Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 587
DOI: 10.1159/000XXXXXX

Accepted: February 23, 2009
Published online: ■■■

A Study on the Association of the Chromosome 12p13 Locus with Sporadic Late-Onset Alzheimer's Disease in Chinese

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Key Words
Alzheimer's disease · Genetics · Chromosome 12 · Case-control study

Abstract
Recent linkage and association studies have implicated the chromosome 12p13 locus as possibly harboring genetic variants predisposed to Alzheimer's disease (AD). We attempted to replicate this association in a Chinese data set comprised of 256 AD cases and 264 age-matched normal controls. A total of 14 single nucleotide polymorphisms (SNPs) were examined. Single marker association revealed the two SNPs in *NCAPD2* (rs7311174 and rs2072374) as showing nominal significant p values (p = 0.0491 and 0.0116, respectively). Haplotype analysis found LD block one to be significantly associated with AD (global p = 0.0250). Haplotypes CGGATG and CAGTCG were also significantly associated with AD (p = 0.0498 and p = 0.0482, respectively). These genetic analyses provide evidence that the chromosome 12p13 locus is associated with AD in Chinese.

Introduction

The pathophysiological process of Alzheimer's disease (AD) is multifactorial but has a genetically heterogeneous background as well. This is evidenced by the widely confirmed genetic risk genes *APP*, *PSEN1*, *PSEN2*, and *APOE*. However, genomewide linkage studies had located multiple genomic regions that might harbor potentially susceptible genes. Among these candidate regions, the chromosome 12p13 locus has recently attracted much attention. In fact, the initial genomic screen described linkage of late-onset AD to the centromeric region markers of chromosome 12, supported by familial associations [1, 2]. Various succeeding replication studies then provided additional evidence linking AD with chromosome 12 [3–5]; in particular, subsequent fine mapping of the chromosome 12 linkage locus and conditional linkage analysis focusing on heterogeneity both found that the linkage to chromosome 12 was independent of the *APOE* ε4 allele [6]. Further association analyses have now pointed to a smaller region of the chromosome 12p13 locus, thus narrowing down late-onset AD association to single genes as shown by the two recent studies. Of note, a large-scale single nucleotide polymorphisms (SNP)-based association study by Li et al. [7] found strong associations with the *GAPD* gene, as well as with other genes *(CNAP1, PKP2P1)* in this re-

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gion. Consequently in 2008, Lee et al. [8] finely mapped this region, revealing more gene association with late-onset AD [7, 8]. In an effort to replicate this finding, we selected the same panel of polymorphism markers and conducted genotyping in our Chinese data set.

Materials and Methods

The research protocol was approved by the Institutional Review Board (IRB) of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB). Informed consent was obtained from all individuals participating in this study. A total of 256 Chinese sporadic AD patients and 264 normal subjects were recruited. Demented subjects were recruited consecutively from the Memory Clinic of Queen Mary Hospital of the University of Hong Kong [9–11]. Normal control subjects were recruited from community elderly social centers. All subjects underwent a standardized, semistructured and detailed cognitive assessment protocol for cognitive impairment and dementia. History of memory impairment and cognitive functioning were obtained from both the subjects and informants (either family members or caregivers). Every subject also received a full physical and neurological examination. Standardized cognitive assessment tools including the Chinese versions of Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale and Delayed 10-Word Recall Test (DWRT) were administered to all subjects. The DWRT has been reported previously. It consists of 10 Chinese words. Every subject was given three immediate registration and immediate recall trials, which were followed by a delayed free recall trial after 10 min. The number of correct freely recalled words was the DWRT score. Cutoff scores of 26 or above and 6 or above were used for the Chinese MMSE score and DWRT, respectively. All subjects were rated by a single rater (L.W.C.) with the Clinical Dementia Rating Scale (CDR). In the CDR, CDR 0 would mean no cognitive impairment (i.e. normal nondemented persons). For AD patients, the CDR would depend on the stage of the dementia illness and range from CDR 0.5 to 3.0 (i.e. 0.5 very mild, 1.0 mild, 2.0 moderate, 3.0 severe or advanced). All subjects were evaluated by a standardized battery of laboratory investigations including thyroid function tests (serum TSH), serum vitamin B_{12} and folate levels, and red blood cell folate level. CT brain scans were done for subjects with AD but not for the normal subjects. All normal subjects had CDR ratings of CDR 0 and had no evidence of any neurological disease, while AD subjects were diagnosed in accordance to the NINCDS/ADRDA criteria for probable AD. Subjects with non-AD types of dementia, secondary causes of dementia and familial AD were excluded from the present study [12]. Family history of AD and dementia in first-degree relatives of subjects (father, mother, brother and/or sister) was reported by family members (spouse, children or sibling) of subjects during the face-to-face interviews. The AD patients' mean age at the time of examination was 79.0 ± 7.2 years (ranging from 65 to 97 years), while the controls' mean age was 72.1 ± 5.6 years (ranging from 65 to 90 years). As for the disease group, 72.3% were females and 27.7% were males, whereas in the control group, 71.7% were females and 28.3% were males.

Genetic Analyses

After obtaining the participants' fully informed consent, blood samples (10 ml) and answers to questionnaires of environmental risk factors were collected. Genomic DNA samples were then isolated from the buffy coat leukocytes, with DNA quality and quantity measured by a DNA fluorometer. Meanwhile, *ApoE* genotypes were determined by a modified method [13, 14].

PCR Amplification/Genotyping

The Sequenom® platform was used for genotyping, while the Mass ARRAY AssayDesign software (Sequenom) was employed to design amplification and allele-specific extension primers for uniplex or multiplexed assays. The PCR reactions were set up in 384-well plates at 6 ml total volume per reaction, the reaction mix containing 5 ng genomic DNA, 0.3 pmol each of specific forward and reverse primers, 200 mM each of dNTP, 3.25 mM $MgCl_2$, and 0.2 unit of HotStarTaq polymerase (5 U/ml, Qiagen, Valencia, Calif., USA). The PCR condition was controlled at 95°C for 15 min, with 45 cycles of 95°C for 20 s, 56°C for 30 s and 72°C for 1 min, followed by 72°C for 3 min. Next, the extension primer was designed to hybridize to the amplicon near the SNP site for the extension of a single or a few bases depending on the allele's genotype. The PCR reactions and PCR product treatment with alkaline phosphatase and mass extend reactions were all performed according to the manufacturer's (Sequenom) protocol. The final base-extension products were later desalted using SpectroClean resin (Sequenom), mixed with 3-hydroxypicolinic acid and analyzed by means of a modified Brucker Autoflex MALDI-TOF mass spectrometer (Brucker, Billerica, Mass., USA).

Statistical Analysis

Statistical differences in allele and genotype frequencies between the case and control groups were calculated using the χ^2-test or Fisher's exact test. Meanwhile, the Hardy-Weinberg equilibrium (HWE) in both groups was performed by the Haploview package v4.0 [15]. Afterwards, the linkage disequilibrium (LD) blocks were estimated using the Gevalt software V2.0 [16]. The LD blocks were defined by Gerbil, an algorithm developed for simultaneous phasing of genotypes into haplotypes as well as block partitioning [17, 18]. As for all the analyzed polymorphisms, individuals with more than 50% missing genotypes were excluded. Finally, the haplotype case/control ratios were predicted through the Haploview software v3.2 [15]. Since there was a priori evidence to support candidacy of each of the SNPs studied, and not all markers within genes were independent (i.e. they were in linkage disequilibrium), we did not apply a multiple testing correction.

Results

The 14 SNPs tested by Lee et al. [8] were examined in our Chinese data set comprised of 256 AD participants and 264 age-matched subjects. All SNPs followed the HWE in both the AD and control groups, except 1 SNP (rs2532500, HWE $p < 0.001$) which was found to be significantly associated with AD as described by Lee et al. [8]. Conversely, the SNPs rs740852 and rs3741924 exhib-

Table 1. Information of genotyped SNPs in a Chinese data set

Marker No.	dbSNP rs No.	Physical position	Dist. from previous marker, bp	Gene name	SNP type	Alleles	Risk allele	Minor allele freq.		HWE, p value		Single marker, p value		
								cases	controls	cases	controls	global	APOE 4 +ve	APOE 4 –ve
1	rs2532501	6433014	–	*TAPBPL*	NSC(M/V)	C/T	T	0.244	0.205	0.401	0.788	0.3378	0.2547	0.1343
2	rs2532500	6433071	57	*TAPBPL*	NSC(T/A)	C/T	–	0.318	0.288	4.659 E-10	3.674 E-8	–	–	–
3	rs2008134	6458706	25,635	*PKP2P1*	Intergenic	A/G	A	0.292	0.375	0.114	0.138	0.0676	0.56	**0.0304**
4	rs2072373	6502149	43,443	*NCAPD2*	IN	G/A	G	0.361	0.388	0.285	0.077	0.5674	0.6396	0.9913
5	**rs7311174**	6505828	3,679	*NCAPD2*	IN	T/A	T	0.258	0.345	0.104	0.309	**0.0491**	0.515	**0.0215**
6	**rs2072374**	6508106	2,278	*NCAPD2*	SC(R)	C/T	C	0.267	0.380	0.179	0.729	**0.0116**	0.7417	**0.0075**
7	rs740850	6508377	271	*NCAPD2*	SC(N)	G/A	A	0.243	0.210	0.163	0.889	0.4091	0.1885	0.1736
8	rs3741916	6514252	5,875	*GAPDH*	5′ UTR	C/G	C	0.243	0.262	0.142	0.477	0.6773	0.334	0.7845
9	rs3741918	6514517	265	*GAPDH*	IN	T/A	A	0.406	0.397	0.096	1.000	0.8488	0.8073	0.5814
10	rs1060620	6514983	466	*GAPDH*	IN	C/T	C	0.461	0.495	0.355	0.577	0.3597	0.6386	0.3952
11	rs1060619	6515042	59	*GAPDH*	IN	G/A	G	0.457	0.490	0.238	0.648	0.2735	0.5646	0.2831
12	rs740852	6520587	5,545	HOMTES-*103*	IN	C/C	–	0.0	0.0	1.0	1.0	–	–	–
13	rs1639122	6581408	60,821	*CHD4*	NSC(E/D)	A/C	A	0.466	0.485	1.0	0.734	0.3089	0.4324	0.5856
14	rs3741924	6600217	18,809	*GPR92*	SC(A)	G/G	–	0.0	0.0	1.0	1.0	–	–	–

NSC = Nonsynonymous coding; SC = synonymous coding; IN = intronic.

ited monomorphism in this Chinese data set. Therefore, the three SNPs were excluded from subsequent statistical analysis.

On the other hand, single SNP association analysis found two SNPs, rs7311174 (SNP5) and rs2072374 (SNP6), as showing nominally significant p values (p = 0.0491 and 0.0116, respectively, table 1). Of note, the T allele of SNP rs7311174 and the C allele of SNP rs2072374 were risk alleles (i.e., their presence predisposes to disease development).

Haplotype analysis was also performed in the 11 SNPs; this revealed two LD blocks spanning this region. On the one hand, LD block one was found to be significantly associated with AD, with a global p value of 0.0250. On the other hand, LD block two did not show any statistical significance. Moreover in LD block one (SNP1–7), haplotypes CGGATG and CAGTCG demonstrated significantly different frequency distributions in the AD and control groups. Haplotype CAGTCG showed significant uncorrected p = 0.0482, while haplotype CGGATG had uncorrected p = 0.0498. As a result, both single marker association and haplotype analysis provided evidence that the chromosome 12p13 locus was associated with AD.

In line with our previous reports on CYP46A1 and ABCA1 using the same Chinese sample pool [14, 19], the classification of samples into *ApoE ε*4 allele carrier and non-*ε*4 allele carrier groups demonstrated a highly significant difference in terms of allele frequency distributions in both the AD and control groups (OR = 3.86, 95%CI 2.53–5.88, $p < 0.0000001$). Given that several independent groups have reported controversial significance after *ApoE ε*4 allele status stratification [6–8], we further analyzed the association in *ApoE ε*4-positive and -negative groups. We then determined that SNPs rs7311174 and rs2072374 continued to be significant (p = 0.0215 and 0.0075) in the absence of the *ApoE ε*4 allele, while another SNP, rs2008134, also exhibited significant association (p = 0.0304). However, no significance could be found for the *ApoE ε*4-positive group (table 1). Detailed information of sample stratification by *ApoE ε*4 allele is listed in online supplementary table 1 (www.karger.com/doi/10.1159/000■■■). Meanwhile, haplotype analysis in the *ApoE ε*4-negative group only confirmed haplotype CGGATG association with an uncorrected p value of 0.0230 (table 2).

Discussion

The chromosome 12p13 region was associated with late-onset and sporadic AD as evidenced in this Chinese data set and as described by Lee et al. [8]. In their Caucasian data set, Lee et al. [8] found a strong significance of single marker association (SNPs rs2532500 and rs740850). Correspondingly, the Chinese data set's SNPs rs7311174 and rs2072374 in this region were found to have an asso-

Table 2. Haplotype distributions in LD block one

Haplotype	Case, CTL freq.	p value	*APOE* 4-negative	
			case, CTL freq.	p value
CAATCG	0.319, 0.303	0.7938	0.343, 0.304	0.4991
CGGATG	0.255, 0.326	0.0497	0.246, 0.348	0.0230
TAGTCA	0.235, 0.202	0.1774	0.247, 0.181	0.0663
CAGTCG	0.134, 0.078	0.0482	0.102, 0.070	0.3398
Global p value		0.025		0.084

CTL = Control; freq. = frequency.

ciation. These two significant SNPs also contributed to the haplotype association, while allele frequencies in controls of the two significant SNPs were similar to those in the Hapmap HCB data set.

The LD block prediction and haplotype analysis provided further evidence that the Chr12p13 region harbored a risk locus for AD. Apparently, the LD block construction was different between the Caucasian and Chinese populations. In the Chinese population, two large LD blocks across the chromosome 12p13 locus were defined in this report. Conversely, Lee et al. [8] predicted three comparatively smaller LD blocks: SNPs1–2 in LD block one, SNPs5–6 (or 5–7) in block two, and SNPs10–11 in block three.

The comparatively longer LD block one in the Chinese data set encompassed the first two significant blocks shown in the study by Lee et al. [8]. This long LD block also included the SNP rs2532500, which did not follow the HWE in our Chinese data set, although it was found significant in Lee et al. [8]. Subsequent haplotype association likewise found the two haplotypes, CGGATG and CAGTCG, to be associated with AD in the Chinese. It was then determined that haplotype CGGATG was a protective haplotype, while haplotype CAGTCG was its risk-conferring counterpart.

Linkage and linkage disequilibrium studies have pointed to several candidate genes on Chr12. Among them *A2M*, *GAPDH*, *LRP*1, *GNB*3 and *NCAPD*2 are the most frequently studied candidate genes. In Lee et al. [8], regions surrounding *GAPDH* and *NCAPD*2 comprised significant signals in both allelic and haplotype associations and the *NCAPD*2 association was replicated in this Chinese study. *NCAPD*2 is short for non-SMC (structural maintenance of chromosomes) condensin I complex, subunit D2, and is a chromosome condensation-related protein. Previous studies relating chromosome and aging have suggested a link between remodeling of chromatin structure and aging, which provided one aspect of functional evidence for the genetic linkage [20, 21].

Worth mentioning in association analyses is that genetic heterogeneity is always a factor leading to ambiguous and controversial results. As in chromosome 12 studies, despite the significant evidence of association shown by initial genome screen [1] and following positive replications [4, 5, 22], Blacker et al. [23, 24] by genome scan had reported equivocal results from prior published case-control and familial studies. Their failure to detect a positive association signal might be due to the mixed sample set they used, which was composed of varied family structure. In addition, the SNP rs3741916 in *GAPDH* were found to be associated with AD in several Caucasian data sets [7, 8, 25], although we could not replicate the findings in our Chinese population. This may be due to this SNP's insufficient power in the replication data set, or genetic heterogeneity among different ethnic groups.

Particularly with AD association, the *ApoE ε*4 allele plays a critical role due to its strong effect in the AD neuropathological process, therefore generating conflicting results in these studies. Indeed, several investigations revealed that in *ApoE ε*4 allele-positive groups, there is an association of the chromosome 12 locus with late-onset AD [5, 8], while other studies described no confounding effect of the *ApoE ε*4 allele [6, 7]. In this analysis, we could confirm that the chromosome 12 locus associated with AD is independent of the *ApoE ε*4 allele.

Conclusion

The association of chromosome 12p13 multiple loci with AD was confirmed in a Chinese data set. Both single marker and haplotypic associations were significant. Nonetheless, future genetic studies to verify this association will need to conduct studies with a larger data set and with other ethnic groups. Additionally, a genomewide association effort to discover other potentially susceptible genetic loci would be of great help to unravel the underlying mechanism of AD development.

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