# CREB1 Gene Polymorphisms are Associated with Alzheimer's Disease-Related Depression and Antidepressant Response

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**Abstract:** cAMP response element binding protein（CREB）is needed in the formation of long-term memory and synaptic plasticity. It also promotes synaptic remodeling and modulates the function of many other neurotransmitters. The current study examined potential association between single nucleotide polymorphisms (SNPs) of the CREB1 gene ( rs10932201, rs3770704) and Alzheimer's disease-related depression (AD-D). Participants included 336 patients with AD; 128 of these patients had AD-D. Response to 8-week paroxetine treatment was also assessed. The frequency of the rs3770704 C allele was significantly lower in AD-D than in the Alzheimer's disease without depression (AD-nD) patients ($p = 0.0075$ after Bonferroni correction). Carriers of the A allele of rs10932201 responded better to the treatment by paroxetine ($p = 0.0053$). These findings support an important role of CREB1 polymorphism in AD-D.

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## 1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by a progressive decline in cognitive function [1]. It is often co morbid with other neuropsychiatric symptoms, most notably depression [2]. Depression occurs in up to 50% of AD patients and has been suggested to contribute to their cognitive impairment [2–4]. Depressive symptoms are related to greater disability in activities of daily life, faster cognitive decline, and a higher frequency of depression and burden in caregivers [5].

Several lines of evidence suggest a link between the cAMP response element binding protein (CREB), a constitutive transcription factor, and depression. The "neurotrophin hypothesis" of depression is based largely on observations that decrease in hippocampal CREB levels are correlated to stress induced depressive behaviors, and that antidepressant treatment enhances the expression of CREB [2,3]In light of this, Results from studies as well as clinical observation have attempted to identify genetic variations within CREB that may underlie a predisposition to depression.

CREB is aconstitutive transcription factor located in the nucleus of eukaryotic organism. It can modulate the transcription of various target genes by binding to the cAMP response elements. CREB is a significant component in the space learning and memory of hippocampus major. Multiple signal transduction pathways converge on CREB, which plays an essential role in the formation of long-term memory and synaptic plasticity. Long-term memory depends on gene expression mediated by CREB. When it is in the condition of active phosphorylation, CREB in cerebral nerves can activate gene related with long-term memory [6]. CREB is an important protein that transforms short-term memory to long-term memory. It is a key point in the development of long-term learning and memory. So it is called a molecule marker of learning and memory.

The dysfunction of CREB contributes to the neuronal dysfunction and degeneration that occur in aging and aging-associated neurological diseases such as Alzheimer's disease. Pristine symptoms of Alzheimer's disease are the dysfunction of cognition and learning memory. Clinical research discover that CREB activity in the brain mantle and hippocampus is low [7]. The dysfunction of learning and memory in rats concerned with the low express of CREB in the ageing hippocampus [8].From the exogenous genes obtained from the ageing rats, the expression of CREB in the hippocampus was high, which improved significantly learning and memory in rats through gene transfer with body cell [9,10]. It is thus clear that the reason of dysfunction in learning and memory is the down regulation of CREB in the aging hippocampus.

Therefore, genetic chromosomal localization and function indicate that CREB is the candidate gene in AD-D. The above observations prompted the

present study, aimed at testing the association between different CREB1, the gene encoding CREB, genetic variations, as single loci and multi-locus haplotypes, and the risk to depression in AD patients. The human CREB1 has been mapped to chromosome 2 , and a common single nucleotide polymorphism (SNP) has been described. For our purpose, we selected the previously studied HapMap haplotype-tagging single nucleotide polymorphisms, htSNPs is strategy. Approach CREB1 gene mononucleotide polymorphism biological function assosciated with AD-D in Chinese population.

## 2. Material and Methods

### Study participants

The study was conducted in accordance with local clinical research regulations. Written informed consent was obtained from all participants. Three-hundred and thirty-six AD patients were consecutively recruited from our hospital. The diagnosis of AD was based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR 2000). The diagnosis of depression was established via a half-hour interview with the patients and a proxy interview based on the DSM-IV criteria for major depression. Patients with depressive symptoms at baseline were adequately treated and reevaluated 2 months later. Depressive symptoms were rated by (a) the subsection of the Neu-ropsychiatric Inventory (NPI) [11], that assesses the presence/absence, frequency and severity of depressive symptoms rated by the caregiver, (b) the 30-item Geriatric Depression Scale (GDS) [12], a self-rating measure of depressive symptoms tailored to elderly individuals, and (c) the 24-item Hamilton Depression Rating Scale (HAMD) [13].

All patients received a general physical checkup and neurological examinations upon recruitment. Participants also received a routine blood test and brain imaging examination (either computed tomography or magnetic resonance). BDNF polymorphism analyses were performed by staff members blinded to patient condition. Global cognitive function assessment was carried out using a set of standardized batteries that included Clinical Dementia Rating Scale (CDR) [14], Mini-mental state examination (MMSE) [15], and Alzheimer's Disease Assessment Scale Instrumental activities of daily living (IADL) [16], and basic activities of daily living index were assessed as well.

Exclusion criteria included: a history of schizophrenia, schizoaffective disorder, delusional disorder or mood disorder with psychotic features, substance use disorder, or mental retardation according to DSM-IV criteria; cerebrovascular disorders, hydrocephalus, or intra-cranial mass as documented by neuroimaging study within the past 12 months; a history of traumatic brain injury or another neurological disease; abnormalities in serum folate and vitamin B12, syphilis serology, or thyroid hormone levels; or other significant medical problems (e.g.,poorly controlled diabetes or hypertension; cancer within the past 5 years; clinically significant hepatic, renal, cardiac or pulmonary disorders); absence of knowledgeable informant who could provide reliable report on patient's behavior.

### Treatment

HAMD was used to detect, rate, and quantify treatment response. Subjects who had at least five of the symptoms required by the DSM-IV (n = 128) received paroxetine treatment (10 mg/d for 8 weeks). The remaining subjects (n = 208) received standard care but no antidepressant. Patient response was assessed at the end of the 8-week treatment. HAMD score at$\leqslant$7 or a 50% improvement was considered remission.

### Haplotype-TaggedSNP identification and selection

To reach enough power to detect small relative risks, we restricted our attention to common SNPs and haplotypes (frequency $\geqslant$ 5%). We selected htSNPs from the HapMap database (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap27_B36/) with the Haploview 4.01 program, focusing on the data from Han Chinese Beijing (HCB) samples, including both the upstream and the downstream 3 kb of the gene CREB1, and aiming for a minimum r2 of 0.8. The selected region was from chr2:208099931 to 208174806 bp. r2 is a measure of correlation between haplotypes defined by all SNPs and haplotypes defined by the selected htSNPs. The CREB1 gene consisted of only one 58 kb Linkage Disequilibrium (LD) block. Nine common SNPs were tagged by 2 htSNPs: rs10932201 (in perfect LD with rs2253206, rs2254137, rs2551645, rs6740584, rs2551640 and rs11904814, r2=1) and rs3770704 (in absolute LD with rs16839883, r2=1), so the 2 htSNPs were chosen for the subsequent genotyping analysis (Figure 1).

### Genotyping

Genomic DNA was extracted from 5-mL peripheral blood samples using standard phenol chloroform protocols. DNA samples were diluted to a concentration of 10 ng/mL and were distributed in 96-well plates.

The genotyping was performed with multiplex PCR and SNP analysis based on Genome Lab SNP stream genotyping platform (Beckman Coulter Inc., Fullerton, CA). The primers for the multiplex PCR and single-base extension reaction (Table 1) were designed for SNP sites by use of web-based software AutoPrimer.com (http://www.autoprimer.com). The

SNP stream genotyping assay was performed according to methods previously described by Bell et al [17].

Genotyping was performed in a blind manner so that the performers did not know the case/control status of the subjects. For quality control, a 10% masked random sample of cases and controls was tested by DNA sequencing.

**Statistical methods**

Allele and genotype frequencies for each individual polymorphism and Hardy-Weinberg equilibrium were evaluated by Chi-square test. Potential association between AD-D and each polymorphism was analyzed using Fisher's exact test or the Pearson Chi-square test. Differences were significant when $p < 0.025$ after Bonferroni correction. These analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). LD and haplotype were analyzed using Haploview 4.01 (http://www.broad.mit.edu/haploview/haploview).

## 3. Results

Demographic and clinical characteristics of the participants are presented in Table 2. Higher NPI, GSD, and HAMD scores were noted in AD-D than that in AD-nD. CDR and IADL did not differ between AD-D and AD-nD patients.

Genotype distribution of the two htSNPs was consistent with the Hardy-Weinberg equilibrium. Genotype distribution, allele frequencies, and statistical analysis of the two htSNPs are listed in Table 3. Genotype distribution and allele frequencies of the CREB1 gene rs3770704 differed significantly between AD-D and AD-nD subjects ($p = 0.0051$ and 0.0075, respectively). The frequency of the C allele in AD-D subjects was significantly lower than that in the AD-nD ($\chi 2 = 6.99$, $p = 0.0075$, OR= 0.61, 95%CI = 0.42-0.88).

The rate of remission after paroxetine treatment was significantly lower in the subjects carrying the rs10932201 G allele in AD-D patients ($\chi 2 = 7.98$, $p = 0.0053$, OR=0.46, 95%CI = 0.26-0.81) (Table 4).

## 4. Discussions

AD-related depression is a complex and likely multifactorial trait with important genetic and non-genetic contributing factors. The understanding of genes that underlie susceptibility to depressive symptoms in AD would be a major advance in our understanding of pathophysiological mechanisms and of newer therapeutic approaches.

Depression is one of the most frequent neuropsychiatric comorbidities of AD [18, 19]. AD patients with depressive symptoms have faster cognitive decline and greater disability in daily living [3]. In our sample, 38.1% of the AD patients had prominent depressive symptoms. Such a rate is consistent with estimates reported by previous studies in other ethnic groups [20, 21]. The present study revealed higher NPI, GDS, and HAMD scores in AD-D, and a strong rank correlation between NPI depression item and GDS.

In the present study, we investigated the genetic correlations of AD-related depression by analyzing sequence polymorphisms within CREB1, which may lead to variations in CREB gene expression or protein metabolism. The most intriguing finding of the current study is the association of CREB1 rs3770704 polymorphism with AD-D. There are a significant excess of allele C in AD-nD compared to the AD-D. We also noted a higher rate of remission after paroxetine treatment in subjects carrying the rs10932201 A allele. To our knowedge, this is the first report of significant association between rs10932201 and treatment response to paroxetine in AD-D.

Previous studies have indicated that CREB1 T allele in rs4675690 is a significant risk to major depression and geriatric depression. CREB1 polymorphism has also been established as a risk factor for AD [22-25]. Results from the current study showed that the association between genotype and allele frequencies of rs3770704 and AD-D also occur in the Chinese population.

Recently, SSRIs have been recommended as the first line treatment for AD-D by many researchers [26, 27]. However, there is a substantial evidence that not all depressed AD patients respond satisfactorily to anti-depressant agents. Previous studies have suggested a link between genetic variation and treatment response to antidepressants. For instance, McCauley and collaborators [28] have reported that the depressed patients with a long form of the SERT gene promoter polymorphism respond better to SSRIs than those with the short form. CREB1 gene has also been found to be associated with response to antidepressant medications. The result of present study supported a role of CREB1 polymorphism in antidepressant response in AD-D patients.

In summary, genetic variation in CREB1 contributes to AD-D by conferring susceptibility or resistance, and responses to antidepressant treatment. Overall, the current study provides further evidence that CREB1 variants play a role in increasing risk for AD-related depression. It is clearly important that independent attempts to replicate this finding are made in large, well-characterized samples in order to establish individual risk profiles of behavioral symptoms in patients with AD, and to further evaluate the complex relationship between CREB1, mood disorders, and neurodegeneration.

**Table 1. Primers and Tagged Extension Probes Used for SNP Detection by GenomeLab SNPstream genotyping platform**

| SNP | Primer | Length of PCR production(bp) | Sequence 5'-3' |
|---|---|---|---|
| rs10932201 | Forward (PCRU) | 99 | AATATTCAATTATTTCCATCTGCG |
| | Reverse (PCRL) | | CTGTCTTCTTTTCAGAGCTGTTATG |
| | Probe (SNPU) | | AGCGATCTGCGAGACCGTATTTCCTAGTTTGCAAGGTATCTTTCC |
| rs3770704 | Forward (PCRU) | 123 | AACGGAAAAAGCTTTACCTGA |
| | Reverse (PCRL) | | AAACAGTGTTTTTATTCATCCTGG |
| | Probe (SNPU) | | CGTGCCGCTCGTGATAGAATCTCTCTTTCTAGAAACTGAAGAAAT |

**Table 2. Clinical characteristic in AD-D (n=128) and AD-nD (n=208)**

| Variable | AD-D | AD-nD |
|---|---|---|
| Age(year) | 71.51±4.52 | 72.50±5.15 |
| Gender(%) | | |
| Male | 32.03(41) | 34.13(71) |
| Female | 67.97(87) | 65.87(137) |
| Education(year) | 11.46±3.21 | 11.73±3.18 |
| Family history(year) | 19(14.84) | 33(15.87) |
| CDR | 1.51±0.98 | 1.56±1.09 |
| MMSE | 18.72±2.83 | 19.51±4.80 |
| IADL, lost | 22.59±5.16 | 21.68±5.28 |
| NPI, total | 26.16±15.14 | 16.82±14.52 |
| GDS | 23.42±6.89 | 15.53±7.71 |
| HAMD | 24.63±5.81 | 15.81±5.91 |
| Hypertension(yes) | 39.06(50) | 40.87(85) |
| Cardiomyopathy(yes) | 30.47(39) | 31.73(66) |
| Diabetes(yes) | 25.78(33) | 25.96(54) |
| Hypercholesterolanemia(yes) | 21.09(27) | 22.12(46) |
| Apolipoprotein(yes) | 26.56(34) | 27.88(58) |

Note: CDR: Clinical Dementia Rating Scale: MMSE: Minin-Mental State Examination: ADL: Activities of Daily Living: NPI: Neuropsychiatry Inwentory: GDS: Geriatric Depression Scale: HAMD: Hamilton depression rating scale. AD-D compared with AD-nD, differences reaching stastistical singnificance are $p<0.01$

**Table 3 . Frequencies of genotypes and allele frequency of CREB1 htSNPs in AD**

| SNPs | Genotype | AD-D(%) (N = 128) | AD-nD (N = 208) | OR* (95%CI) | *P** |
|---|---|---|---|---|---|
| rs3770704 | T/T | 80 (62.5%) | 110 (52.9%) | 1 | |
| | C/T | 45 (35.2%) | 75 (36.1%) | 0.83 (0.52-1.32) | |
| | C/C | 3 (2.3%) | 23 (11.1%) | 0.18 (0.05-0.62) | 0.0051 |
| | T allele | 205 (80%) | 295 (71%) | 1 | |
| | C allele | 51 (20%) | 121 (29%) | 0.61 (0.42-0.88) | *0.0075* |
| rs10932201 | A/A | 64 (50%) | 102 (49%) | 1 | |
| | A/G | 51 (39.8%) | 95 (45.7%) | 0.86 (0.54-1.36) | |
| | G/G | 13 (10.2%) | 11 (5.3%) | 1.88 (0.80-4.46) | 0.2 |
| | A allele | 179 (70%) | 299 (72%) | 1 | |
| | G allele | 77 (30%) | 117 (28%) | 1.10 (0.78-1.55) | *0.587417* |

Note: *AD-D compared with AD-nD, differences reaching statistical significance are $p < 0.025$.

**Table 4. The distribution of CREB1 htSNPs genotype and allele in AD-D responded to paroxetine**

| SNPs | Genotype | Rp(%) (N =86) | Non-Rp(%) (N = 42) | OR* (95%CI) | *P** |
|---|---|---|---|---|---|
| rs3770704 | T/T | 50 (58.1%) | 30 (71.4%) | 1 | |
| | C/T | 34 (39.5%) | 11 (26.2%) | 1.85 (0.82-4.20) | |
| | C/C | 2 (2.3%) | 1 (2.4%) | 1.20 (0.10-13.81) | 0.32 |
| | T allele | 134（78%） | 71（85%） | 1 | |
| | C allele | 38（22%） | 13（15%） | 1.55 (0.77-3.10) | *0.21* |
| rs10932201 | A/A | 50 (58.1%) | 14 (33.3%) | 1 | |
| | A/G | 30 (34.9%) | 21 (50%) | 0.40 (0.18-0.90) | |
| | G/G | 6 (7%) | 7 (16.7%) | 0.24 (0.07-0.83) | 0.021 |
| | A allele | 130（76%） | 49（58%） | 1 | |
| | G allele | 42（24%） | 35（42%） | 0.46 (0.26-0.81) | 0.0053 |

Note: * Rp group compared with Non-Rp, differences reaching statistical significance are $p < 0.025$

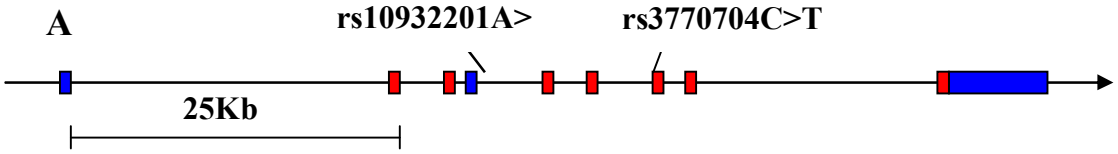


**Figure 1. The structure of CREB1 polymorphisms related to the human genomic location and pair-wise linkage disequilibrium analysis**

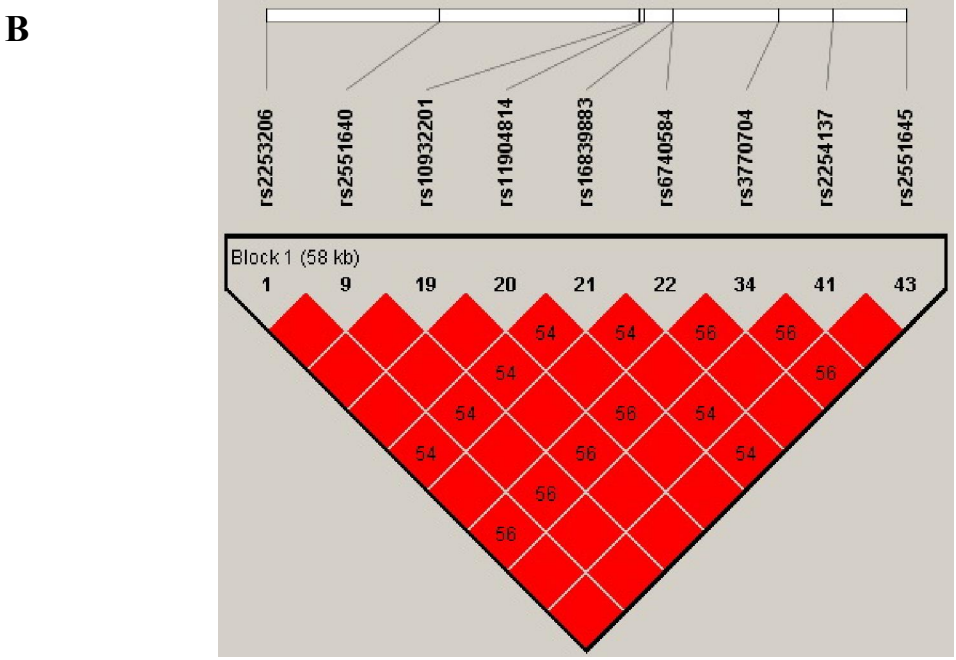


**Figure 1**. (*A*) Genomic location of SNPs identified in relation to the exon/intron structure of the human *CREB1* gene. The 9 exons are marked with *boxes*, in which *blue areas* represents untranslated regions. Positions for SNPs are relative to the first nucleotide of open reading frame of the *CREB1* gene. (*B*) SNP positions and data on pair-wise linkage disequilibrium were obtained from the HapMap database (HCB sample; http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap27_B36/). Pairwise LD was measured by D′ and $r^2$. The color boxes correspond to the paired $r^2$ between the SNPs.(Red boxes $r^2$=1, white boxes $r^2$=0, others = $1 > r^2 > 0$). Squares without a number indicate D′=1. 2SNPs in 2 tests captured 9 of 9 (100%) alleles at $r^2 1 \geq 0.8$. Mean max $r^2$ is 1.0.

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