Gene association study of the Urokinase Plasminogen Activator and its Receptor gene in Alzheimer's Disease

Running Title: suPAR association

Ozde **Cetinsoy** [1]; Ijeoma **Anyanwu**[1]; Harikrishnan **Krishnanand**[1]; Gokulakrishnan **Natarajan**[1]; Naveen **Ramachandran**[1]; Alan **Thomas**[2]; Keeley, J **Brookes** [1*]

1. Biosciences, Clifton Campus, Nottingham Trent University, Nottingham UK
2. Director of Brains for Dementia Research; Faculty of Medical Sciences, Newcastle University, Newcastle, UK

*Corresponding Author: Keeley Brookes keeley.brookes@ntu.ac.uk

Abstract:

Background: The role of the innate immune system has long been associated with Alzheimer's disease (AD). There is now accumulating evidence that the soluble Urokinase Plasminogen Activator Receptor pathway, and its genes, *PLAU* and *PLAUR* may be important in AD, and yet there have been few genetic association studies to explore this.

Objectives: This study utilises the DNA bank of the Brains for Dementia Research cohort to investigate the genetic association of common polymorphisms across the *PLAU* and *PLAUR* genes with AD.

Methods: TaqMan genotyping assays were used with standard procedures followed by association analysis in PLINK.

Results: No association was observed between the *PLAU* gene and AD, however two SNPs located in the *PLAUR* gene were indicative of a trend towards association but did not surpass multiple testing significance thresholds.

Conclusions: Further genotyping studies and exploration of the consequences of these SNPs on gene expression and alternative splicing are warranted to fully uncover the role this system may have in AD.

Keywords: Alzheimer's Disease, suPAR, *PLAUR*, *PLAU*, BDR; Association; Innate immune system

Introduction:

Neuroinflammation is now established as one of the key hallmarks and possible contributors of Alzheimer's Disease (AD) [1], with both the role of inflammation and gene associated with the innate immune system providing key evidence, which is extensively reviewed in the literature [2–5]. The accumulation of AD hallmarks (amyloid-β plaques and tau tangles) in the brain are thought to invoke the central nervous systems innate immune system via microglial activation [6]. Microglia are the resident immune cells of the human brain. Under normal conditions, microglia act to help clear amyloid-β and regulate inflammatory processes; however, over-activation is suspected to be key in the neuropathology of AD. These microglia release pro-inflammatory markers creating chronic neuroinflammation in the brain, with this neuroinflammation hypothesised to be the cause of neuronal cell death and cognitive decline [1,7].

Similarly, systemic inflammation has consistently been associated with AD [8]. Some evidence suggests that the presence of persistent systemic inflammation can lead to neuroinflammation [9] and could be mediated by increased permeability of the blood-brain barrier [10]. The elevation of systemic inflammation could be seen as an early marker of an overactive immune system which could also serve as a biomarker for individuals at high risk from AD.

Multiple studies demonstrate that C-reactive protein (CRP), a non-specific marker of inflammation, is elevated with age, and is associated with age-related comorbidities [11], with meta-analyses indicating an increased level for CRP and other inflammatory markers in AD and dementia [8,12]. Systemic inflammation can be caused by several lifestyle factors including smoking, poor diet, and lack of exercise; these same lifestyle factors have been associated with AD and are seen as modifiable risk factors which

could account for around a third of dementia cases [13]. However, evidence for the efficacy in using anti-inflammatory drugs to prevent dementia is conflicting with multiple confounders to consider [14,15].

Genetic associations have been made between AD and genes (e.g., *CR1, CLU, TREM2*) with roles within the innate immune system that function both in the brain and systemically [16–19], and could perhaps reflect variations in the immune system activation status, with those associated with increased risk leading to an immune system that is more likely to over activate.

suPAR: A Biomarker for Immune System Activation

Although CRP is seen as the "gold-standard" for measuring levels of inflammation, it has recently been proposed that these measurements are of acute inflammation rather than a measurement of immune system activation [20]. The presence of soluble Urokinase Plasminogen Activator Receptor (suPAR) is triggered by pro-inflammatory markers leading to the "shedding" of the membrane-bound receptor to its soluble form [21] and has been suggested to provide a general measurement of persistent, low grade immune system activation rather than being an inflammatory marker itself [20,22,23].

The membrane-bound urokinase Plasminogen Activator Receptor (uPAR) is mainly expressed on immunological cells. It is a receptor for urokinase Plasminogen Activator (uPA), which when bound catalyses the conversion of inactive plasminogen to active plasmin [24], playing a role in extracellular matrix degradation. In addition, the receptor has also been shown to interact with multiple molecules, including Vitronectin and be involved in several processes including cell adhesion, migration, proliferation, survival, coagulation and homeostasis [25,26].

In relevance to AD, uPA expression is observed to be upregulated by the presence of aggregated amyloid-β. This induced expression could lead to higher levels of plasminogen being activated to plasmin, which has been found to degrade amyloid-β fibrils [27].

The cleavage of uPAR is governed by several enzymes including uPA; cleavage of the membrane-bound receptor occurs at its Glycosylphosphatidylinositol (GPI)-anchor connecting it to the cell membrane but also in the linker region found between domains I and II [28,29]

Soluble Urokinase Plasminogen Activator Receptor is found in plasma, serum, and various other bodily fluids, including cerebrospinal fluid (CSF), and is highly correlated with inflammatory biomarkers, such as TNF-α, IL-1β and IL-6 [20]. In addition, suPAR levels have been found to be impacted by several of the lifestyle factors associated with AD [30] and has been observed to be elevated (>4ng/ml) in several inflammatory disorders, predicting mortality [21]. Measuring suPAR is already being used in emergency rooms in Europe to aid triage of patients for adverse outcomes [31,32] and so could easily become part of an early-warning mid-life health screen.

Previous investigations have observed higher levels of suPAR in the CSF of those individuals with HIV-dementia and are correlated with cognitive deficits in HIV patients [33–36] . Further to this a recent investigation measuring plasma levels of suPAR in a longitudinal population study identified that participants who displayed the greatest increases in suPAR levels between the ages of 39 and 45 years, also displayed signs of accelerated aging and cognitive decline [37]. Most recently, uPA levels in CSF of patients with cerebral amyloid angiopathy were significantly higher than controls and is a suggested biomarker for this disease [38]

Emerging evidence suggest that suPAR could be used as a biomarker for those at risk from dementia, but is there an underlying genetic predisposition of the uPA/uPAR genes to lead to alteration in suPAR levels and therefore with AD? Therefore, this is a small exploratory investigation of genetic variation within the genes encoding for uPA (*PLAU*; chr10q22) and its receptor (*PLAUR*; chr19q13,) with AD using pathologically confirmed AD samples from the Brains for Dementia Research cohort.

Methods:

Samples: The Brains for Dementia Research (BDR) project is an established semi-longitudinal programme to provide a wealth of information for researchers investigating dementia, which includes post-mortem brain tissue donations [39]. Alongside the cognitive, lifestyle and neuropathological detail obtained during life and upon death, DNA has been extracted from samples of post-mortem brain tissue to create a DNA bank for research purposes and freely available whole genome data for scientific exploration [40].

The DNA bank currently stands at 1078 samples from deceased participants for whom a diagnosis has been made based on clinical and neuropathological features for genetic analyses. This cohort contains a mix of different dementias including AD, Vascular Dementia, Dementia with Lewy Bodies and Frontal Temporal Lobe Dementia alongside mixed pathologies, those with Mild Cognitive Impairment and cognitively normal controls. For this study only participants with neuropathologically confirmed AD (Clinical diagnosed with dementia with AD relevant pathology) (n=434) and controls without cognitive deficits, or neurodegenerative comorbidities/pathology (n=349) were analysed. Details on the demographics for key AD covariates can be found in Table 1, with all covariates suggesting a significant difference between the groups on ratio of females, age at death and presence of the APOE ε4 isoform.

SNP Selection & Genotyping: SNPs were selected from across the gene loci to capture genetic variation within individual linkage disequilibrium blocks (r^2>0.8) using Haploview software [41], and 1000 Genomes European genotype data with minor allele frequencies above 1%. Four SNPs were selected across the *PLAU* locus (rs2227580; rs2227562; rs2227564; rs2227571) and four across the *PLAUR* locus (rs4251909; rs4251876; rs397374; rs4251854).

In-house genotyping of the polymorphisms was conducted using TaqMan assays for these SNPs following standard protocols (Applied Biosystems/ThermoFisher Scientific). Reactions were run on the Aria Mx real-time PCR machine (Agilent Technologies).

Analysis: Association analysis was carried out in PLINKv1.9 [42]. Individual SNP association analysis was carried out using a logistic regression test correcting for the covariates biological sex, age at death and APOE ε4 allele count.

Results:

The entire BDR cohort was genotyped for eight SNPs across the *PLAU* and *PLAUR* loci. Sample duplicates for positive genotyping controls were 100% concordant. The genetic analysis presented here consists of the current neuropathology-confirmed diagnosed samples of AD (n=434) and controls (n=349) with an overall genotyping call rate of 99.1%.

Demographics of the analysis sample (Table 1) were similar to those previously reported for the BDR cohort [40], with a significant increase for age at death (p=0.0004) and a higher proportion of females in the control group (p=0.018). As expected there was a highly significant increase in the proportion of APOE ε4 positive participants in the AD group compared to the controls (p<0.00001).

	Controls (n=349)	*AD (n=434)*	*P value*
% Females	57.6%	49.1%	0.018
Average Age at Death	85.9 years (SD=10.1)	83.4 years (SD=8.6)	0.0004
Presence APOE ε4	26.6%	69.6%	<0.00001

Table 1: Demographics of the Alzheimer's disease (n=434) and control (n=349) samples explored for association in this study. Known covariates with the phenotype, biological sex, age at death and presence of the APOE ε4 isoform were all significantly different between the AD and control groups.

Quality control revealed no significant deviation from Hardy-Weinberg equilibrium ($p<0.0001$) nor 'missingness" between phenotype groups ($p>0.05$). Minor allele frequencies in the control group were similar to population estimates (Table 2).

Logistic regression analysis controlling for covariates revealed no association between the *PLAU* gene SNPs and AD phenotype, however three of the four SNPs investigated in the *PLAUR* gene demonstrated suggestive association with the AD phenotype. One SNP, rs4251854, demonstrated a significant association ($p<0.05$) with rs4251909 and rs4251876 showing a trend towards significance, however none survived Bonferroni correction at the study-wide level ($p<0.00625$).

Interestingly the effect size of the SNPs suggestive of association were in opposite directions with the minor allele (A) for rs4251876 showing a protective effect, and minor alleles for rs4251909 & rs4251854 (T and C respectively) demonstrating a risk effect.

SNP	*Chr (hg38)*	*Minor Allele*	*1000G Frequency*	*Genotyping Rate (%)*	*MAF Controls*	*MAF AD*	*OR (95% CI)*	*p value*
PLAU:								
rs2227580	10:73911598	T	0.011	98.5	0.007	0.001	0.497 (0.08-3.1)	0.455
rs2227562	10:73913203	A	0.158	99.4	0.170	0.150	0.911 (0.67-1.24)	0.549
rs2227564	10:73913343	T	0.208	99.6	0.239	0.270	1.135 (0.88-1.47)	0.340
rs2227571	10:73914982	C	0.427	98.9	0.446	0.456	1.031 (0.82-1.30)	0.796
PLAUR:								
rs4251909	19:43652589	T	0.048	98.9	0.042	0.062	1.634 (0.96-2.77)	0.068
rs4251876	19:43656898	A	0.067	99.0	0.069	0.043	0.624 (0.39-1.00)	0.053
rs397374	19:43659629	T	0.241	98.7	0.220	0.244	1.165 (0.89-1.52)	0.258
rs4251854	19:43659842	C	0.127	99.5	0.097	0.140	1.448 (1.02-2.08)	0.035

Table 2: Association results and genomic location of SNPs mapped on gene schematics from UCSC genome browser (GRCh38/hg38). None of the SNPs investigated in the *PLAU* gene demonstrated association with the AD phenotype. Conversely SNPs located within the *PLAUR* locus were suggestive of association with a mix of risk and protective alleles ($p \leqslant 0.05$). MAF = Minor Allele Frequency; OR = Odds Ratio

Discussion:

This investigation sought to find an association between polymorphisms located within the *PLAU* and *PLAUR* genes and AD, highlighting a potential genetic predisposition to an elevated innate immune system. No association was found between *PLAU* polymorphisms and AD, whereas three out of four SNPs investigated across the *PLAUR* gene were suggested of association, one was significant at the alpha level of significance but did not withstanding multiple-testing corrections.

PLAU: Despite the absence of association in the BDR cohort, previous studies have observed associations of *PLAU* polymorphisms with AD [43–46]. The *PLAU* gene lies within a replicated linkage peak for AD under chr10q21-24 [47], and observations of a potential role of plasmin (activated by uPA) to degrade amyloid-β deposits [27] have led to this gene being seen as a potential candidate for dementia.

This prompted Riemenscheider *et al* [46] to fine map the gene, genotyping 56 SNPs across the loci. The study identified two key blocks of linkage disequilibrium, one at the 5' end of the gene and one at the 3'end of the gene, with a significant break between to the blocks surrounding the rs2227564 SNP located in exon 6, a mis-sense variation changing a proline to lysine amino acid. Riemenscheider and colleagues observed the minor T-allele to be associated with increased risk for AD (p=0.02) in a much larger dataset (n=2359) but consisted of a similar number of AD cases as the BDR (n=422). However, a significant proportion of the cases had an onset of symptoms prior to 65 years old. When the sample was divided by age of onset the association was only seen in those with early-onset dementia. This study supported the earlier association finding for the Exon 6 rs2227564 (P141L) SNP; however, the observation was in the opposite direction with the original studies observing the major C-allele conferring risk for AD [45]. More recently a further association study in a Han Chinese population [48] also looked at this SNP in relation to AD, again findings an association but with the C-allele similar to Finckh et al study [45].

In addition to rs2227564 that Reimenscheider (2006) investigated the SNP rs2227562 was also in common with the polymorphisms genotyped in this study. Again, in the Reimenscheider study this SNP was found to be significantly associated ($p=0.019$) however it was found that the major G-allele increased risk for AD, whereas in the current study it was observed that the minor A-allele was more frequent in cases though not significantly different. In total the Reimenscheider study found nine SNPs to be significantly associated with AD at $p<0.05$ significance level with a further three SNPs downstream to the gene indicating suggestive association. However, this is likely due to the large haplotype blocks observed in this gene.

In addition, quantitative trait analyses have also yielded some interesting results for the *PLAU* gene [43,44]. The T-allele of the rs2227564 has been associated with AD, and age-dependent amyloid-β load in plasma [44]. Whilst the study conducted by Ozturk and colleagues [43] found evidence of a modest association with AD, as well as quantitative traits for age of onset, and disease duration, the association was found with a SNP located in the 3'UTR of *PLAU* (rs4065), but not with the rs2227564 SNP.

In contrast to the above and in-line with this study's observations, other studies have failed to find an association of these SNPs with AD [49–51]. Furthermore, sequencing of the exons of the *PLAU* gene in 96 cases, and 96 ethnicity and age-matched controls did not find any novel polymorphisms within the coding sequence. Additional case-control analysis in a larger independent dataset (cases n=652, controls n=824) did not find an association with the rs2227564, nor with two rarer coding SNPs in exon 2 and 8 [49]. A later study using a much smaller cohort also did not find any association with rs2227564 nor an association with age of onset [50]. Finally, a study of two small independent European cohorts also did not find an association with this SNP, nor with an effect on cognitive abilities [51]. Interestingly this study noted significant differences in genotype and allele frequencies between its European cohorts (Swiss and Greek) and therefore admixture may be biasing the results for this SNP [51].

Recently a meta-analysis has been conducted on the rs2227564 *PLAU* SNP to assess the inconsistencies observed in previous investigations. A total of 27 cohorts, analysing 6100 AD cases, and 5718 controls, demonstrated that there was a significant effect of the T-allele conferring risk for AD using a dominant model (OR 1.123, 95% CI 1.025-1.231) with only low and moderate heterogeneity between the studies using a "leave-one-out" approach [52].

The rs2227564 SNP lies in the kringle domain of the serine protease, which has been shown to be important for uPA binding to its receptor, uPAR [53]. Further to this, the SNP itself has been shown to affect the activity of uPA with the minor allele (T-allele) resulting in a lower affinity for fibrin clots [54], which may also translate to a lower affinity for plasminogen resulting in lower break up of amyloid-β plaques. Conversely it may also have a lower affinity for its receptor resulting in lower suPAR levels; this is supported by an investigation on the heritability of suPAR levels.

PLAUR: In this study we found two out of the four SNPs investigated to be suggestive of an association with AD. There has been little in the literature to suggest any previous genetic associations, however exploration of large GWAS summary statistics [17,55–57], found no association for the *PLAU* SNPs, whereas *PLAUR* SNPs rs4251909 and rs4251876 were suggestive of association in the Jansen [55] dataset (p=0.049 and p=0.057 respectively, Table 3).

Interestingly though, the *PLAUR* gene has been identified with AD through other various avenues. The expression of *PLAUR*, also known as CD87, is induced by several stimuli and is a marker of immune system activation, therefore a study incubating post-mortem brain derived microglia cells with amyloid-β peptides observed that both mRNA and protein expression of the *PLAUR* gene was increased in comparison to other pro-inflammatory agents. This increase in uPAR protein expression was also found in several AD brain tissues compared to controls [58]. The *PLAUR* gene has also been identified indirectly with network analyses from transcriptome investigations in mouse model microglial in relation to AD [59,60]. Intriguingly, in a study looking at the beneficial effect of music on AD, *PLAUR* was identified as

a gene of interest as having previously been associated with musical aptitude and consistently appearing in the AD literature [61]. This is accompanied with *in silico* analyses suggesting *PLAUR* expression is one of 25 genes that could be used as a biomarker for AD [62].

SNP	Lambert et al [17]	Jansen et al [55]	Bellenguez et al [57]	Dowsett et al [63]
rs2227580	Not present	0.934	0.665	0.606
rs2227562	0.720	0.502	0.384	0.001
rs2227564	0.487	0.857	0.801	1.57×10^{-62}
rs2227571	0.652	0.764	0.422	5.63×10^{-69}
rs4251909	0.519	0.049	0.671	8.6×10^{-09}
rs4251876	0.422	0.057	0.364	5.7×10^{-06}
rs397374	0.924	0.804	0.089	0.047
rs4251854	0.612	0.308	0.337	0.074

Table 3: Summary table of GWAS findings for the *PLAU* and *PLAUR* SNPs investigated in this study. Columns 1-3 show results of GWAS studies for Alzheimer's disease, where the 4th column presents data for these SNPs in association with measured suPAR levels in plasma. Where there is minimal evidence for an association with AD in the large heterogenous GWAS studies, a strong association of the SNPs with suPAR levels is shown.

Univariate twin analyses conducted suggested that additive genetics contributed to as much as 60% of the variation in suPAR levels, and estimated heritability to be around 12.5% [63]. Their GWAS study conducted on almost 48,000 participants with plasma measurements of suPAR, suggested that genetic variation in the *PLAU* and *PLAUR* genes along with others was associated with suPAR levels (Table 3), including SNPs investigated here.[63].

232 Interestingly two alternative transcripts for *PLAUR* have been observed. These transcripts utilise two
233 mutually exclusive 3'exons, with the 7th exon (7b) producing a shorter product lacking the GPI-anchor
234 leading to a secreted soluble receptor product [64]. Therefore, it is feasible that variation in suPAR levels
235 may also be influenced by alternative transcription rather than cleavage of the GPI-anchor. Further to
236 this several alternative splicing events associated with exons 3,4,5 and 6 have been observed and
237 identified with various disorders or uPAR functions [65–68], however none have been investigated in
238 relation to DNA variants and inspection of the Genotype-Tissue Expression [GTEx; 69] database does
239 not have data for polymorphisms associated with expression or splicing of the *PLAUR* gene.

240 The BDR is currently limited in sample size but is a growing cohort (estimated n=3200), and therefore in
241 subsequent analyses the original observations of SNPs displaying a trend towards significance may in
242 time surpass the threshold required. As discussed in a recent publication [70], cohorts such as the BDR
243 which hold detailed neuropathological data for diagnosis may afford a more homogenous sample for
244 study when complete. The larger GWAS studies are subject to greater levels of heterogeneity in disease
245 aetiology and may mask more subtle but key gene associations, especially those that may be subject to
246 environmental exposures. The number of SNPs investigated in this study is limited but served as an
247 exploratory examination of these genes to guide future research.

248 Future work exploring SNP influence on alternative splicing and whether increases in suPAR are driven
249 by the expression of the 7b exon transcript is warranted, this may require additional fine mapping of
250 SNPs that were not captured in the linkage blocks formed from the 1000G dataset. This, alongside
251 measurements of suPAR levels and lifestyle information may yet support a role for these genes in
252 dementia aetiology [71,72].

253 This study provides additional data to the accumulating evidence on genes involved in the innate
254 immune system with AD, whether in a causal role or modifying role it is clear more investigations are
255 required. Alongside the wealth of information suggesting a role of suPAR and its genes in neuronal

survival and development in the brain [71,72], this study supports continued investigation into this system in relation to AD.

Genetic data for the BDR cohort is freely available via the Dementias Platform UK server, combined with the extensive neuropathological, cognitive and lifestyle data available for this cohort, it provides a powerful resource for more complex analyses to uncover genetic associations and their pathway to disease.

Author Contributions:

Ozde Cetinsoy (Investigation, Formal Analysis, writing – original draft); Ijeoma Anyanwu (Investigation); Harikrishnan Krishnanand (Investigation); Gokulakrishnan Natarajan (Investigation); Naveen Ramachandran (Investigation); Alan Thomas (Resources, writing – review & editing); Keeley, J Brookes (Investigation, formal Analysis, Supervision, Data Curation, writing – Original Draft)

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Conflict of Interest:

The authors have no conflict of interest to report.

Data Availability:

The data supporting the findings of this study are available on request from the corresponding author and will be freely available via the Dementias Platform UK within 12 months of this manuscript being published.

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