ELSEVIER

Alzheimer's & Dementia 9 (2013) 546–553

Alzheimer's & Dementia

Association of GWAS-linked loci with late-onset Alzheimer's disease in a northern Han Chinese population

Lan Tan[a,*], Jin-Tai Yu[a,*], Wei Zhang[a], Zhong-Chen Wu[a], Qun Zhang[a], Qiu-Yan Liu[a], Wei Wang[a], Hui-Fu Wang[a], Xiao-Ying Ma[a], Wei-Zhen Cui[b]

[a]*Department of Neurology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, PR China*
[b]*Department of Gerontology, Qingdao Mental Health Center, Qingdao, PR China*

Abstract

Objective: Five genomewide association studies (GWAS) in white populations have recently identified and confirmed 9 novel Alzheimer's disease (AD) susceptibility loci (*CLU*, *CR1*, *PICALM, BIN1*, *ABCA7*, *MS4A* gene cluster, *CD2AP, CD33,* and *EPHA1*). These studies have been conducted almost exclusively in white populations and it is unclear whether these observations generalize to populations with different ethnicities.

Methods: We recruited 1224 unrelated northern Han Chinese subjects comprising 612 patients with a clinical diagnosis of late-onset AD (LOAD) according to the criteria of the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association and 612 healthy age- and sex-matched control subjects. Because of our previous study investigating *CLU, CR1,* and *PICALM* in the Han population, we limited the current analysis to *BIN1*, *ABCA7*, *MS4A* gene cluster, *CD2AP*, *CD33*, and *EPHA1*.

Results: In a multivariate analysis, associations of *MS4A6A* (rs610932; odds ratio = 0.632, Bonferroni corrected $P = .019$) and *CD33* (rs3865444; odds ratio = 1.492, Bonferroni corrected $P = .017$) with LOAD were replicated successfully. When these data were stratified by apolipoprotein E (*APOE*) ε4 status, both rs610932 and rs610932 were evident only among subjects without the *APOE* ε4 allele. For *BIN1*, assuming a dominant model of inheritance, a positive association for rs7561528 in *APOE* ε4 carriers was observed. This association, however, did not remain significant after Bonferroni correction. As for *ABCA7*, *CD2AP,* and *EPHA1* single nucleotide polymorphisms from recent GWAS, despite the similar directional effects, no significant differences in genotype and estimated allele frequency distribution between patients and control subjects were observed.

Conclusions: This study provides the first independent evidence that *MS4A* and *CD33* loci are associated with the risk of LOAD in northern Han Chinese population. Genotypes at the two loci confer risk predominantly in *APOE* ε4-negative subjects.

© 2013 The Alzheimer's Association. All rights reserved.

Keywords: Alzheimer's disease; Polymorphism; *MS4A*; *CD33*; Genomewide association studies

1. Introduction

Alzheimer's disease (AD) is by far the most common cause of dementia in the elderly, affecting more than 13% of the population older than 65 years and 43% older than 85 years [1,2]. Multiple rare mutations in the *APP*, *PSEN1*, and *PSEN2* genes cause early-onset AD [3], and twin studies indicate that susceptibility alleles may contribute as much as 80% to the risk of the more common form, late-onset AD (LOAD) [4]. Until recently, the most well-replicated genetic association for LOAD is the variant of the *APOE* gene [5]; however, it has been estimated that variation at the *APOE* locus may account for 50% or less of LOAD risk [5], suggesting that additional risk loci remain to be discovered.

*Corresponding authors. Tel.: +86-532-8890-5659; Fax: +86-532-85968434.

E-mail address: dr.tanlan@163.com (L.T.); yu-jintai@163.com (J.-T.Y.)

1552-5260/$ - see front matter © 2013 The Alzheimer's Association. All rights reserved.
http://dx.doi.org/10.1016/j.jalz.2012.08.007

Multiple approaches have been used to identify additional loci that contribute to LOAD. Recent advances in large-scale genotyping technologies provide a powerful tool to perform unbiased, comprehensive genomewide association studies (GWASs) to investigate the genetic components of LOAD. Five large-scale LOAD GWASs have identified and confirmed nine novel loci (*CLU*, *CR1*, *PICALM*, *BIN1*, *ABCA7*, *MS4A* gene cluster, *CD2AP*, *CD33,* and *EPHA1*) associated with the disease with some degree of consistency in results across studies [6–10]. In 2009, two large-scale GWASs from the United Kingdom [6] and France [7] highlighted three novel AD genes (*CLU*, *CR1,* and *PICALM*). All three of these loci have since been supported by overwhelmingly consistent results from independent follow-up studies [11–14]. Carrasquillo et al [15] and Reiman et al [16] performed a three-stage analysis of previously published LOAD GWASs [15,16], and new data were published from the CHARGE consortium [8]. In addition to replicating the association between *CLU* and *PICALM*, Seshadri et al highlighted two potential additional AD risk genes— *BIN1* and *EXOC3L2*) [8]. Variants in *BIN1* have been reported to show a replicable association with risk for LOAD in three European populations [17] and in a Caribbean Hispanic cohort [14]. Furthermore, an association between a variant in *BIN1* and AD-related neuroimaging measures has been reported [18]. Two recent GWASs implicated independently *ABCA7*, *MS4A* gene cluster, *CD2AP*, *CD33,* and *EPHA1* as putative novel AD risk loci in European and American populations [9,10]. Both GWASs also confirmed the association of previously reported loci (in *BIN1*, *CR1*, *CLU,* and *PICALM*) with LOAD.

Successful replications of the novel GWAS-linked loci in different populations are important for the validation of these novel findings, especially considering the importance of effects related to ethnicity in GWAS analysis. It should be noted that these GWASs and follow-up replication studies were conducted almost exclusively in populations of European ancestry, and the effects of these risk loci in other populations are as yet unknown. Understanding the effects of these variants in different populations is extremely important in terms of interpreting the cause-and-effect relationship and disease mechanisms. Therefore, in the current study, we assessed whether the genetic association of the putative novel GWAS-linked loci with LOAD can be reproduced in a large case-control study that includes 1224 subjects from a northern Han Chinese population. In previous work, we examined *CLU*, *CR1,* and *PICALM* in this population [19–21], and replicated successfully the association of two variants (rs9331888 of *CLU* and rs6656401 of *CR1*). Therefore, the current study was restricted to the analysis of the association between single nucleotide polymorphisms (SNPs) located at the other six GWASs-linked loci (*BIN1*, *ABCA7*, *MS4A* gene cluster, *CD2AP*, *CD33,* and *EPHA1*) and risk for LOAD.

2. Methods

2.1. Subjects

We investigated 1224 subjects comprising 612 sporadic LOAD patients (age at onset, ≥65 years) and 612 healthy control subjects matched for gender and age. All the LOAD patients and control subjects were unrelated northern Han Chinese residents originally from Qingdao. The patients were recruited from the Department of Neurology at Qingdao Municipal Hospital, and several other hospitals in Qingdao. All patients were subjected to neuropsychological examination, structural neuroimaging consisting of brain computed tomography and/or magnetic resonance imaging. A consensus clinical diagnosis of probable AD was established by at least two neurologists according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association [22]. All patients were defined as sporadic because none of their first-degree relatives had dementia in their family history. Age at onset and family history were determined from caregivers. The age- and gender-matched healthy control subjects were collected from the Health Examination Center of each collaborating hospital and were confirmed healthy and neurologically normal by medical history, general examination, laboratory examination, and Mini Mental State Examination by physicians and neurologists. The Health Examination Center provides regular health examinations for early screening of illness and diseases. Demographic details of the sample set are shown in Table 1. An informed consent to participate in this study was obtained from each subject or from a guardian, and the study protocol was approved by the institutional ethics committees.

2.2. SNP selection and genotyping

We selected 10 representative SNPs from GWASs—*BIN1* (rs7561528 and rs744373), *ABCA7* (rs3752246 and rs3764650), *MS4A* gene cluster (rs4938933, rs610932, and rs670139), *CD2AP* (rs9349407), *CD33* (rs3865444), and *EPHA1* (rs11767557)—for analysis. The genetic variants analyzed in this study also included two SNPs (rs429358 and rs7412) within the *APOE* gene. Genotyping for all 12 SNPs was carried out using the polymerase chain reaction–ligase detection reaction using TaqMan genotyping assays on an ABI Prism 377 Sequence Detection System (Applied Biosystems, Foster City, CA) [23,24], with technical support from the Shanghai Genesky Biotechnology Company (genotyping details are available from the corresponding author). Randomly selected DNA samples from each genotype were sequenced to validate the genotyping using the ligation detection reaction method. Results of the ligation detection reaction method corresponded with the results of sequencing.

Download English Version:

https://daneshyari.com/en/article/5623059

Download Persian Version:

https://daneshyari.com/article/5623059

Daneshyari.com