



Influence of Alzheimer's disease genes on cognitive decline: the Guangzhou Biobank Cohort Study



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ABSTRACT

Cognitive decline is a reduction in cognitive ability usually associated with aging, and those with more extreme cognitive decline either have or are at risk of progressing to mild cognitive impairment and dementia including Alzheimer's disease (AD). We hypothesized that genetic variants predisposing to AD should be predictive of cognitive decline in elderly individuals. We selected 1325 subjects with extreme cognitive decline and 1083 well-matched control subjects from the Guangzhou Biobank Cohort Study in which more than 30,000 southern Chinese older people have been recruited and followed up. Thirty single-nucleotide polymorphisms in 29 AD-associated genes were genotyped. No statistically significant allelic associations with cognitive decline were found by individual variant analysis. At the level of genotypic association, we confirmed that the APOE ϵ 4 homozygote significantly accelerated cognitive decline and found that carriers of the ACE rs1800764_C allele were more likely to show cognitive decline than noncarriers, particularly in those without college education. However, these effects do not survive after multiple testing corrections, and together they only explain 1.7% of the phenotypic variance in cognitive score change. This study suggests that AD risk variants and/or genes are not powerful predictors of cognitive decline in our Chinese sample.

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1. Introduction

Clinical dementia is becoming more prevalent because of changing demographics, particularly in developing countries like China with a rapidly aging population (Ferri et al., 2005). For those subjects with a clinical diagnosis of dementia in Hong Kong, Alzheimer's disease (AD) was the most common likely cause (73.5%), whereas 22.4% had vascular dementia, and 3.9% had dementia with symptoms of Parkinson's disease (Lam et al., 2008). AD usually begins with subtle and poorly recognized failure of memory and slowly becomes more severe and eventually incapacitating.

Generally reflected by increasing difficulties with memory or speed of information processing, cognitive decline deterioration in cognitive function is usually associated with aging. The appearance

of significant cognitive decline predicts the progression to mild cognitive impairment and then dementia (including AD), if not already at one of these stages (Cherbuin et al., 2009; Dik et al., 2000). Because cognitive decline is often a prodromal symptom of AD, understanding of AD would uncover potential reasons for cognitive decline or vice versa (Daviglus et al., 2010).

Though twin studies showed cognition performance or cognitive decline is highly heritable (Lee et al., 2010), even the APOE locus is not consistently associated with cognitive decline across different samples or populations (Devore et al., 2009; Dik et al., 2000; Lee et al., 2003). Therefore, more genes are expected to be found to explain the phenotypic variance of this complex trait, although this will require very large studies. Genetic risk factors from genome wide association studies (GWAS) as well as large systematic reviews for AD can serve to select candidate genes for cognitive decline (Bertram et al., 2007; Sleegers et al., 2010). Genetic variants from *CLU*, *CR1*, *PICALM*, and *BIN1* genes have been repeatedly reported to be associated with AD (Bertram et al., 2008; Harold et al., 2009; Hu

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et al., 2011b; Kamboh et al., 2012; Lambert et al., 2009), and some of them are reported to be also involved in the trajectories of cognitive function (Sweet et al., 2012). These newly found AD genes are clustered in biological pathways (amyloid pathway, lipid metabolism pathway, chaperone, and chronic inflammatory pathway) which play an important role in the development of late-onset AD (Slegers et al., 2010) and probably also in disease progression from cognitive decline. Most studies investigating the effect of AD genes on cognitive decline or performance have been conducted in Caucasian populations (Barral et al., 2012; Hu et al., 2011a; Sweet et al., 2012); therefore, there is a need to evaluate AD genes for cognitive decline in Asian subjects.

Initiated in 2003, the Guangzhou Biobank Cohort Study (GBCS) has recruited more than 30,000 southern Chinese older people and collected multidimensional data, including demographic, epidemiologic, and biochemical variables, with both an initial and follow-up assessment separated by around 3 years (Jiang et al., 2006). Several cross-sectional studies have been done for cognitive measurement and environmental factors (Au Yeung et al., 2010; Heys et al., 2010; Xu et al., 2011). Here, we aimed to examine the impact of 30 known genetic risk variants (within 29 genes) for AD on cognitive decline. Meanwhile, potential genetic risk factors were co-investigated with risk factors (sex, age, education level, and neurologic disease status) previously demonstrated to be associated with decline (Xu et al., 2014) to evaluate their independent effects and genetic by environment interactions.

2. Methods

2.1. Participants

The subjects in GBCS were recruited from a community social and welfare association, the Guangzhou Health and Happiness Association for the Respectable Elders, which has more than 110,000 members accounting for more than 7% of Guangzhou's permanent residents aged 50 years or older (Jiang et al., 2006). Data on demographic and socioeconomic characteristics, lifestyle factors, occupational exposure, cognitive function, and disease history were collected from standardized interviews at both baseline (September 2003 to January 2008) and the follow-up examination (March 2008 to September 2012). Blood samples were also collected at the baseline with informed consent and plasma was extracted and stored in a -80°C freezer. By September 2012, around 15,000 subjects were successfully examined at 2 time points.

2.2. Cognitive measurement

The Delayed Word Recall Test (DWRT) (DeCarli, 2003; Welsh et al., 1994), adapted into Chinese by us, was used previously and to assess cognitive function for each participant at baseline and follow-up (Au Yeung et al., 2010; Jiang et al., 2006). During the interview, 10 Chinese words (soy sauce, arm, letter, chairman, ticket, grass, corner, stone, book, and stick) were read out to the participants one by one, pausing for 1 second between each. Participants were asked to recall the words they heard immediately after the last word. This procedure was repeated 3 times, and then after 5 minutes, the participants were asked to recall as many of the words as possible. Participants were given 1 point for each successfully recalled word, with a maximum possible score of 10. Details of this test have been described elsewhere (Heys et al., 2009). This test has been shown to very effectively discriminate dementia from subjects with low education or depression in Chinese (Prince et al., 2003).

2.3. Sample ascertainment

Of ~30,000 subjects collected in the complete cohort, 15,498 subjects were successfully examined for DWRT scores at both baseline and follow-up stages. The difference in DWRT scores from the 2 stages was used for sample ascertainment. Subjects with an extreme decline in DWRT scores (difference ≥ 3 words, corresponding to 1 standard deviation above mean) who constituted about 10% of all participants (1299 subjects), and extremely low cognitive scores (0 or 1) at both stages (26 subjects) were selected as cognitive decline cases because they were probably at a pre-stage to later dementia, such as mild cognitive impairment or even AD. The controls, or cognitively normal subjects, were selected as those whose score difference was within the range of a decline of 1 word to an increase of 3 words, baseline cognitive score ≥ 7 , and baseline age ≥ 60 years, because the likelihood of dementia or cognitive decline in this subsample would be extremely small. This resulted in 1325 cognitive decline cases and 1083 cognitively normal controls.

2.4. Selection of AD genes

AD genes were selected from GWAS on late onset AD and large-scale systematic reviews for functional candidate genes. Genes with manual curation were retrieved from GWAS catalog (<http://www.genome.gov/gwastudies/>; update till January 2012) and AlzGene database (<http://www.alzgene.org/>; update till April 2011). Only the most significant single-nucleotide polymorphisms (SNPs) were selected from each gene, except *APOE* in which 2 SNPs (rs429358, rs7412) were used to determine ϵ genotype corresponding to the 4 possible proteins produced via this gene. Finally, 30 SNPs in 29 genes (Supplementary Table 1) were chosen to maximize the capacity of multiplex genotyping in 1 single pool.

2.5. Genotyping

For those ascertained 2408 subjects, DNA was extracted from 0.8 mL of plasma using the QIAamp Blood MiniKit (Qiagen, Hilden, Germany) following the manufacturer's recommendations. All 30 SNPs were genotyped simultaneously on 1 multiplex using the Sequenom iPLEX Gold platform (Beijing CapiBio Corporation, Beijing, China). PLINK was used to perform standard quality assessment and control on genotyping data (Purcell et al., 2007). The subjects were removed if missing genotyping rate at all 30 SNPs was $>10\%$; accordingly, 632 subjects (209 cases and 423 control subjects) were filtered out. SNPs were excluded if one or more of these criteria were satisfied: total missing rate $>10\%$ in remaining 1776 genotyped subjects, minor allele frequency <0.05 , or genotype frequencies deviate from expectation of Hardy–Weinberg equilibrium ($p < 0.001$) in 660 genotyped healthy control subjects. Consequently, in total 4 SNPs (including *CR1* rs6656401, *TNF* rs4647198, *APOE* rs7412, and *PCDH11X* rs2573905) were excluded. The information on quality detail for each SNP (after sample filtering) is provided in Supplementary Table 1.

2.6. Outcomes and confounders

Two measures of interest were used as outcome: (1) the change in DWRT score across the 2 time points of measurement from the complete cohort; (2) the binary status of being decline case or normal control for all genotyped samples. Both outcomes were adjusted by baseline age (in years), gender (male and female), education level (\leq primary school, $<$ college but $>$ primary school, and \geq college), and neurologic disease status (binary variable for whether affected by depression, confused speech, schizophrenia,

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