
Access from the University of Nottingham repository:  
http://eprints.nottingham.ac.uk/32208/5/2015_Braae%20ABO%20ACE%20NoA%20paper%202014%20corr%20AB.pdf

Copyright and reuse:

The Nottingham ePrints service makes this work by researchers of the University of Nottingham available open access under the following conditions.

This article is made available under the Creative Commons Attribution Non-commercial No Derivatives licence and may be reused according to the conditions of the licence. For more details see: http://creativecommons.org/licenses/by-nc-nd/2.5/

A note on versions:

The version presented here may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the repository url above for details on accessing the published version and note that access may require a subscription.

For more information, please contact eprints@nottingham.ac.uk
Blood type gene locus has no influence on ACE association with Alzheimer's disease.

Anne Braae, Christopher Medway, Minerva Carrasquillo, Steven Younkin, Alzheimer's Research UK (ARUK) Consortium, Patrick G Kehoe and Kevin Morgan

1Human Genetics Group, Translational Cell Sciences, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, UK;

2Department of Neuroscience, Mayo Clinic, College of Medicine, Jacksonville, FL, USA

3Dementia Research Group, University of Bristol, Level 1, Learning & Research, Southmead Hospital, Bristol, UK.

*The Alzheimer’s Research UK (ARUK) Consortium comprises Peter Passmore, David Craig, Janet Johnston, Bernadette McGuinness, Stephen Todd, Western Health and Social Care Trust, Altnagelvin Hospital, UK; Reinhard Heun, Royal Derby Hospital, UK; Heike Kölsch, University of Bonn, Germany; Patrick G. Kehoe, University of Bristol, UK; Emma R.L.C. Vardy, Newcastle University, UK; Nigel M. Hooper, David M. Mann, Stuart Pickering-Brown, University of Manchester, UK; Imelda Barber, Christopher Medway, James Lowe, Kevin Morgan, University of Nottingham, UK; A. David Smith, Gordon Wilcock, Donald Warden, University of Oxford (OPTIMA), UK; Clive Holmes, University of Southampton, UK.

Corresponding author: Patrick G Kehoe, Patrick.Kehoe@bristol.ac.uk, Dementia Research Group, University of Bristol, Level 1, Learning & Research, Southmead Hospital, Bristol, UK.
Abstract
The ABO blood group locus was recently found to contribute independently as well as via interactions with ACE gene variation to plasma levels of angiotensin converting enzyme (ACE). Variation in ACE has also previously been implicated as conferring susceptibility for Alzheimer’s disease (AD), but has also been proposed to confer risk via interactions with other as yet unknown genes. More recently, larger studies have not supported ACE as a risk factor for AD, while the role of ACE pathway in AD has come under increased levels of scrutiny with respect to various aspects of AD pathology and possible therapies. We explored the potential combined involvement of ABO and ACE variation in the genetic susceptibility of 2067 AD cases compared to 1376 non-demented elderly. Including the effects of ABO haplotype did not provide any evidence for the genetic association of ACE with AD.

1. Introduction
The renin angiotensin system (RAS) has become a biological pathway of increasing interest in the pathogenesis of Alzheimer’s disease (AD) and potentially as a basis for future interventions. Previous genetic associations between ACE, that encodes for angiotensin converting enzyme (ACE), one of the key enzymes in the RAS, played a significant role in the growing interest of this system in AD. This was aided by the fact that the suggested ACE risk variant contributed to lower levels of plasma ACE while it was also shown that ACE degraded amyloid-β peptide, which is widely involved in the pathology of AD (reviewed in Kehoe and Wilcock, 2007). However, more recent haplotype studies and Genome Wide Association Studies (GWAS) have not supported the role of ACE as a genetic risk factor for AD. Previous meta-analyses have suggested however the possibility that ACE may mediate risk via epistatic interactions with other genetic risk variants (Lehmann et al., 2005).

Recently it was shown that the variants in the ABO blood group locus, independently and when combined with ACE variants, explained a greater proportion of the population variance of ACE in plasma than ACE alone (Terao et al., 2013). In particular, alleles tagging the ABO blood group Type A1 were associated with the lowest plasma ACE activity, while alleles tagging Type B were associated with increased ACE activity and Type A2 and O alleles were associated with intermediate activity (Terao et al., 2013). Given the previously suggested role of ACE activity in AD (Miners et al., 2008) we investigated whether variation in ABO when combined with ACE variation might be associated with increased risk of AD.
2. Methods
A combined GWAS dataset of 3448 samples from Alzheimer’s Research UK (ARUK) and the Mayo Clinic genotyped on Illumina HumanHap300v1 was used. All samples were of European descent, 1487 males and 1922 females, 2069 cases with average age at death of 73.5 years (range 51-108) and 1379 controls with average age at death of 73.4 years (range 54-97 years), with APOE alleles: ε2 - 5.7%; ε3 - 65.9%; ε4 - 28.4%. The power of the study to detect an association with AD was calculated in QUANTO v1.2.4.

The ABO and ACE regions were imputed against 1000 Genomes Phase I haplotypes in IMPUTE2. Imputed data was further quality control checked resulting in 4599 SNPs in ACE for association testing. ABO blood group haplotypes were determined from the imputed ABO region and included as a covariate for the merged dataset. The imputed ACE region was association tested in PLINK (Purcell et al., 2007) using logistic regression corrected for sex, age at onset and APOE ε4 allele and including ABO type as an interaction term. The association test was also run including the blood group B allele and A1 allele separately as interaction terms. The power of the study to detect the interaction was calculated post-hoc using G*Power. For further details please see the supplementary materials.

3. Results
Power calculations in QUANTO v1.2.4 indicated 71% to 99% power at this sample size to detect an association with a genetic variant with MAF of 1% to 5% assuming a genetic odds ratio of 1.2 to 1.5.

ABO blood group haplotype was determined for 3396 samples, as the genotype was not available for all samples. The logistic regression model corrected for sex, age at onset and APOE ε4 allele dose and provided no evidence to support an ACE association with disease in this dataset (Suppl. Table 2, Suppl. Fig 1-3).

Additionally, the interaction terms of ABO blood type and ACE variant and the interaction terms for the presence of a B allele or A1 allele and ACE variants were not significantly associated with disease status and failed to improve the model containing only covariates (Suppl. Table 2, Suppl. Fig 4,5). Post-hoc power analysis showed that the effective power was 77% to 83%.

4. Discussion
In this report we have determined if ABO blood type can potentially modify any association of ACE gene variation with AD. To address this issue we have used ABO haplotypes (both A1 and B alleles),
modelling interactions reported for ABO with ACE on plasma ACE levels, to explore whether it had any additional effects on ACE SNP associations with AD (Suppl. Fig 1-5). It should be noted that the majority of these cases were pathologically confirmed as AD so the contribution to vascular AD, which is biologically plausible, remains to be determined.

In summary, we find no evidence to support a role for ACE, modelled with ABO locus genotypes, being associated with the risk of developing AD.

Acknowledgements
We would like to thank the advice of Professor Bernard Keavney, University of Manchester, for his input on the manuscript and his helpful insights into the interactions between the ABO and ACE gene associations. We would also like to thank Dr Hui Shi for the initial quality control of the merged GWAS dataset. The Nottingham lab was funded by Alzheimer’s Research UK and the Big Lottery Fund.

Disclosure statement
The authors declare that there are no conflicts of interest. Approval was obtained from the ethics committee or institutional review board of each institution responsible for the collection of samples. All individuals who participated in this study gave written informed consent.

Appendices
Supplementary Methods and Results, Supplementary table 1, 2 and Supplementary figures 1, 2, 3, 4 and 5.

References


