log (OR) by its standard error, and thus derived a z-score and $P$ value, relying on the approximate normality of log (OR) estimates from large samples. In the main analysis of candidate SNPs, we used a Bonferroni corrected association threshold of $P < .002$ based on the testing of a lead SNP from 24 independent loci derived from studies of AD [18] and DBL [19].

Although the typical samples sizes that are required to discover novel genome-wide significant risk factors in complex disorders are in the thousands, there are some precedents of strong genetic effects detected with small but phenotypically homogenous samples, including variants at APOE in AD [20], PRNP in prion disease [21], and complement factor H in age related macular degeneration [22]. We therefore performed an exploratory genome-wide association study using established methodologies that account for population structure and with imputation of SNPs not present on the genotyping arrays. As PCA is a clinical syndrome that may be due to pathologies other than AD, we also assessed the odds ratios at SNPs of interest in a subset of patients with biomarker/autopsy evidence for underlying AD pathology.

3.2. Comparisons at known genetic loci for AD and DBL

Results of the genetic analysis of candidate risk factors for the whole PCA cohort are shown in Table 2. First, we considered 24 SNPs known to be genetic risk factors in AD and/or DBL. The best proxy genotyped for the APOE E4 AD-risk allele, rs2075650, located on chromosome 19 in the TOMM40 gene and 13kb upstream of APOE, was identified as a strong risk factor for PCA (OR 2.03, [95% CI = 1.68–2.46], $P = 6 \times 10^{-14}$, $P_{GC} = 3 \times 10^{-13}$; Fig. 1 and Fig. 2B). rs3818361 located on chromosome 1 in CR1 was also significantly associated (ORs = 1.38 [1.14–1.67], $P = 7 \times 10^{-4}$, $P_{GC} = 1 \times 10^{-3}$; Fig. 2). rs3764650 in ABCA7 (OR = 1.39 [1.07–1.8], $P = .02$, $P_{GC} = .02$) and

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical features and demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of DNA samples received</td>
<td>302</td>
</tr>
<tr>
<td>Number (%) male</td>
<td>124 (41%)</td>
</tr>
<tr>
<td>Mean ± SD age at onset (y)</td>
<td>58.9 ± 6.9</td>
</tr>
<tr>
<td>Number (%) with young onset dementia (onset &lt;65 y)</td>
<td>249 (83%)</td>
</tr>
<tr>
<td>Number with biomarker/path evidence for AD*</td>
<td>82 (27%)</td>
</tr>
<tr>
<td>Number (%) with known age of death</td>
<td>34</td>
</tr>
<tr>
<td>Mean ± SD age at death (y)</td>
<td>67.9 ± 7.7</td>
</tr>
</tbody>
</table>

9 samples failed genetic QC

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<tr>
<th>Table 3</th>
<th>Total number of DNA samples passing QC and entering analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of DNA samples passing QC and entering analysis</td>
<td>293</td>
</tr>
<tr>
<td>Number (%) male</td>
<td>120 (41%)</td>
</tr>
<tr>
<td>Mean ± SD age at onset (y)</td>
<td>58.8 ± 6.9</td>
</tr>
<tr>
<td>Number (%) with young onset dementia (onset &lt;65 y)</td>
<td>243 (83%)</td>
</tr>
<tr>
<td>Number with biomarker/path evidence for AD*</td>
<td>77 (26%)</td>
</tr>
<tr>
<td>Number (%) with known age of death</td>
<td>33</td>
</tr>
<tr>
<td>Mean ± SD age at death (y)</td>
<td>67.8 ± 7.8</td>
</tr>
</tbody>
</table>

*No individual with biomarker/path evidence for a non-AD diagnosis were included.
rs744373 upstream of BIN1 (OR = 1.2 [1.01–1.43], P = .04, $P_{GC} = .05$) reached nominal significance but did not surpass our Bonferroni corrected threshold of $P < .002$. Other candidate SNPs showed no evidence of association.

In the subset of individuals with either biomarker (CSF or amyloid PET) or pathologic evidence for underlying AD ($n = 82$), rs2075650 (at the APOE/TOMM40 locus, subsequently referred to as APOE) was again identified as a risk factor with a similar OR to the whole group (OR = 2.00 [1.39–2.89], $P = 9 \times 10^{-5}$, $P_{GC} = 1 \times 10^{-4}$). rs3818361 (CRI) and rs3764650 (ABCA7) both showed nominally significant differences compared with controls (CR1 OR = 1.7 [1.20–2.41], $P = .003$, $P_{GC} = .004$; ABCA7 OR = 1.83 [1.17–2.86], $P = .009$, $P_{GC} = .01$). There was no evidence for an effect of BIN1 (OR = 1.08 [0.76–1.52], $P = .65$) in the biomarker cohort.

Fig. 1. Manhattan plot of autosomes with threshold for genome-wide significance ($P < 5 \times 10^{-8}$) indicated by the red line. Four loci achieved statistical significance at APOE (chromosome 19), SEMA3C (chromosome 7), FAM46A (chromosome 6), and CNTNAP5 (chromosome 2).

Fig. 2. SNP annotation and proxy (SNAP) plots for five regions of interest. These plots illustrate the statistical evidence of association at a locus together with information about nearby genes and linkage disequilibrium between the most strongly associated SNP and its neighbors on the chromosome.
3.3. Comparing risk for PCA to typical AD

Comparing odds ratios and the nominal risk conferred in the whole PCA cohort against the most recently published meta-meta studies of typical AD [16], the effect size seen at the APOE locus was significantly less strong in PCA than for typical AD (PCA: OR 2.03, typical AD: OR 2.83, \( P = 0.0007, P_{GC} = 0.01 \), see methods). Although there was no evidence for risk in PCA vs controls, the risk effects at \( P = 0.02, P_{GC} = 0.02 \) and showed any evidence of association with typical AD on chromosome 6, downstream of FAM46A (OR 3.2 [2.1–4.9], \( P = 1.1 \times 10^{-9}, P_{GC} = 3 \times 10^{-9} \), Fig. 2E) were all associated with PCA. 

Restricting the analysis to the 82 individuals with biomarker/pathology evidence for underlying AD pathology, the corresponding odds ratios were similar: 3.8 [1.8–8.2], \( P = 2.8 \times 10^{-4} \) for rs2525776; 1.8 [1.2–2.7], \( P = 2.1 \times 10^{-3} \) for rs6854344; and 2.5 [1.0–6.1], \( P = 2.7 \times 10^{-2} \) for rs72907046. None of these three loci showed any evidence of association with typical AD on the IGAP AD-risk GWAS meta-analysis. A full list of suggestive associations \( P < 10^{-4} \) based on the SNPs represented on case and control arrays (the intersection SNPs) is available in a Supplementary Table 2, and the entire data set is available at the NHGRI-EBI GWAS Catalog.

3.4. Exploratory GWAS

As several different array platforms were used in the study, only 210,670 SNPs were genotyped across all samples. In this set, there was little evidence of inflation in the association test statistic (\( \lambda = 1.05 \)). Only the proxy for the APOE E4 AD-risk allele, rs2075650, achieved genome-wide significance. We went on to analyze 5.9-M SNPs in the imputed data set. Aside from chromosome 19 (APOE locus), three loci on chromosomes 7, 2, and 6 respectively were of interest (Fig. 1). At \( P = 3.25 \times 10^{-7} \) on chromosome 7, upstream of SEMA3C (OR 3.3 [2.1–5.1], \( P = 1.4 \times 10^{-8}, P_{GC} = 4 \times 10^{-8} \), Fig. 2C); rs6854344 on chromosome 2, upstream of CNTNAP5 (OR 1.9 [1.5–2.3], \( P = 8.0 \times 10^{-10}, P_{GC} = 2 \times 10^{-9} \), Fig. 2D), and rs72907046 on chromosome 6, downstream of FAM46A (OR 3.2 [2.1–4.9], \( P = 1.1 \times 10^{-9}, P_{GC} = 3 \times 10^{-9} \), Fig. 2E) were all associated with PCA. Restricting the analysis to the 82 individuals with biomarker/pathology evidence for underlying AD pathology, the corresponding odds ratios were similar: 3.8 [1.8–8.2], \( P = 2.8 \times 10^{-4} \) for rs2525776; 1.8 [1.2–2.7], \( P = 2.1 \times 10^{-3} \) for rs6854344; and 2.5 [1.0–6.1], \( P = 2.7 \times 10^{-2} \) for rs72907046. None of these three loci showed any evidence of association with typical AD on the IGAP AD-risk GWAS meta-analysis. A full list of suggestive associations \( P < 10^{-4} \) based on the SNPs represented on case and control arrays (the intersection SNPs) is available in a Supplementary Table 2, and the entire data set is available at the NHGRI-EBI GWAS Catalog.

4. Discussion

We report findings from a consortium to study genetic risk factors in PCA, a rare predominantly early-onset cognitive disorder characterized by progressive and disproportionately posterior cortical dysfunction and atrophy, and usually associated with AD-type pathology. Our primary aim was to explore the relationship between PCA and a pre-determined list of candidate SNPs derived from studies of
statically significant, the four risk loci we report for typical AD (Table 3). CRII has multiple functions including the regulation of complement and phagocytosis of immune complexes and pathogens, which are increasingly though to be relevant to AD pathogenesis [26]. ABCA7 may play a role in AD through regulation of phagocytosis or lipid metabolism. BNI1 mechanisms in AD are unclear but may be involved in endocytosis and the recycling of endocytic vesicles [27].

Although they did not confer significant alteration of PCA risk, we found that odds ratio confidence intervals for SNPs at or near to INPP5D and NME8 in PCA did not overlap those of typical AD and showed directionally opposite effects, INPP5D was identified as a risk factor for AD in a recent large meta-analysis and plays an important role in a number of inflammatory processes. There is little evidence for the function of NME8 in the central nervous system, although a role in modification of oxidative stress has been proposed [28]. Although these findings were only nominally significant and need independent replication, they do raise the possibility that syndromic variants of AD may be differentially associated with alterations in certain risk genes, perhaps through altered responses to inflammation or stress.

The results of our exploratory genome-wide study implicate three potential strong risk loci, near to CNTNAP5, FAM46A, and upstream of SEMA3C. The regions of strong LD with these associations did not include directly genotyped SNPs across all platforms, and therefore false-positive associations related to differential accuracy of imputation between case and control arm of the study remain possible. With the caveat that these findings must therefore be considered preliminary and require follow-up replication in an independent sample and by direct genotyping, it is notable that all three genes have roles in processes potentially relevant to PCA. Contactin-associated protein-like 5 gene (CNTNAP5) belongs to a subgroup of the neurexin family of multidomain transmembrane proteins involved in cell adhesion and intercellular communication in the central nervous system and has been implicated as a risk factor for bipolar disorder and autism spectrum disorders [29]. Family with sequence similarity 46, member A1 (FAM46A), originally C6orf37, is preferentially expressed within the neural retina [30] and has been implicated in cell signaling pathways related to retinal neurodegeneration [31]. Class III semaphorins including Semaphorin 3C (SEMA3C) have been examined as potential modifying factors in neurodegeneration through interactions with plexins and neuropilins. SEMA3C has been identified as a chemotrophic molecule influencing attractive guidance for cortical axon development [32]; the expression of SEMA3C and its receptors have been shown to influence the maturation of the visual system [33]; and SEMA3C is also expressed in the hippocampus, where it has a role in influencing the afferent connections of the developing hippocampus and in particular the ingrowth of septo-hippocampal connections [34], the major cholinergic connections implicated in learning and memory [35]. Finally, SEMA3C expression has been
shown to correlate with functional network connectivity within the brain [36]. Although at this stage speculative, it is possible therefore that perhaps subtle differences in cortical development might influence where pathology starts and/or how it spreads through the brain if a neurodegeneration process is initiated later in life. The fact that all three of these novel genetic risks showed nominal associations in the relatively small subset of individuals with biomarker evidence for AD and the absence of similar evidence of association in any of these genes with IGAP studies of typical AD suggest that if confirmed, these loci may be specific risks for PCA due to Alzheimer’s disease.

The main limitation of our study is the necessarily modest sample size of this very rare disorder, noting that the case numbers presented here were only achievable through the establishment of an international consortium. We plan to continue to collect further samples to allow for replication in due course. Based on standard power calculations in case-control studies, even in the favorable situation of completely accurate imputation of the functional SNP we are only adequately powered to detect effect sizes of OR >1.5, for common candidate SNPs, and the only common genetic risk factor of this strength in typical AD is APOE. We made comparisons with studies of patients diagnosed with typical AD; however, these patients and/or studies are different in multiple ways including the genotyping platforms used, later age at clinical onset, potential pathologic heterogeneity, and most probably differences in geographical location, all of which could confound the comparison. Although PCA is underpinned by AD pathology in most cases, we only had evidence for underlying AD in a proportion (~1/4), and we cannot confirm that the genetic risks we have determined are specific for the AD variant of PCA rather than the syndrome of PCA or for young onset AD. However, allowing for the fact that the confidence intervals are inevitably large, it is notable that the estimates for the odds ratios for APOE, CR1, and ABCA7, and the putative genes identified in our exploratory GWAS were similar or larger in the proportion with molecular evidence for AD, suggesting that the risk we identify are likely to be for the AD variant of PCA, rather than for the syndrome per se.

One of the major outstanding issues in neurodegenerative disease research is an explanation for the often very striking phenotypic heterogeneity underpinned by the same broad core pathology. Possibilities for phenotype modification include demographic and environmental factors, including age at onset, or perhaps more likely complex gene and/or environment interactions and/or factors related to the misfolded proteins and their propagation, tissue or network selectivity and toxicity. The results of this study suggest that subtle differences in established risk factors may be associated with some of this heterogeneity and provide testable suggestions for novel genes that may influence the development of the hippocampal and visual system, which may influence the development of the PCA phenotype relative to other syndromes. If confirmed in future studies, next generation sequencing may be useful in determining whether these findings might be underpinned by rare variants with large effect sizes. More broadly, genetic investigation of well-phenotyped AD variants may provide important insights into disease biology in typical AD.

Acknowledgments

We acknowledge the support of the Alzheimer’s Association’s International Society to Advance Alzheimer’s Research and Treatment (ISTAART), Alzheimer’s Research UK, the UK Alzheimer’s Society and the Raena Franklin-Pollen Fund. This work was supported by the NIHR UCL/UCLH Biomedical Research Centre, the NIHR Queen Square Dementia Biomedical Research Unit, the Wolfson Foundation, and the UK Medical Research Council. The Dementia Research Centre is an Alzheimer’s Research UK Coordinating Center. N.C.F. and M.N.R. are NIHR senior investigators. J.T.B. receives funding from the UK Alzheimer’s Society. This work was also supported by the Medical Research Council Dementias Platform UK (MR/L023784/1 and MR/009076/1); Alzheimer’s Research UK (Senior Research Fellowship to S.C., Research Fellowship to T.S.); the Dunhill Medical Trust (grant number R337/0214 to S.C.); ESRC/NIHR (ES/K006711/1 to S.C.); EPSRC (EP/M006093/1 to S.C.); Alzheimer’s Association (MNIRGD 2013 award to M.M.C.); Mayo Alzheimer’s Disease Research Center (P50 AG0016574 to D.W.D., N.E.-T., N.R.G.-R., B.F.B., D.S.K., R.C.P.); National Institute on Aging (R01 AG032990 and U01 AG046139 to N.E.-T.; R01-AG045611 to G.D.R.); National Institute of Neurological Disorders and Stroke (R01 NS080820 to N.E.-T.; John Douglas French Alzheimer’s Foundation (to G.D.R., B.L.M.); and State of California Department of Health Services Alzheimer’s Disease Research Centre of California (04-33516, B.L.M.). D.G. and E.S. are supported by Italian Ministry of Health (Ricerca Corrente). W.M.d.v.D., P.S. receive funding from PERADES-JPND. E.L. receives funding from Stichting Dioraphte. Case ascertainment in Australia was funded by grants from the National Health and Medical Research Council of Australia (NHMRC program grant #1037746) and the Australian Research Council Centre of Excellence in Cognition and its Disorders Memory Node (#CE110001021); G.H. is a NHMRC senior principal research fellow (#10709679). We would like to thank the participants in the Framingham, Geisinger, WTCCC, and KORA studies used as controls in this article. The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University (Contract No. N01-HC-25195). This article was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or NHLBI. SHARE Illumina genotyping was provided under an agreement between Illumina and Boston University. Samples and data in this study
were also provided by the Geisinger MyCode Project. Funding for the MyCode project was provided by a grant from Commonwealth of Pennsylvania and the Clinic Research Fund of Geisinger Clinic. Funding support for the genotyping of the MyCode cohort was provided by a Geisinger Clinic operating funds and an award from the Clinic Research Fund. The data sets used for the analyses described in this article were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession number phs00381v1.p1. This study also makes use of the data generated by the Wellcome Trust Case Control Consortium. A full list of the investigators who contributed to the generation of the data is available from www.wtccc.org.uk. Funding for the project was provided by the Wellcome Trust under award 076113.

Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jalz.2016.01.010.

RESEARCH IN CONTEXT

1. Systematic review: Reviewing the literature for publications investigating the genetics of posterior cortical atrophy (PCA), there is conflicting evidence for the role of APOE in the PCA variant of Alzheimer’s disease AD), and limited evidence for the more recently identified genetic risks for AD.

2. Interpretation: Through the establishment of an international consortium to create the largest study exploring the genetics of PCA to date, we demonstrate that (1) APOE is a risk factor for PCA but confers a smaller risk than for typical AD; (2) some of the genetic risks for typical AD are also associated with PCA risk; and (3) nominate three novel risk loci for PCA.

3. Future directions: These data provide clear directions and testable hypotheses for future studies, including (1) the establishment of a replication cohort and (2) investigation of the identified genes as factors influencing selective vulnerability in AD.

References


