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Association between BACE1 gene polymorphisms and focal seizures in a Chinese Han population

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Abstract

Background: Beta-secretase 1 (BACE1) is attracting increasing attention for its vital role in pathogenesis of many neuropsychiatric disorders and many studies also have indicated BACE1 as a possible risk factor for seizures, but not any studies have reported association between BACE1 gene polymorphisms and seizures. Therefore, we investigated the possible association between focal seizures and BACE1 gene polymorphisms in the present study.

Methods: A total of 162 patients and 211 health controls were enrolled in this study and polymorphisms of BACE1 gene were detected using polymerase chain reaction (PCR)-ligase detection reaction method.

Results: The frequency of genotype AT for BACE1 rs535860 (A>T) was significantly higher (24.1%) in patients compared to controls (14.7%) (OR = 1.836, 95% CI = 1.086–3.102, $P = .023$). Intriguingly, we only found the significant difference of BACE1 SNP genotype and allele frequency among males but not females. However, no statistically significant results were presented for the genotype distributions of rs525493 (G>T) and rs638405(C>G) polymorphisms between patients and controls.

Conclusion: Our study demonstrated there may exist an association between BACE1 rs535860 (A>T) polymorphism and focal seizures in Chinese Han males.

Abbreviations: BACE1 = beta-secretase, Na_v = voltage-gated sodium channels, NRG1 = neuregulin-1.

Keywords: BACE1, focal seizures, gene polymorphisms

1. Introduction

Epilepsy is a chronic episode of noncommunicable disorder in the brain due to abnormal excessive or synchronous neuronal activity and it affects about 70 million people worldwide,[1] accounting for approximately 1% of the population currently.[2,3] It is reported that 1 epilepsy patient may affected about 4 normal people at some point in time.[4] Focal seizures (also called partial seizures) are one of the most common types of epilepsy and are characterized by affecting initially only one hemisphere of the brain. It can be split into 2 main categories: simple partial seizures and complex partial seizures. The symptoms of the focal seizures will vary on the base of where the seizure occurs.[5,6]

Beta-secretase 1 (BACE1) is an enzyme encoded by the BACE1 gene in human and also known as beta-site amyloid precursor protein cleaving enzyme 1.[7] It is important in the formation of myelin sheaths in peripheral nerve cells.[8] It is widely accepted that BACE1 cleaves amyloid precursor protein (APP) at the N-terminal end of the β-amyloid peptide (Aβ) and is identified as the Alzheimer's β-secretase.[9,10] It has been validated that some of the BACE1 substrates may conducive to the synaptic deficits seen with BACE blockade, including the seizure-related gene 6.[11] Seizures is also associated with BACE1, since that the patients displaying seizures symptom show earlier onset of cognitive decline and faster transition into severe dementia.[12,13] Additionally 2 groups have reported that BACE1 knockout mice develop epileptic seizures.[14,15] Moreover, BACE1 can hydrolyze the neuregulin (NRG1), which show antiepilepsy effect [8] and one of our previous studies indicate that the SNP of NGR1 is associated with the seizures susceptibility.[16] Based on these findings, we speculate that the gene polymorphisms of the BACE1 may increase the risk of seizure onset. The rs535860, rs525493, and rs638405 were the most studied BACE1 gene polymorphisms and showed potential effect of different alleles, the coding position of which are c.*404T>A, c.261+3543A>C, and c.579G>C, respectively, located in Chromosome11. The aim of this present study was to investigate the role of BACE1 (rs535860, rs525493, rs638405) gene polymorphisms in Chinese focal seizures population, which were indeed more widely investigated in Caucasians but less explored among Chinese Han population, which constitutes

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approximately 92% of the population of China and is the nationality with the largest population in the world.

2. Materials and methods

2.1. Subjects

A total of 162 unrelated Chinese patients (male:female = 91:71) younger than 14 years participated in this study and they were recruited at the outpatient clinic of the Second Xiangya Hospital of Hunan Province from November 2013 to August 2015. The patients were diagnosed according to the "Classification of Epilepsies and Epileptic Syndromes" proposed by the Commission on Classification and Terminology of the International League Against Epilepsy. The mean age at seizure onset was 5.5 ± 3.6 years (range 0.08–13.5 years), and the mean duration of epilepsy was 2.1 ± 1.7 years (range 0–6.3 years). The diagnosis of focal seizures for each patients was made on the basis of a range of clinical seizure semiology, interictal and ictal EEG, typical mesio-temporal auras, and MRI criteria, which was carried out by epileptologist from Second Xiangya Hospital. None of the patients had mass malformations of cortical development, traumatic brain injury or lesion from vascular malformation or tumor. Anyone had mental retardation, psychiatric difficulties, or early psychiatric manifestations were excluded. 211 healthy individuals (males: female = 104:107), less than 15 years of age, ethnicity and sex matched from the same area were enrolled to form the control group. None of the control participants had any history of central nervous system disorder or any other medical disorders. Patients and controls (their parents, and children (if ≥12 years) provided written informed consent to participate in this study approved by the Institutional Ethics Committee.

2.2. DNA isolation and genotyping

About 1 mL venous blood was collected and purified from the subjects using SQ Blood DNA Kit II (D0714-250, Omega Bio-Tek, Norcross, UK) according to the manufacturer's instructions. All DNA samples were genotyped using the polymerase chain reaction (PCR)-ligase detection reaction method. The PCR of the 3 target single-nucleotide polymorphisms was amplified by the following primers:

for rs535860, forward 5′-AGGGAAACAAGCTTGGTCTC-3′ and reverse 5′-CAGAAGTACTGGCATCACAC-3′;

for rs525493, forward 5′-GTCTCTTCCTGAAAGATTGC-3′ and reverse 5′- TTGGCCTTCAGATATAAGGG -3′;

for rs638405, forward 5′-TCTCTGGTATACACCCATCC-3′ and reverse 5′- TCCTTGCAGTCCATTTTCAG -3′. A DNA sequencer was applied to detect the amplified products. More than 10% of the samples were randomly selected and retested to verify the validity of this procedure, and the results of the retested samples were consistent with those obtained from the original sample.

2.3. Statistical analysis

All genotyping results in focal seizures patients and in controls were tested for Hardy–Weinberg Equilibrium (HWE) by applying Chi-square test (χ^2 test). Differences in genotype distributions and allele frequencies in cases and controls were compared between groups for statistical significance by Chi-square statistics (χ^2 test). The associations between the genotypes and the focal seizures were evaluated via the odds ratio (OR), with a 95% confidence interval (CI) (95% CI). A two-sided *P* value below .05 was considered statistically significant. All statistical analyses were performed with SPSS 17.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

The observed BACE1 (rs535860, rs525493, rs638405) genotype frequencies were in accordance with the Hardy–Weinberg equilibrium in both study groups. We then analyzed the allele and genotype frequencies of the BACE1 SNP in 162 focal seizures patients and 211 controls. The distributions of BACE1 rs535860 (A>T), rs525493 (G>T), rs638405 (C>G) SNP restriction site genotypes in the focal seizures patients and the controls are presented in Table 1. It was observed that there was no

Table 1

Genotypic and allelic distribution of the BACE1 gene between all patients (n = 162) and controls (n = 211).

SNP	Genotype/allele	Case (%)	Control (%)	*P* value* (χ^2)	OR (95% CI)	*P* value†
rs535860	AA	122 (75.3)	178 (84.4)	.069 (5.356)	1.00	Referent
	AT	39 (24.1)	31 (14.7)		1.836 (1.086–3.102)	.023**
	TT	1 (0.6)	2 (0.9)		0.730 (0.065–8.137)	.798
	AT+TT	40 (24.7)	33 (14.6)	.029 (4.770)	1.769 (1.056–2.961)	.030**
	A	283 (87.3)	387 (91.7)	.051 (3.809)	1.00	Referent
	T	41 (12.7)	35 (8.3)		1.602 (0.995–2.579)	.053
rs525493	GG	95 (58.6)	130 (61.6)	.839 (0.351)	1.00	Referent
	GT	60 (37.1)	73 (34.6)		1.125 (0.730–1.732)	.594
	TT	7 (4.3)	8 (3.8)		1.197 (0.420–3.416)	.763
	GT+TT	67 (41.4)	81 (38.4)	.561 (0.338)	1.108 (0.781–1.570)	.561
	G	250 (77.2)	333 (78.9)	.567 (0.329)	1.00	Referent
	T	74 (22.8)	89 (21.1)		1.108 (0.781–1.570)	.567
rs638405	CC	66 (40.8)	82 (38.9)	.925 (0.157)	1.00	Referent
	CG	77 (47.5)	96 (45.5)		0.997 (0.641–1.550)	.998
	GG	19 (11.7)	33 (15.6)		0.715 (0.373–1.371)	.313
	CG+GG	96 (59.2)	129 (61.1)	.866 (0.029)	0.925 (0.609–1.193)	.866
	C	209 (35.5)	260 (61.6)	.417 (0.658)	1.00	Referent
	G	115 (64.5)	162 (38.4)		0.883 (0.654–1.193)	.417

CI = confidence interval, OR = odds ratio.

* *P* value for genotype and allele frequencies in cases and controls using 2-sided χ^2 test.

† *P* values adjusted by age and gender using logistic regression.

** $P < .05$.

Table 2

Genotypic and allelic distribution of the BACE1 gene between male patients (n = 91) and controls (n = 104).

SNP	Genotype/allele	Case (%)	Control (%)	*P* value* (χ^2)	OR (95% CI)	*P* value†
rs535860	AA	66 (72.5)	90 (86.5)	.027 (7.191)	1.00	Referent
	AT	24 (26.4)	12 (11.6)		2.727 (1.273–5.845)	.010**
	TT	1 (1.1)	2 (1.9)		0.628 (0.061–7.678)	.757
	AT+TT	25 (27.5)	14 (13.5)	.015 (5.955)	2.435 (1.177–5.039)	.016**
	A	156 (85.7)	192 (92.3)	.036 (4.391)	1.00	Referent
	T	26 (14.3)	16 (7.7)		2.000 (1.036–3.860)	.039**
rs525493	GG	52 (57.1)	67 (64.4)	.580 (1.088)	1.00	Referent
	GT	35 (38.5)	33 (31.7)		1.367 (0.752–2.486)	.306
	TT	4 (4.4)	4 (3.9)		1.288 (0.308–5.397)	.729
	GT+TT	39 (42.8)	37 (35.6)	.298 (1.082)	1.358 (0.762–2.420)	.299
	G	139 (76.4)	167 (80.3)	.348 (0.880)	1.00	Referent
	T	43 (23.6)	41 (19.7)		1.260 (0.777–2.043)	.349
rs638405	CC	40 (44.0)	44 (42.3)	.973 (0.054)	1.00	Referent
	CG	39 (42.8)	46 (44.2)		0.933 (0.510–1.707)	.821
	GG	12 (13.2)	14 (13.5)		0.943 (0.390–2.278)	.896
	CG+GG	51 (56.0)	60 (57.7)	.817 (0.054)	0.935 (0.530–1.650)	.817
	C	119 (65.4)	134 (64.4)	.843 (0.039)	1.00	Referent
	G	63 (34.6)	74 (35.6)		0.959 (0.632–1.455)	.843

CI = confidence interval, OR = odds ratio.

* *P* value for genotype and allele frequencies in cases and controls using 2-sided χ^2 test.

† *P* values adjusted by age and gender using logistic regression.

** $P < .05$.

statistically significant difference between patients and controls for the genotype and allele distributions of rs525493 (G>T) and rs638405(C>G) polymorphisms. However, the frequency of rs535860 genotype with AT was significantly higher among the focal seizures patients relative to the controls (OR = 1.836, 95% CI = 1.086–3.102, $P = .023$). Moreover, the genotype of AT+TT for rs535860 showed a significant association with focal seizures group (OR = 1.769, 95% CI = 1.056–2.961, $P = .030$) while there was no significant difference in allele frequency of BACE1 rs535860 (A>T).

It was interesting that the statistically significant difference of BACE1 rs535860 genotype only existed among males (OR = 2.727, 95% CI = 1.273–5.845, $P = .010$ for AA vs AT; OR = 2.435, 95% CI = 1.177–5.039, $P = .016$ for AA vs AT + TT; Table 2) while there was no statistically significant difference among females (OR = 1.241, 95% CI = 0.583–2.640, $P = .576$ for AA vs AT, Table 3). Additional, the rs535860 allele frequency also existed a statistically difference among males (OR = 2.000, 95% CI = 1.036–3.860, $P = .039$ for A vs T; Table 2).

4. Discussion

Alzheimer's disease (AD) is a common age-related and devastating neurodegenerative disorder involving a decline in memory

Table 3

Genotypic and allelic distribution of the BACE1 gene between female patients (n = 71) and controls (n = 107).

SNP	Genotype/allele	Case (%)	Control (%)	*P* value* (χ^2)	OR (95% CI)	*P* value†
rs535860	AA	56 (78.9)	88 (82.2)	.575 (0.314)	1.00	Referent
	AT	15 (21.1)	19 (17.8)		1.241 (0.583–2.640)	.576
	TT	0 (0)	0 (0)	–	–	–
	AT+TT	15 (21.1)	19 (17.8)		1.241 (0.583–2.640)	.576
	A	127 (89.4)	195 (91.1)	.596 (0.281)	1.00	Referent
	T	15 (10.6)	19 (8.9)		1.212 (0.594–2.473)	.597
rs525493	GG	43 (60.6)	63 (58.9)	.951 (0.101)	1.00	Referent
	GT	25 (35.2)	40 (37.4)		0.916 (0.486–1.724)	.785
	TT	3 (4.2)	4 (3.7)		1.099 (0.234–5.518)	.905
	GT+TT	28 (39.4)	44 (41.1)	.823 (0.050)	0.932 (0.505–1.720)	.823
	G	111 (78.2)	166 (77.6)	.894 (0.018)	1.00	Referent
	T	31 (21.8)	48 (22.4)		0.966 (0.579–1.611)	.894
rs638405	CC	26 (36.6)	38 (35.5)	.327 (2.235)	1.00	Referent
	CG	38 (53.5)	50 (46.7)		1.111 (0.578–2.135)	.753
	GG	7 (9.9)	19 (17.8)		0.538 (0.198–1.464)	.225
	CG+GG	45 (63.4)	69 (64.5)	.880 (0.023)	0.953 (0.511–1.780)	.880
	C	90 (63.4)	126 (58.9)	.197 (1.666)	1.00	Referent
	G	52 (36.6)	88 (41.1)		0.827 (0.535–1.280)	.395

CI = confidence interval, OR = odds ratio.

* *P* value for genotype and allele frequencies in cases and controls using 2-sided χ^2 test.

† *P* values adjusted by age and gender using logistic regression.

and other cognitive functions. Epilepsy is another distinct neurological disorders according to its major presenting symptoms. AD and epilepsy show numerous similar pathological features including temporal lobe atrophy, neuronal death, gliosis, neuritic alterations, and inflammation. The human and animal studies had proved that there exists a link between AD and seizures or epileptiform neuronal activity[17,18] and the incidence for the seizures increased in individuals with AD-type dementia, especially in early onset cases.[19] BACE1 has become infamous for playing a critical role in the pathogenesis of Alzheimer's disease and is the key rate-limiting enzyme for the genesis of amyloid-β (Aβ) peptides, the main constituents of the amyloid plaques in the brains of AD patients. Given that the relationship between AD and seizures and the key function of BACE1 at AD, we explored the relevance between BACE1 gene polymorphism and focal seizures in a Chinese Han population for the first time.

The Sez6 gene is a highly conserved gene in both mice and humans, and it has been proved that the mutations and/or altered expression of sez6 are associated with seizures.[11,20] Its 3 family members, Sez6, Sez6-like (Sez6L), and Sez6-like 2 (Sez6L2), were identified as BACE1 substrates[18] and Sez6 is a prime candidate for involvement in the synaptic dysfunction seen with BACE inhibition.[17] Thus, there exists a possibility that the BACE1 gene polymorphism may affect the development of seizures.

NRG1 is one of the epidermal growth factor (EGF)-like proteins and has a series of physiological functions in the peripheral and central nervous systems, such as myelination, remyelination, synaptic plasticity, and maintenance of muscle spindles. NRG1 is a substrate of BACE1, which is critical for NRG1's cleavage and can affect its biological functions. Our previous study had proved that there is an association between NRG1 (rs35753505) gene polymorphisms and temporal lobe epilepsy. Considering the close relation between BACE1 and NRG1, we further studied effect of the BACE1 gene polymorphisms on the focal seizures.

In addition to be able to affect the brain by cleavage of APP and proteolysis, BACE1 can act on ion channels, which has also been identified as epilepsy genes.[19] Voltage-gated sodium channels (Na_v) were the first ion channels to be identified as targets of BACE1.[21] In 2010, BACE1 cleavage sites were mapped in the β2 subunit of Na_v.[22] In support of the involvement of BACE1 in epilepsy, some researchers found that neurons from BACE1-deficient mice have lower levels of Na_v compared to their wild type counterparts. It has been proved that the mutations in both α- or β-subunits were associated with epilepsy.[23] Voltage-gated potassium channel was another prominent channel affected by BACE1, especially the KCNQ family, KCNQ2 and KCNQ3 of which are the principal components of neuronal M-current.[24] KCNQ2 and KCNQ3 mutations can emphasize the vital role of M-current in keeping the balance between excitation and inhibition of neuronal and can result in an infantile epilepsy syndrome.[25]

The epidemiology of epilepsy in humans indicates that the prevalence of epilepsy is slightly higher in males compared to females.[26] One of the striking results of this research is that there exists difference between male patients and controls on the genotype frequency of rs535860, while no difference between female patients and controls was found, which was in accordance with the gender difference of epilepsy occurrence. rs535860 located in BACE1 3′ UTR (untranslated region), which were minor allele count T = 0.1096/549 (for T) and Ref SNP Alleles A/T, showing conserved functional role throughout the evolution. One study showed that BACE1 miRNA genetic variability has no major role in risk for Alzheimer disease, while the authors did observe the statistical interaction between rs535860 and the near miR29a rs34772568. Combining with our research results, the rs535860 may play important function on nervous system disease.[27] In addition, in line with our findings, in one study using transgenic mice that conditionally express dominant-negative KCNQ2 subunits in brain, Peters et al[28] found that most male mutants showed frequent 'stargazer'-like dorsal head and neck extensions, which were likely indicative of partial seizures, but no spontaneous seizure activity was observed in any of the female mutants.

5. Conclusion

In summary, as far as we know, this is the first report that provides a potential link between the BACE1 polymorphism (rs535860) and focal seizures in a Chinese Han population. These results may inspire new evidence of seizures and should promote replication studies in ethnically disparate populations in cohort study samples and with variants covering the whole gene. However, considering the present study is limited by the relative small sample size, these findings need to be consolidated by further studies involving more ethnics and a larger group of patients.

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Data curation: P. Xu, X. He.
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