Neurobiology of Aging 35 (2014) 1513.e1–1513.e5

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Brief communication

Polymorphisms in *BACE2* may affect the age of onset Alzheimer's dementia in Down syndrome☆

Kin Y. Mok[a,b,*,1], Emma L. Jones[c,1], Marisa Hanney[d], Denise Harold[e], Rebecca Sims[e], Julie Williams[e], Clive Ballard[c], John Hardy[a,b,f]

[a] *Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK*
[b] *Reta Lila Weston Institute, UCL Institute of Neurology, London, UK*
[c] *Wolfson Centre for Age-Related Diseases, King's College London, London, UK*
[d] *Northgate Hospital, Morpeth, Northumberland, UK*
[e] *MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Henry Wellcome Building for Biomedical Research, Heath Park, Cardiff, UK*
[f] *The London Down Syndrome (LonDownS) Consortium, UK*

ARTICLE INFO

Article history:
Received 16 September 2013
Received in revised form 3 December 2013
Accepted 19 December 2013
Available online 27 December 2013

Keywords:
Down syndrome
BACE2
Alzheimer's disease
rs2252576

ABSTRACT

It is known that Alzheimer's disease (AD) presents at an early age in people with Down syndrome (DS). The trisomy 21 in DS provides an opportunity to study the effect of duplicated genes in AD. *APP* and *BACE2* are 2 genes located in chromosome 21 and related to AD. We looked into our cohort of 67 DS cases with dementia for the effect of *BACE2* variants in age of onset of dementia. Of the 83 single-nucleotide polymorphisms (SNPs), 6 were associated with age of onset and another 8 SNPs were borderline associated. Our finding also replicated a previous study showing association of rs2252576 with AD.

1. Introduction

Down syndrome (DS), or trisomy 21, is caused by an extra copy of chromosome 21. The prevalence of Alzheimer's disease (AD) and dementia in the general population and in people with DS increases with age (Margallo-Lana et al., 2007; Murray et al., 2013). In DS, the densities of senile plaques and neurofibrillary tangles increase with aging but can occur in people as young as 37 years (Mann et al., 1990). Despite the pathologic changes, the age of onset (AOO) of dementia varies (Prasher and Krishnan, 1993), suggesting that factors other than trisomy of *APP* in DS are important.

The study of genetic roles in AD contributes to understanding dementia in DS. We have previously shown that in DS polymorphisms in *PICALM* and *APOE* are associated with AOO of dementia, and there is a nonsignificant trend in risk allele loading derived from AD meta-analysis (Jones et al., 2013). Conversely, study of dementia in DS, particularly the role of trisomy in chromosome 21, allows us to understand mechanisms of AD. *APP* and *BACE2* are both located on chromosome 21. We previously showed that haplotypes in *BACE2* are associated with AD (Myllykangas et al., 2005). However, other studies suggested that *BACE2* might not play a significant role in AD (Cheon et al., 2008; Holler et al., 2012). We attempted to look into the role of *BACE2* in AOO of dementia in DS.

2. Methods

The cohort, genotyping and quality control measures were as previously reported (Jones et al., 2013). In brief, this comprised of 94 samples from 2 clinical trials (DOWNSLIT [http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=5927] and MEADOWS; Hanney et al., 2012) and 64 brain samples from various brain banks (details in Supplementary Data). For samples from clinical trials, AOO of dementia was as recorded by the trial psychiatrist. Mean duration of dementia before death in people with DS is approximately 5 years, and AOO for the autopsy cohort was defined as the age of death minus 5, which assumes all individuals over the age of 34 years had dementia before death.

* Corresponding author at: Department of Molecular Neuroscience, UCL Institute of Neurology, Room 908 Queen Square House, Queen Square, London WC1N 3BG, UK. Tel.: +44 (0) 20 3448 4320; fax: +44 (0) 20 3448 4017.
E-mail address: k.mok@ucl.ac.uk (K.Y. Mok).
[1] These authors contributed equally to this study.

0197-4580/$ – see front matter © 2014 The Authors. Published by Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2013.12.022

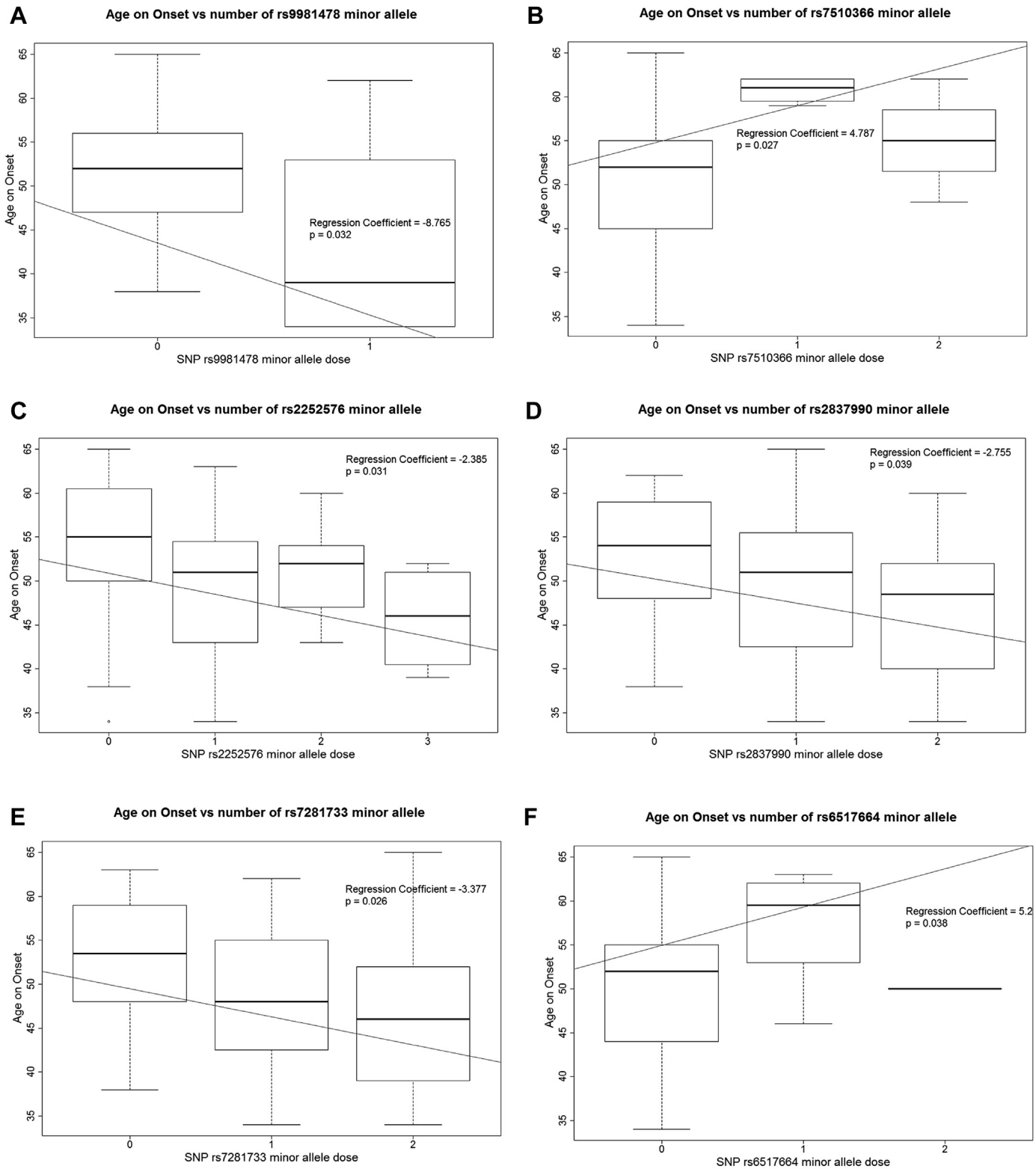

Fig. 1. Plot of 6 SNPs with significant association with AOO around *BACE2*. Median age of onset of dementia according to genotype. 0 = homozygous major allele, 1 = 2 major alleles and 1 minor allele, 2 = 1 major allele and 2 minor alleles, and 3 = homozygous trisomy of minor allele. (A) rs9981478 C/T (minor/major); (B) rs7510366 T/C; (C) rs2252576 T/C; (D) rs2837990 A/G; (E) rs7281733 A/G; and (F) rs6517664 T/C. Abbreviations: AOO, age of onset; SNP, single-nucleotide polymorphism.

DNA was obtained from blood or brain using the commercially available DNeasy Blood and Tissue kit (Qiagen, UK). Genotyping was done in the UCL Genomics Centre using HumanOmniExpress-12v1_H beadchips. After the initial quality control check, 129 samples remained (males: 72; females: 57). Of these, only 70 samples were classified as having dementia and only 67 samples were AOO documented. This formed the cohort for current analysis and was as previously reported (Jones et al., 2013) (details in Supplementary Table 1).