PAPER

Genetic variability in the insulin signalling pathway may contribute to the risk of late onset Alzheimer’s disease

D Liolitsa, J Powell, S Lovestone

Objective: To test the hypothesis that polymorphic variation in insulin signalling genes may underlie the shared risk of dysfunctional insulin signalling and late onset Alzheimer’s disease (AD). The p85α subunit of phosphatidyl inositol 3 kinase (PIK3R1) and the regulatory subunit 3 of protein phosphatase 1 (PPP1R3) were selected as candidate genes because both encode key proteins involved in insulin signalling and because polymorphisms in these genes have been previously implicated in insulin resistance or type II diabetes.

Methods: Analysis of the Met326Ile PIK3R1 and the Asp905Tyr PPP1R3 polymorphisms in 202 patients with late onset AD and 160 or 170 age matched normal subjects.

Results: Logistic regression analysis using the recessive genetic model showed significant differences in genotype and allelic frequencies between the AD group and normal controls (genotypes: odds ratio (OR) 2.09, 95% confidence interval (CI) 1.17 to 3.74, \( p = 0.01 \); alleles: OR 1.99, 95% CI 1.17 to 3.40, \( p = 0.01 \) for the Met326Ile PIK3R1 polymorphism that were female specific. Additionally, in the dominant genetic model a marginally significant association in genotype frequencies between the Asp905Tyr PPP1R3 polymorphism and AD was observed (genotypes: OR 1.85, 95% CI 1.03 to 3.30, \( p = 0.04 \); alleles: OR 1.68, 95% CI 0.98 to 2.88, \( p = 0.06 \)). Both polymorphisms were tested for their interactions with sex and the presence of the apolipoprotein E ε4 allele.

Conclusions: The results support the hypothesis for a common genetic aetiology predisposing to insulin resistance and AD.

METHODS

Subjects

Two hundred and two patients with late onset AD were recruited from the Camberwell/Southwark Dementia Case Register, a community based study in South London.

The diagnostic process for this group of patients has been described previously and, in brief, includes a clinical interview, an assessment with the Manchester and Oxford University scale for the psychological assessment of dementia, a Cambridge examination for mental disorders of the elderly, a mini-mental state examination, and a physical examination. Dementia was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria, the National Institute of Neurological Disorders and Stroke in association with the Association Internationale pour la Recherche et l’Enseignement en Neurosciences criteria for vascular dementia, and the Newcastle criteria for dementia with Lewy bodies. Only patients who met the NINCDS-ADRDA criteria for probable or possible AD participated in this study. Where patients had the capacity, consent was obtained. Where they lacked such capacity, agreement from a near relative was obtained. The subjects were aged above 70 years and were white. The control group consisted of a subset of 160/170 elderly people over 75 years old resident in the UK from the

Abbreviations: AD, Alzheimer’s disease; ADRDA, Alzheimer’s Disease and Related Disorders Association; APP, amyloid precursor protein; GSK 3, glycogen synthase kinase 3; IGF 1, insulin-like growth factor 1; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke; OR, odds ratio; PIK3, phosphatidylinositol 3 kinase; PIK3R1, p85α regulatory subunit of phosphatidylinositol 3 kinase; PKB, protein kinase B; PPI, protein phosphatase 1; PPP1R3, regulatory subunit 3 of protein phosphatase 1

A lzheimer’s disease (AD) is the most common cause of dementia in the old population and is characterised by progressive loss of cognition and personality changes. Several genetic risk factors have been identified but little is known about the complex aetiology of AD linked to the pathogenesis of the disease. Recent epidemiological evidence suggests that cardiovascular disorders and their risk factors such as hypertension and type II diabetes are also risk factors for late onset AD. Furthermore, it was reported that the prevalence of the insulin resistance syndrome is also associated with AD. Postmortem studies have found no significant differences in the concentrations of insulin in the brain between control and AD subjects; nevertheless, there is evidence of altered insulin signalling as the abundance of insulin receptors is increased and tyrosine kinase activity is decreased in the brain of AD patients compared with control subjects. Moreover, biochemical evidence indicates that insulin dysfunction may be directly related to the two histopathological hallmarks of AD, the presence in the brain of amyloid plaques and neurofibrillary tangles. These findings suggested that an impaired insulin mediated signal transduction system may underlie the pathogenesis of this disorder and may imply a common genetic aetiology for AD and vascular disease.

Here, we targeted phosphatidyl inositol 3 kinase (PI3-K) and protein phosphatase 1 (PP1) because they are key components of the insulin signalling pathway. They are also involved in the regulation of tau phosphorylation and amyloid precursor protein (APP) processing. PI3-K and PP1 comprise regulatory and catalytic subunits, and we examined the relation with AD of the 1020G→A (Met326Ile) polymorphism in the p85α regulatory subunit of PI3-K (PIK3R1) and the 2713G→T (Asp905Tyr) polymorphism in the regulatory subunit 3 of PP1 (PPP1R3).
Morphism of PPP1R3 was carried out by polymerase chain reaction using MgCl₂ and 0.05 U Taq polymerase in 1 × Taq enzyme buffer consisting of 10 mM Tris Cl (pH 8.3), 50 mM KCl, and 0.001% wt/vol gelatin. After initial denaturation at 94°C for five minutes, 30 cycles of amplification were performed with denaturation at 94°C for 30 seconds, annealing for 30 seconds at the temperature optimised for each primer pair, and extension at 72°C for 45 seconds, followed by a final extension at 72°C for 10 minutes. The bands were visualised with silver stained polyacrylamide gels (10%).

Genetic analysis
DNA was extracted from peripheral blood leucocytes using the Nucleon BACC2 kit (Amersham Biosciences, Little Chalfont, UK) and following a standard procedure involving deproteinisation with sodium perchlorate and chloroform/NucleonResin extraction. The DNA was diluted to 25 ng/µl and stored in 96 deep well plates at −20°C for their use in the experiments. Genotyping for the Met326Ile polymorphism in the p85α regulatory subunit of phosphatidylinositol 3 kinase (PIK3R1) was carried out by mismatched polymerase chain reaction followed by NdeI restriction enzyme digestion, as previously described. Genotyping for the Asp905Tyr polymorphism in PPP1R3 was carried out by polymerase chain reaction and followed by restriction enzyme digestion with Ddel as described previously. DNA was amplified in a 25 µl volume containing 50–100 ng genomic DNA, 0.5 pmol of each primer, 200 µM deoxynucleotide triphosphates, 2.0–2.5 mM MgCl₂, and 0.05 U Taq polymerase in 1× enzyme buffer consisting of 10 mM Tris Cl (pH 8.3), 50 mM KCl, and 0.001% wt/vol gelatin. After initial denaturation at 94°C for five minutes, 30 cycles of amplification were performed with denaturation at 94°C for 30 seconds, annealing for 30 seconds at the temperature optimised for each primer pair, and extension at 72°C for 45 seconds, followed by a final extension at 72°C for 10 minutes. The bands were visualised with silver stained polyacrylamide gels (10%).

Association study
The case and control groups were compared by logistic regression analysis to test for variation in the genotypic and allelic frequencies between AD subjects and controls, and p < 0.05 was considered significant. Odds ratios (OR) with 95% confidence intervals (CI) were estimated for the effects of high risk genotypes and alleles. All comparisons were adjusted for the effects of apolipoprotein E allele e4 on AD. The values for statistical power of the samples were estimated with the aid of the computer package EpInfo (version 6, Epidemiology Program Office, Atlanta, Georgia, USA), and in each case 95% was the level of confidence. Compliance with the Hardy–Weinberg equilibrium was examined in χ² tests using the EpInfo software package.

RESULTS
The average (SD) age at onset of AD in patients was 82.3 (6.7) years and in the control group (n = 170) was 80.4 (4.3) years. Case and control groups were genotyped for the Met326Ile polymorphism in PIK3R1 and the Asp905Tyr in PPP1R3. Genotype and allele frequencies of the Met326Ile polymorphism in PIK3R1 subunit did not differ significantly between the total AD group (75% for 1020-G/G and 25% for 1020-G/A plus 1020-A/A) and the controls (66 and 34, respectively; OR 1.60, 95% CI 0.98 to 2.62, p = 0.06; table 1). Examination of the interactions between sex, apolipoprotein E e4, and PIK3R1 genotype showed that there is an interaction between the 1020-G/G genotype and female sex. Therefore, the association was analysed after stratification by sex, confirming that the frequency of the 1020-G/G genotype was significantly higher than the sum of 1020-G/A and 1020-A/A genotype frequencies only in the female members (76 and 24, AD female group v 61 and 39, control female group, p = 0.01). The OR for the effect of the 1020-G/G genotype was 2.09 (95% CI 1.17 to 3.74). Similarly, allele-wise comparisons resulted in significance for the female group due to a higher frequency of the 1020-G allele and a lower 1020-A allele frequency in AD female subjects than in normal female controls (87% for 1020-G and 13% 1020-A, respectively, p = 0.01; table 1). Calculation of the OR indicated that carriers of the 1020-G allele were 1.99 times more likely to develop AD (95% CI 1.17 to 3.40). These effects remained significant after Bonferroni correction in the stratified sample (p = 0.03 for the 1020-G/G genotype and p = 0.02 for the 1020-G allele).

Table 1 Genotype and allele frequencies of the Met326Ile p85α regulatory subunit of phosphatidylinositol 3 kinase (PIK3R1) polymorphism resulting from the 1020-G/A base substitution in 202 patients with Alzheimer’s disease (AD) and 170 age matched controls for the total population and after stratification by sex. Results from logistic regression analysis are also presented.

<table>
<thead>
<tr>
<th>Alleles</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD (n=202)</td>
<td>Controls (n=170)</td>
<td>AD (n=44)</td>
</tr>
<tr>
<td>Alleles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>151 (0.75)</td>
<td>112 (0.66)</td>
<td>32 (0.73)</td>
</tr>
<tr>
<td>A</td>
<td>48 (0.24)</td>
<td>54 (0.32)</td>
<td>11 (0.25)</td>
</tr>
<tr>
<td>O</td>
<td>3 (0.01)</td>
<td>4 (0.02)</td>
<td>1 (0.02)</td>
</tr>
<tr>
<td>G OR</td>
<td>1.60, CI 0.98 to 2.62, p=0.06</td>
<td>1.60, CI 0.98 to 2.62, p=0.06</td>
<td>1.60, CI 0.98 to 2.62, p=0.06</td>
</tr>
<tr>
<td>A OR</td>
<td>0.83, CI 0.34 to 2.03, p=0.68</td>
<td>0.83, CI 0.34 to 2.03, p=0.68</td>
<td>0.83, CI 0.34 to 2.03, p=0.68</td>
</tr>
<tr>
<td>G+G</td>
<td>151 (0.75)</td>
<td>112 (0.66)</td>
<td>32 (0.73)</td>
</tr>
<tr>
<td>A+G</td>
<td>54 (0.13)</td>
<td>62 (0.18)</td>
<td>13 (0.16)</td>
</tr>
<tr>
<td>G+G</td>
<td>151 (0.75)</td>
<td>112 (0.66)</td>
<td>32 (0.73)</td>
</tr>
</tbody>
</table>

CI, 95% confidence interval; OR, odds ratio. *p<0.05. Data are number (%).
dosage \( (p = 0.01) \). All above comparisons were adjusted for the effects of sex on AD. Significance remained after Bonferroni correction for multiple testing \( (p = 0.02 \text{ for GG genotype and } p = 0.02 \text{ for G allele}) \). Therefore, the Met326Tyr polymorphism of PIK3R1 modifies the risk for AD in the female members and for patients where the AD phenotype is not explained by the effects of apolipoprotein E.

A significant association was also found between the genotypes of the Asp905Tyr PPP1R3 polymorphism and AD, with the T allele-bearing genotypes being more frequent among the AD group \( (76\% \text{ for } 2713-G/G \text{ and } 24\% \text{ for } 2713-G/T \text{ plus } 2713-T/T, \text{ AD group } v 84\% \text{ and } 16\%, \text{ respectively for the control group}) \). Logistic regression analysis showed that the association was significant for the total group of subjects \( \text{(genotypes: OR 1.85, CI 1.03 to 3.30, } p = 0.04; \text{ alleles: OR 1.68, CI 0.98 to 2.88, } p = 0.06; \text{ table 3}) \). No significant interactions were found between sex or apolipoprotein E \( e^4 \text{ allele and the PPP1R3 genotype. Stratification by apolipoprotein E } e^4 \text{ allele of the AD patients and controls resulted in slightly reduced effects compared with the non-stratified sample, with a nearly significant increased risk for AD by the presence of GT and TT genotypes in the non-apolipoprotein E e^4 carriers)}.

### Table 2

<table>
<thead>
<tr>
<th>Genotype and allele frequencies of the Met326Ile PIK3R1 polymorphism resulting from the 1020-G/A base substitution in female patients with AD and age matched controls stratified by apolipoprotein E ( e^4 ) allele carriers and apolipoprotein E ( e^4 ) allele non-carriers, and results from statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIK3R1</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Genotypes</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>GG</td>
</tr>
<tr>
<td>GA</td>
</tr>
<tr>
<td>AA</td>
</tr>
<tr>
<td><strong>Alleles</strong></td>
</tr>
<tr>
<td>G</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>OR 1.92, CI 1.05 to 3.51, ( p = 0.03^* )</td>
</tr>
</tbody>
</table>

*p<0.05. Data are number [%].

### Table 3

<table>
<thead>
<tr>
<th>Genotype and allele frequencies of the Asp905Tyr polymorphism of regulatory subunit 3 of protein phosphatase 1 (PPP1R3) resulting from the 2713-G/T base substitution in 202 patients with AD and 160 age matched controls for the total population and after stratification by apolipoprotein E ( e^4 ) allele. Results from logistic regression analysis are also presented</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPP1R3</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Genotypes</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>GG</td>
</tr>
<tr>
<td>GT</td>
</tr>
<tr>
<td>TT</td>
</tr>
<tr>
<td>OR 1.85, CI 1.03 to 3.30, ( p = 0.04^* )</td>
</tr>
<tr>
<td><strong>Alleles</strong></td>
</tr>
<tr>
<td>G</td>
</tr>
<tr>
<td>T</td>
</tr>
<tr>
<td>OR 1.68, CI 0.98 to 2.88, ( p = 0.06 )</td>
</tr>
</tbody>
</table>

*p<0.05. Data are number [%].

### Table 4

Comparison of probable with possible AD according to National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association criteria

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3R1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable + possible</td>
<td>1.60</td>
<td>0.98 to 2.62</td>
<td>0.83</td>
</tr>
<tr>
<td>Probable</td>
<td>1.24</td>
<td>0.79 to 2.37</td>
<td>0.61</td>
</tr>
<tr>
<td>Possible</td>
<td>1.86</td>
<td>0.92 to 3.78</td>
<td>3.80</td>
</tr>
<tr>
<td>PPP1R3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable + possible</td>
<td>1.85</td>
<td>1.03 to 3.30</td>
<td>1.95</td>
</tr>
<tr>
<td>Probable</td>
<td>1.56</td>
<td>0.82 to 2.60</td>
<td>0.39</td>
</tr>
<tr>
<td>Possible</td>
<td>2.02</td>
<td>1.04 to 3.92</td>
<td>2.41</td>
</tr>
</tbody>
</table>

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e4 carriers (OR 1.95, 95% CI 0.98 to 3.85, p = 0.06) and no effect among the e4 carriers (OR 1.62, 95% CI 0.35 to 4.77, p = 0.38; table 3). This was probably due to loss of power in the reduced size of the sample after stratification. The results did not remain significant after Bonferroni correction.

Finally, to determine whether confidence of diagnosis affected the strength of the associations, we separately analysed probable from possible AD. In most analyses ORs did not differ much between possible AD and probable AD, but the sample is too small to test confidently for an association in these multiply stratified analyses (table 4). For PIK3R1 no analysis gave a significant OR that was greater for possible AD than for probable AD, suggesting that these associations are true associations with AD and not with other dementias. For PPP1R3 the OR for both the apolipoprotein E e4 positive group and the combined apolipoprotein E groups was higher for possible AD than for probable AD (95% CI 1–1 in each).

DISCUSSION

Increasing evidence suggests that late onset AD has some phenotypic and pathological features in common with type II diabetes (non-insulin dependent diabetes mellitus), suggesting that the two disorders may share a similar aetiology. Epidemiological studies have shown that the complications of type II diabetes, namely stroke and hypertension, are also risk factors for dementia or AD. Case-control and prospective studies have suggested that cognition is impaired in patients with non-insulin dependent diabetes mellitus, and cross sectional studies have reported that diabetes is a risk factor for dementia in general and even specifically for AD. Type II diabetes may increase the risk of AD through the known vascular consequences such as stroke and hypertension. However, insulin resistance is also a risk factor for AD, suggesting that the risk is through a failure of insulin signalling itself rather than the consequences of that failure. In line with this, the abundance of insulin receptors in the AD brain is increased, possibly to compensate for an impaired insulin signal transduction system, and insulin activity is reduced.

If insulin signalling has an important role in AD pathogenesis then polymorphic variation in the normal population, underlining variation in the genes encoding components of the insulin transduction system, and leading to the quantitative trait of relative insulin resistance, would also underlie population variation in the risk of AD. Indeed, studies in our laboratories have found evidence for an association between late onset AD and polymorphic variation in the gene encoding angiotensin I converting enzyme, which has also been identified as a risk factor for insulin resistance abnormalities. Firstly, we examined whether polymorphic variation in the gene encoding PIK3R1 is associated with genetic risk for late AD because PI3-K holds a key position in mediating multiple downstream metabolic effects of insulin. The p85 subunit exists in two isoforms; p85α (PIK3R1) and p85β (PIK3R2). We identified a female specific significant association between the homozygous form of the Met326Tyr PIK3R1 polymorphism and AD. This polymorphism has been previously associated with insulin response but not with type II diabetes per se. Another study reported an association of the homozygous form of Met326 with type II diabetes in Pima women, a finding consistent with the sex specificity of the effect in our study. The frequency of the polymorphism in our sample was similar to that of the Centre d’Etude du Polymorphisme humain samples (0.83 and 0.17 for the Met-326 and Ile-326 alleles, respectively) and slightly lower than the frequency among the Pima population (0.75 and 0.25, respectively). Therefore, there seem to be ethnicity specific and sex specific differences in the frequency distribution of the Met326Tyr PIK3R1 polymorphism. We also assessed the frequency of this polymorphism after stratification of the sample by apolipoprotein E allele e4. The association was more profound among the female non-carriers of apolipoprotein E allele e4, suggesting that these polymorphisms explain the risk of AD independently of apolipoprotein E. This is consistent with the finding of changes in plasma insulin concentrations, which are suggestive of insulin resistance, in patients with AD who are non-e4 carriers.

Subsequently, we examined whether polymorphic variation in the gene encoding PPP1R3 is a risk factor for AD because of the observed role of PPI1 in insulin stimulated inhibition of glycogen synthase kinase 3 (GSK 3) and the previously reported associations of polymorphisms in PPP1R3 and insulin resistance abnormalities. Furthermore, PPI1 regulates downstream events leading to the generation of neurofibrillary tangles, and recent studies have suggested that PPI1 can maintain low levels of phosphorylation of tau when it is bound to microtubules. PPI1 is a serine-threonine phosphatase consisting of at least three isoforms of catalytic subunit—PPP1CA, PPP1CB, and PPP2CA—encoded by different genes. All three subtypes bind to PPP1R3, also named glycogen associated subunit of PI1. We looked at the Asp905Tyr polymorphism and we identified an increased prevalence of the Tyr905 allele-bearing genotypes among the AD group compared with the controls. The association was in the same direction as that identified by Hansen and colleagues for features of the insulin resistance syndrome. It is noteworthy that such an association with insulin resistance has not been found universally in different ethnic groups.

It is possible that the association between dementia and diabetes is with vascular dementia and not AD, although community based studies continue to find an association with both vascular dementia and AD independently. Perhaps this is not surprising, as even in AD there is some vascular change and in turn isolated vascular disease is not a common cause of dementia. We think it unlikely that our sample was significantly contaminated with true vascular dementia. Previously the clinical diagnostic accuracy of the Camberwell case register was examined with respect to postmortem examination, finding a positive predictive value of 0.92 for probable AD according to the NINCDS criteria. However, in our sample as in all other studies there were high rates of mixed pathology and so we cannot exclude an effect of the polymorphic variation we identified on the secondary pathology often found in AD. PIK2R1 is as strongly associated with probable as with possible AD but the strength of the association is more robust between PPP1R3 and possible AD than it is with probable AD. As possible AD is most likely to be a mixed dementia, this might indicate that polymorphic variation in PPP1R3 is associated with increased non-AD pathology—vascular disease, for example. However, the number of possible AD cases in this sample is relatively small for such analyses to be treated with confidence and we would not want to put too much weight on a small difference between possible and probable AD.

It is more likely, however, that the findings of the present study, showing genetic variability in PIK3R1 and PPP1R3 in association with late onset AD, indicate a common underlying aetiology for insulin resistance and late onset AD due to genetic variation in genes encoding components of the insulin triggered cascade. The two hallmark processes of AD are the metabolism of APP leading to amyloid production and deposition in plaques, and the phosphorylation and aggregation of tau in neurofibrillary tangles. Insulin has been shown to have a role in both. Tau is phosphorylated in cells and in neurons by GSK 3, a kinase first discovered through its role in insulin signalling. Insulin signalling leads to inhibition of GSK 3 and in neurons leads to a decrease in tau phosphorylation. Mutations in PS-1 causing AD also interact with insulin signalling through protein kinase B (PKB), leading to an increase in GSK 3β activity. Starvation induced hypoglycaemia and subsequent reduced insulin availability in mice results in tau hyperphosphorylation in the hippocampus. 

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Insulin signalling may therefore protect against the tau phosphorylation component of AD pathogenesis.

Recent evidence suggests that insulin may also be protective of the amyloid component. APP is metabolized either by α-secretase to yield non-amyloidogenic products or by β and γ-secretase to produce amyloid. Insulin increases soluble APPβ42.

Furthermore, both insulin and insulin-like growth factor 1 (IGF 1) enhance amyloid resistance and late-onset AD share a common genetic effect of IGF 1 are compensated by presenilin 1 mutations. Nonetheless, the present findings suggest that genetic scales for the psychopathological assessment of dementia (MOUSEPAD).

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Competing interests: none declared

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