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Polymorphism −116C/G of Human X-box-Binding Protein 1 Promoter is Associated with Risk of Alzheimer's Disease

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SUMMARY

Aim: Alzheimer's disease (AD) is a multifactor disease that has been reported to have a close association with endoplasmic reticulum (ER) stress response. In the response, the regulator factor human X-box-binding protein 1 (XBP1) has been shown to facilitate the refolding and degradation of misfolded proteins, prevent neurotoxicity of amyloid-beta (Aβ) and tau, and play an important role in the survival of neurons. The aim in the study was to analyze the potential association between the −116C/G polymorphism of *XBP1* and the risk of AD. **Methods:** The association between −116C/G polymorphism of *XBP1* promoter and possible risk of AD was assessed among 276 patients with AD and 254 matched healthy individuals in a case–control study. **Results:** Overall, there was a significantly statistical difference in genotype ($P = 0.0354$) and allele frequencies ($P = 0.0150$, OR = 1.3642, 95% CI = 1.0618–1.7528) between the AD subjects and control subjects, showing that the −116C/G polymorphism of *XBP1* might lead to increased susceptibility for AD in a Chinese Han population. In addition, the −116CG and −116GG genotypes were significantly associated with increased AD risk in female ($P = 0.0217$) and in subjects with APOE ε4 (−) ($P = 0.0070$) in stratified analyses, and the −116CC genotype was significantly associated with fast cognitive deterioration in the AD patients ($P = 0.0270$). **Conclusion:** The study supports a role for the −116C/G polymorphism of *XBP1* gene in the pathogenesis of AD, and further studies with a larger sample size and detailed data should be performed in other populations.

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Introduction

Senile plaques and neurofibrillary tangles are prominent pathologic hallmarks in the brains of patients with Alzheimer's disease (AD). Despite decades of exploration, the molecular mechanism of the disorder remains elusive. However, increasing evidence suggests that a specific cellular response known as endoplasmic reticulum (ER) stress response that has an important function in synthesis, post-translational modification, and folding of protein in cell [1] might be relevant to the understanding of the disorder. Intracellular accumulation of amyloid-beta (Aβ) and phosphorylated tau proteins is a characteristic feature of AD [2]. These misfolded and aggregated proteins are a quality problem in neurons and can trigger ER stress. To alleviate the stress-induced disturbances in cellular homeostasis, the ER stress response is activated to defend the neuron [3]. Therefore, it is not surprising that a number of studies have provided evidence that ER stress response is present in AD. For instance, in postmortem studies, ER stress response was activated in hippocampal neurons of AD brains and neurons displayed elevated levels of the ER chaperone Grp78/BiP, and phosphorylation (activation) of the ER stress response sensor PERK and its target eIF2α [4]. Further, detection of immunoreactivity also determined activated ER stress response transducer PERK launching the most immediate response to ER stress, and the downstream effectors of PERK and eIF2alpha in sections of the hippocampus of AD patients [5]. In addition, in studies of cell

model, exogenous Aβ induced the phosphorylation of ER stress response sensor PERK to protect for cultured neuronal cells, whereas exogenous Aβ enhanced neuronal cell death when silencing of PERK by small interfering RNA in Aβ-treated neuronal cells [6]. Therefore, it is possible that ER stress response is activated to protect neuron homeostasis and prevent neurodegeneration linked to AD pathogenesis.

In the ER stress response, human X-box-binding protein 1 (XBP1), an important transcription factor, has been shown to play a crucial role in protection of neurons by facilitating the refolding and degradation of Aβ and tau proteins [3,7]. Overexpression of spliced XBP1 could prevent cell death mediated by exposure to Aβ in two different AD models of Drosophila melanogaster neurons and mammalian PC12 cells, whereas knockdown of *XBP1* exacerbated Aβ toxicity [8]. Moreover, reducing XBP1 function with a loss of function *XBP1* allele or an RNAi against XBP1 significantly increased apoptosis mediated by expression of tau in a transgenic Drosophila model of AD, whereas wild type of *XBP1* improved tau toxicity [7]. In addition, genomewide screen has identified a number of XBP1-regulating ER stress target genes associated with AD. XBP1 can bind to the UBQLN1 promoters controlling APP trafficking to generate Aβ and can also bind to the gene promoters involved in APP trafficking and processing as well as in AD pathogenesis [9]. These findings demonstrate that XBP1 is activated in tissues suffering from neurodegeneration and support the idea that XBP1 activation is a neuroprotective response.

XBP1, the gene encoding for XBP1, is located on chromosome 22q12 and is a pivotal gene involved in a complex cascade of events in the ER stress response [10]. A recent study has confirmed that a genetic variant (−116C/G, rs2269577, changing the consensus motif ACGT into AGGT) at nucleotide −116 of *XBP1* gene identified by Kakiuchi et al. was associated with an aberrant *XBP1* transcriptional activity [11]. In the study, the −116C→G polymorphism in the promoter region of the *XBP1* gene was demonstrated to abolish the putative XBP1-binding motif and impair the XBP1 loop in lymphoblastoid cells. After ER stress was induced by thapsigargin, XBP1-dependent transcription activity of the −116G allele was lower than that of the −116C allele, and induction of XBP1 expression was markedly reduced in the lymphoblastoid cells with the G allele when response to ER stress. These findings indicated that −116C→G polymorphism compromised XBP1-involved regulatory mechanism in ER stress response [11]. The role of this polymorphism has been extensively studied in many diseases including dermatological and neuropsychological diseases. Ren et al. [12] showed that the transcriptional modulation of XBP1 expression by −116C/G polymorphism had an impact on the development of vitiligo. Chen et al. [13] reported polymorphism of −116C/G in *XBP1* gene was a genetic risk factor for schizophrenia. Masui et al. [14] demonstrated that there was a possible association between the single-nucleotide polymorphism (−116C/G) of the *XBP1* gene and lithium prophylaxis in bipolar disorder.

However, whether the −116C/G polymorphism in the *XBP1* gene is associated with AD in populations has not yet been reported. Thus, a hospital-based case–control study was performed to explore the association of the *XBP1* −116C/G polymorphism with AD risk and related traits in a Chinese Han population.

Patients and Methods

Study Population

Consecutive patients with AD as case series were enrolled from the Department of Neurology at the first affiliated hospital of Harbin Medical University based on criteria consistent with the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) Alzheimer's Criteria extensively updated in 2007 [15] for diagnosis. Meanwhile, unrelated controls were recruited from healthy people who were performed physical examination, were given clinical, mental, and neurological examination, and had mini-mental status examination >27 in above hospitals. All the above subjects were Northern Han Chinese in origin. Subjects who had evidence of vascular and "mixed" dementia, history of cancers, coronary artery disease, cerebrovascular diseases, and diabetes were excluded. A written informed consent was obtained from each participant after the study was explained in detail. The study was performed with the approval of the ethical committee of Harbin Medical University.

The demographic, physical, and biochemical characteristics were extensively assessed from both the patients with AD and the controls. The characteristics in our study included age, gender, body mass index (BMI, BMI was calculated as weight (kg)/height^2 (m^2)), total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and APOE ϵ4 carrier status.

A large subset (n = 196, the mean age was 72.9 $\pm$ 7.3 and the gender [male/female] ratio was 1:1.20) of the patients were followed up for 2 years, and cognitive performances were recorded. Longitudinal cognitive decline was assessed by MMSE scores according to the method suggested elsewhere [16], and patients were divided into three groups with different degree of deterioration rate (fast = decrement of more than 5 points/year; intermediate = 2–4.9 points/year; slow = less than 2 points/year).

SNP Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using QIAGEN QIAamp DNA Mini Blood Kit (Hilden, Germany). A total of 50 ng genomic DNA was amplified in a 100 μL final volume PCR reaction containing 10× buffer, 200 μmol/L each of dATP, dCTP, dGTP, dTTP, 1.5 mmol/L $MgCl_2$, 10 pmol of each primer, and 0.5 unit *Taq* polymerase (Takara, Shiga, Japan). Primers for rs2269577 were designed: 5′-CGACAGAAGCAGAACTTTAG-3′ (forward primer) and 5′-CTGAGGTAATTCTCTGTTAG-3′ (backward primer) [17]. The amplification was performed at 95°C for 5 min with an initial denaturation, followed by 35 cycles of 95°C for 1 min, 55°C for 1 min, and 72°C for 1 min and a final extension of 5 min at 72°C. About 1 μL of amplified PCR products was mixed with 1 μL of formamide containing dextran blue dye, which was subjected to 3% agarose gels and visualized by staining with ethidium bromide. The SNPs were detected by GeneScan analysis software (ABI, Foster City, CA, USA). APOE genotyping was performed as described previously [18].

Statistical Analysis

In univariate analyses, *U*-test for quantitative data and chi-squared test (or Fisher's exact test) for qualitative data were used to determine whether there was a significant difference in relevant factors between cases and controls. Chi-squared test was carried out to assess the deviations from the Hardy–Weinberg equilibrium (HWE) and frequencies of Genotype and allele in *XBP1* among cases and controls. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated to compare cases to controls in association with genotypes and alleles. All statistical tests were two-sided with SPSS 11.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was taken as P value < 0.05.

Results

Baseline Characteristics

The baseline characteristics of all participants in the study were summarized in Table 1. In 530 participants, 276 were patients with AD and 254 were healthy controls. The mean age was 73.8 years (±7.6 years) for the AD subjects and 71.2 years (±6.4 years) for the control subjects. The gender (male/female) ratio was 1:1.09 in the case group, and the gender ratio was 1.05:1 in the control group. The AD subjects had older mean age ($P < 0.05$), higher BMI ($P = 0.0142$) and more APOE ε4+ frequencies ($P < 0.0001$) than the control subjects had.

Table 1 Baseline characteristics of subjects in case group and control group

Characteristics	Case group	Control group	*P* value
Total, N	276	254	
Mean age (years)	73.8 ± 7.6	71.2 ± 6.4	<0.05
Gender			
Male	132	130	0.4403
Female	144	124	
Education (years)	8.87 ± 3.65	9.32 ± 3.73	0.1612
BMI (kg/m^2)	24.52 ± 4.19	23.64 ± 4.03	0.0142
Waist circumference (cm)	86.37 ± 10.07	87.64 ± 10.96	0.1650
Total cholesterol (mmol/L)	4.49 ± 0.82	4.57 ± 0.85	0.2707
Triglyceride (mmol/L)	1.62 ± 0.78	1.64 ± 0.83	0.7750
HDL-C (mmol/L)	1.21 ± 0.35	1.17 ± 0.30	0.1601
LDL-C (mmol/L)	2.85 ± 0.92	2.79 ± 0.75	0.4133
APOE ε4 (+)	117	48	<0.0001

Continuous data are expressed as the means ± SEM.

Polymorphism of XBP1 Gene and the Risk of AD

The genotype and allele frequencies of −116C/G polymorphism in the study were shown in Table 2. The deviation from Hardy–Weinberg equilibrium for the polymorphism examined was not found in the distributions of genotypes in patients and controls (data not shown).

Comparison of genotype distributions between AD subjects and control subjects by the chi-squared test revealed that there was a statistical association ($\chi^2 = 6.6813$, $P = 0.0354$) between the −116C/G polymorphism of *XBP1* and the risk of the AD with higher frequency of CG ($\chi^2 = 4.2045$, $P = 0.0403$; OR = 1.9794, 95% CI = 1.1721–3.3426) and GG ($\chi^2 = 6.6309$, $P = 0.0100$; OR = 1.3642, 95% CI = 1.0618–1.7528) in AD cases. In addition, a significant difference was observed in the frequency of the *XBP1* C-116G alleles between AD cases and controls ($\chi^2 = 5.9133$, $P = 0.0150$; OR = 1.3642, 95% CI = 1.0618–1.7528), with the frequency of the −116G allele being higher in AD cases (Table 2).

The Association of XBP1 Gene Polymorphisms with Demographic Characteristics

The association of *XBP1* gene polymorphism with demographic characteristics was shown in Table 3. When the sample was stratified by age, no significant differences of genotype or allele frequencies were found between AD cases and controls in either <65 years samples and ≥65 years samples. In the stratified analysis by gender, the increased risk associated with the variant genotypes (−116CG and −116GG) tended to be more evident in female subjects ($P = 0.0217$). But in male subjects, the association between the *XBP1* polymorphism and AD risk was not statistically significant. After the sample was stratified by APOE e4 carrier status, no significant differences of the genotype or allele frequencies between the AD cases and the controls were detected in the APOE e4 (+) samples. However, in the APOE e4 (−) samples, the −116 (CG + GG) genotype and −116G allele frequencies in the AD patients were, respectively, higher than those in the controls, and the difference was statistically significant for the genotypes (CG

Table 2 Distribution of genotype and allele frequencies of the *XBP1* C-116G polymorphism among case group and control group

Reference SNP ID	Geno-type and allele	Case group (N = 276), n (%)	Control group (N = 254), n (%)	OR (95% CI)	χ^2	*P* value
rs2269577	CC	31 (11.23)	48 (18.90)	1	6.6813	0.0354†
	CG	121 (43.84)	109 (42.91)	1.7189 (1.0214–2.8927)	4.2045	0.0403*
	GG	124 (44.93)	97 (38.19)	1.9794 (1.1721–3.3426)	6.6309	0.0100**
	C	183 (33.15)	205 (40.35)	1	5.9133	0.0150
	G	369 (66.85)	303 (59.65)	1.3642 (1.0618–1.7528)		

†*P* value for comparison of three genotypes between case group and control group. **P* value for comparison of CG versus CC. ***P* value for comparison of GG versus CC.

Table 3 The relationship of baseline characteristics to genotypes and alleles among subjects in case group and control group

	Case group, n (%)					Control group, n (%)						
	Genotype			Allele		Genotype			Allele			
Characteristics	CC	CG	GG	C	G	CC	CG	GG	C	G	P_G	P_A
Age												
<65 years	9 (9.28)	41 (42.27)	47 (48.45)	59 (30.41)	135 (69.59)	17 (21.79)	29 (37.18)	32 (41.03)	63 (40.38)	93 (59.62)	0.0683	0.0517
≥ 65 years	22 (12.29)	80 (44.69)	77 (43.02)	124 (34.64)	234 (65.36)	31 (17.61)	80 (45.45)	65 (36.93)	142 (40.34)	210 (59.66)	0.2840	0.1164
Gender												
Male	18 (13.64)	54 (40.91)	60 (45.45)	90 (34.09)	174 (65.91)	22 (16.92)	58 (44.62)	50 (38.46)	102 (39.23)	158 (60.77)	0.4875	0.2221
Female	13 (9.03)	67 (46.53)	64 (44.44)	93 (32.29)	195 (67.71)	26 (20.97)	51 (41.13)	47 (37.90)	103 (41.53)	145 (58.47)	0.0217	0.0268
APOE geno-type												
APOE ϵ4 (+)	17 (14.53)	47 (40.17)	53 (45.30)	81 (34.62)	153 (65.38)	5 (10.42)	25 (52.08)	18 (37.50)	35 (36.46)	61 (63.54)	0.3642	0.7501
APOE ϵ4 (−)	14 (9.94)	74 (45.96)	71 (44.10)	102 (32.08)	216 (67.92)	43 (20.87)	84 (40.78)	79 (38.35)	170 (41.26)	242 (58.74)	0.0070	0.0109

P value of difference in genotypes (P_G) and alleles (P_A) between case group and control group.

vs. CC: $\chi^2 = 8.5957$, $P = 0.0034$, OR = 2.7058, 95% CI = 1.3718–5.3368; GG vs. CC: $\chi^2 = 8.8503$, $P = 0.0029$, OR = 2.7604, 95% CI = 1.3943–5.4649) and statistically significant for the alleles ($\chi^2 = 6.4793$, $P = 0.0109$, OR = 1.4876, 95% CI = 1.0949–2.0211).

The Association of XBP1 Gene Polymorphisms with Cognitive Ability

The association between SNPs and quantitative traits related to cognitive ability was analyzed in subset (n = 196) of the Chinese Han patients with clinical diagnosis of AD followed up for 2 years (Table 4). Patients were divided into three cohorts according to the degree of cognitive deterioration (fast, intermediate, and slow) and stratified by the XBP1 genotypes. Among the examined genotypes, an increased representation of the −116CC genotype was observed in AD patients with fast (29.55%) cognitive deterioration rate in comparison with those in patients with intermediate (12.82%) and slow (10.81%) deterioration rate ($P = 0.0170$).

Discussion

Accumulation of cytotoxic protein aggregates, extensive oxidative stress, and diminished brain metabolism is the characteristic features of AD [19]. ER is a highly sensitive organelle that can recognize disturbances in cellular homeostasis, and therefore, it is not surprising that a number of studies have demonstrated that ER stress response is present in AD brains [20]. Although the exact implications of ER stress response in AD is unclear, elevated levels of protective ER stress response proteins such as transcription factor XBP1 are observed in the frontal cortex of AD patients, suggesting that ER stress response can defend the host by activating the adaptive signaling pathway [21].

Recently, the protective activity of XBP1 against amyloid-β1-42 (Aβ42) neurotoxicity has been identified by Casas Tinto et al. [8]. Their results showed that XBP1 overexpression could prevent Aβ neurotoxicity and produced neuroprotective activity mediated by the downregulation of a specific isoform of the ryanodine Ca21 channel, RyR3 in the two different AD models (flies expressing Aβ and mammalian cultured neurons treated with Aβ oligomers), while reduction of the endogenous *XBP1* function by RNAi exacerbated the Aß42 phenotype. Therefore, the gene encoding XBP1 can be viewed as an interesting candidate for AD.

Promoter variants of *XBP1* exert functional effects on the activity of the *XBP1* itself and thus may lead to aberrant XBP1 expression. −116C/G polymorphism of *XBP1* has been shown to have a

Table 4 Genotype distribution of the C-116G polymorphism in *XBP1* among AD patients stratified according to the rate of cognitive decline

	Genotype, n (%)	
Cognitive decline	CC	CG + GG
Fast (n = 44)	13 (29.55)	31 (70.45)*
Intermediate (n = 78)	10 (12.82)	68 (87.18)
Slow (n = 74)	8 (10.81)	66 (89.19)

*$\chi^2 = 8.1471$, $P = 0.0170$.

role in the ER stress response because of differential transcription activity among patients with the different alleles [11]. The level of XBP1-dependent transcription activity of the G allele is lower than that of the C allele; therefore, the −116C/G polymorphism may lead to variability in the ER stress response and causes an impairment of its positive feedback system, which increases the risk of bipolar disorder and schizophrenia [11,13]. The functional effect of the −116G polymorphism, together with the protective role of XBP1 in AD, highlights the possibility that inheritance of the −116G allele of *XBP1* may increase susceptibility to AD. Our observation that the variant −116G allele was more frequent in patients with AD is therefore in accordance with the hypothesis. We speculate that *XBP1* −116C/G polymorphism could eventually influence the ability of ER stress response to maintain the neuron homeostasis, and thereby accelerate the apoptosis of neurons. To the best of our knowledge, this is the first study to show a genetic link between AD and the *XBP1* gene, and we found that the variant genotypes [−116(CG + GG)] exhibited an association with AD with relative risk of 1.49 ($P = 0.025$). In addition to increase the risk of overall disease when compared with the wild-type genotype, −116C/G polymorphism was also related to gender and APOE ϵ4 status-adjusted occurrence of AD as well as decline of cognitive ability. Taken together, these results suggest a potential mechanism linking the mutation to AD, which has not been explored so far.

The stratified analysis by gender revealed that, among female, those with the variant genotypes had significantly higher risk of AD ($P = 0.0217$), while among male, no statistical significance was noted. The findings suggest a gender-dependent genetic component in AD. This observation is not surprising, because there is substantial evidence for sex differences in the pathogenesis and pathophysiology of AD, which may have arisen from interplay between sex hormones and gene. According to the report of Sengupta, XBP1 expression is estrogen regulated at the transcriptional level and recruitment of estrogen receptor alpha (ERα) on the XBP1 promoter as well as enhancer regions has been confirmed using chromatin immunoprecipitation (ChIP) followed by tiled microarray on human chromosomes 21 and 22 [22,23]. Further, epidemiological evidence also has shown that estrogen deficiency had an important effect on development of AD [24]. Therefore, it is possible that −116C/G polymorphism in *XBP1* is associated with susceptibility to AD by coordinating with estrogen deficiency in the older women. Additionally, another explanation for the gender difference of AD risk is that the maintenance of higher testosterone levels may prove beneficial for cognitive and brain function in elderly men. The mechanism may be as follows: (i) testosterone has been reported to bind to androgen receptors (AR) to protect for hippocampus and the surrounding regions that are usually the first to be decline-prone in function during AD pathogenesis [25]. In AR-dependent mechanism, testosterone may protect neuronal damage from oxidative stress to which hippocampal neurons are particularly sensitive [26] and prevent neuronal apoptosis, which is thought to play an important role in both cognitive decline and AD [27]. (ii) Testosterone has been demonstrated to prevent the hyperphosphorylation of tau and reduce tangle formation [28]. (iii) Testosterone has been shown to downregulate β-secretase to reduce Aβ accumulation and upregulated Neprilysin (NEP) to enhance Aβ disruption [29]. Therefore, it is possible that the higher testosterone levels in male than in female lead to difference in susceptibility to AD.

It is well established that *APOE ϵ4* plays an important role in the pathogenic mechanism of AD by regulating the formation of Aβ, and the *APOE ϵ4* is the only established genetic risk factor for AD [18]. Stratification analyses according to *APOE ϵ4* status in the study showed that there were significant differences in genotype and allele in the *APOE ϵ4* (−) sample with a higher frequency of the G allele among AD subjects than that among the control subjects. This may be attributable to the independent role of the −116C/G polymorphism on AD development. In fact, several investigations have reported the *APOE4*-independent genetic effects on risk of AD. Li et al. [30] showed that *RAGE* G82S polymorphism was associated with risk of AD development independently of *APOE ϵ4*. Lin et al. [31] reported that rs11833579 polymorphism of *NINJ2* gene still was significantly associated with AD among non-*APOE ϵ4* carriers after controlling for false discovery rate (OR = 0.38, 95% CI = 0.18–0.82). Cellini et al. [32] also documented that the late-onset AD association for this rs661057 SNP was confined to APOEε4 noncarriers for both the T/T genotype ($P = 0.002$; OR = 1.86, 95% CI = 1.22–2.85) and T allele ($P = 0.002$; OR = 1.61, 95% CI = 1.18–2.21). Given the paucity of known major risk factors in this group, this observation calls for further attention and independent replication.

Our findings showed that the *XBP1* −116C/G polymorphism was associated with a differential clinical cognitive deterioration in AD patients, because the CC genotype was associated with a fast rate of decline. On the other hand, the G carrier status was more represented in the group of patients with slow rate of cognitive decline. Therefore, this polymorphism appears to modify the clinical expression of the disease and may be considered a disease modifier factor. This result is contrary to our expectation, and the potential mechanism accounting for this phenomenon is unknown. In fact, although the initial participation of the ER stress response in AD pathogenesis might be neuroprotective, sustained activation of the ER stress response in AD might initiate or mediate neurodegeneration. Prolonged activation of the ER stress response can be detrimental to neurons because a delayed defense decreases the viability of neurons and can shift the ER stress response to switch on an apoptotic program [33]. Additionally, by sequestering chaperones or reducing protein translation, the chronic ER stress response has the potential to impair the function of astrocytes, compromising their ability to support and maintain neurons. These scenarios, all potentially modified by the *XBP1* variant, represent a potential explanation for the slow cognitive deterioration in −116G carriers.

In the study, all subjects are from Han race, although avoiding the bias of ethnicity, which led to inability to generalization of results. So far, many studies on population-dependent variations in the allele −116C frequency of *XBP1* polymorphism have been performed. Within Asian populations, −116C allele frequencies were observed from 29.3 to 38.0% in Japanese healthy control populations [11, 14, 17, 34–37]; 31.37% in Korean healthy control population [38]; 33.7–43.0% in Chinese healthy control populations [12, 39]. Within European populations, −116C allele frequencies were observed from 42.5 to 43.6% in Turkish healthy control populations [40,41]; 29.23% in German healthy control population [42]; 34.57% in Polish healthy control population

[42]; 34.70% in Swedish healthy control population [42]. Observed varieties demonstrate a different distribution pattern of *XBP1* allele −116C in various populations. Thus, similar investigations in ethnically different populations are recommended to clarify the role of *XBP1* gene polymorphism in susceptibility to AD. In conclusion, these results suggest that *XBP1* is a novel susceptibility gene in Chinese AD patients, and furthermore, that *XBP1* polymorphism may be related to severe clinical symptoms of AD. Our results indicate that the genetic polymorphism of *XBP1* can contribute to the cognitive decline in AD patients and support the hypothesis that the genetic polymorphism of *XBP1* may provide an important point for intervention. However, our finding needs to be confirmed by extended studies involving an independent cohort of patients before drawing a final conclusion regarding the association of the *XBP1* polymorphisms with AD.

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Conflict of Interest

The authors declare no conflict of interest.

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