**NEURAL REGENERATION RESEARCH**
Volume 7, Issue 2, January 2012
www.nrronline.org

**Cite this article as:** Neural Regen Res. 2012;7(2):96-100.

# Correlation between human seizure-related gene 6 variants and idiopathic generalized epilepsy in a Southern Chinese Han population☆

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## Abstract

This study sought to analyze the genotype and gene mutations of human seizure-related gene 6 in 98 patients with idiopathic generalized epilepsy (non-febrile seizures), who were selected from three generations of the Chinese Han population living in Shanghai, Zhejiang Province, Wuxi of Jiangsu Province, and Jiangxi Province of Southern China. Twenty-six patients' parents were available as a first-degree relatives group and 100 biologically unrelated healthy controls were collected as the control group. Based on the age of onset and seizure type, the patients were divided into six subgroups. Polymerase chain reaction and DNA direct sequencing analysis showed that the most frequent mutations c.1249dupC (p.Gly418Argfx31) and c.1636A > G (p.Thr546Ala) were detected in some idiopathic generalized epilepsy patients and their asymptomatic first-degree relatives (30.6% *vs*. 19.2% and 11.2% *vs*. 26.9%). A novel mutation c.1807G > A (p.Val603Met) was found in a patient with late-onset idiopathic generalized epilepsy. There was no significant difference in the incidence of these three mutations among the different subgroups of idiopathic generalized epilepsy and controls. Thus, further analysis of a larger population is needed to confirm the assumption that human seizure-related gene 6 is a susceptibility gene for idiopathic generalized epilepsy with various sub-syndromes.

**Key Words:** human seizure-related gene 6; non-febrile seizure; generalized epilepsy; mutation; polymorphism, genetic; neural regeneration

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Received: 2011-10-25
Accepted: 2011-12-12
(N20110909001/WJ)

Jiang JM, Chen XL, Liu WT, Zhao Y, Guan YT, Han Y, Wang F, Lu JJ, Yu ZL, Du ZF, Zhang XN. Correlation between human seizure-related gene 6 variants and idiopathic generalized epilepsy in a Southern Chinese Han population. Neural Regen Res. 2012;7(2):96-100.

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doi:10.3969/j.issn.1673-5374.2012.02.003

## INTRODUCTION

Epilepsy is a frequently-occurring nervous disease with an incidence of 0.5–2.0% in the general population[1-2]. The etiology of epilepsy and epileptic seizures is multifactorial. Genetic factors are believed to contribute to some epilepsy syndromes, especially idiopathic epilepsy[2]. Idiopathic generalized epilepsy (IGE; OMIM: 600669), a common form, usually has no evidence of an underlying cause and is believed to be largely genetic in origin[3]. IGE is clinically characterized by absence, myoclonic seizures, and tonic-clonic seizures, typically beginning in childhood or adolescence with the characteristic electroencephalographic pattern of generalized spike-wave discharge. Based on the age of onset and seizure type, IGE can be divided into four syndromes according to the still valid classification of the International League Against Epilepsy: childhood absence epilepsy, occurring after the neonatal period; juvenile absence epilepsy; juvenile myoclonic epilepsy; and IGE with tonic–clonic seizures alone[4]. In addition, adult-onset IGE has also been described[5-6]. Although mutations in >25 genes have been linked to epilepsy, the relationship between the molecular defect and the clinical phenotype varies greatly[2-3, 7-8].

Seizure-related gene 6 (*SEZ-6*) was originally identified as a gene with an mRNA that is upregulated in the cortex after administration of the convulsant drug pentylenetetrazole in mice[9]. Restriction of the expression pattern of SEZ-6 protein to cortical neurons implies that it plays an important role in the development of the forebrain and cognitive function in the adult mouse brain[10]. SEZ-6 protein contains one threonine-rich domain, five short consensus repeats, two CUB-like domains (CUB: Clr/Cls, urinary epidermal growth factor, and bone morphogenic protein), one transmembrane domain, and one short cytoplasmic segment in the C-terminal region, which suggests that it is involved in membrane receptor signaling[11-12].

An association between human *SEZ-6*

mutations and febrile seizure has been found[13-14]. Another recent genome-wide linkage study of a Finnish family with various epilepsy phenotypes has suggested the presence of an epileptic underlying gene on chromosome 17q12–q24, around the region also associated with the *SEZ-6* gene[15]. This raises the question: is *SEZ-6* a susceptibility gene for IGE, with complex inheritance? The aim of the present study was to investigate the distribution of specific mutations or polymorphisms of *SEZ-6* in Chinese IGE patients.

## RESULTS

### Quantitative analysis of subjects

A total of 224 subjects was included in this study and divided into three groups: an IGE group ($n$ = 98), a first-degree relatives group ($n$ = 26) and a control group ($n$ = 100). All of the individuals were included in the final analysis without drop-outs.

### Frequency of *SEZ-6* gene variants

Genomic DNA was amplified by PCR and direct DNA sequencing to identify *SEZ-6* gene variants or polymorphisms. Of the 98 IGE patients examined, 34 (34.7%) showed *SEZ-6* mutations (Table 1). Of these 34 subjects, genomic DNA was available from 26 sets of parents and 21 of them also carried the mutations. Results showed the genotypes in IGD patients and controls were in accordance with the Hardy-Weinberg equilibrium.

Table 1 Epileptic phenotypes of 98 IGE patients screened for *SEZ-6* variations

| Syndrome phenotypes | Numbers of patients ($n$) | Patients with *SEZ-6* changes (frequency, position) |
|---|---|---|
| Childhood absence epilepsy | 11 | 3 (27.5%. c.1249dupC, c.1636A > G) |
| Juvenile absence epilepsy | 22 | 5 (22.7%. c.1249dupC, c.1636A > G) |
| Juvenile myoclonic epilepsy | 31 | 17 (54.8%. c.1249dupC, c.1636A > G) |
| IGE with tonic-clonic seizures alone | 17 | 4 (23.5%. c.1249dupC) |
| Adult onset IGE | 8 | 3 (37.5%. c.1249dupC, c.1807G > A ) |
| Unclassified IGE with non-fever-sensitive seizure | 9 | 2 (22.2%. c.1249dupC) |
| Total | 98 | 34 (34.7%) |

IGE: Idiopathic generalized epilepsy; *SEZ-6* : human seizure-related gene 6. Frequency of *SEZ-6* gene variants = Numbers of patients with mutation / Total numbers of the IGE sub-group. Data were analyzed by chi-square test.

### Distribution of the most common variant of *SEZ-6* in the subjects

#### *c.1249dupC*

The most common variant was a single nucleotide duplication at position 1 249 within exon 5, c.1249dupC, resulting in a translational reading frameshift and a premature stop codon: p.Gly418Argfx31. Thirty of the IGE patients (30.6%) had this variant, among whom those with juvenile myoclonic epilepsy made up a high percentage (16/31, 51.6%), while the frequency in first-degree relatives was 19.2% (5/26) (Table 2). Most of c.1249dupC mutation was heterozygous, compared with the wild-type DNA sequence (Figures 1A and B). The homozygous mutation form was rarely identified in some patients with juvenile myoclonic epilepsy and IGE with tonic-clonic seizures alone, as well as their parents (Figure 1C). In addition, three of 100 unrelated healthy controls were found to carry the heterozygous form of this variant (3%).

Table 2 IGE patients and their available relatives with the commonest variant, c.1249dupC

| c.1249dupC | CAE | | JAE | | JME | |
|---|---|---|---|---|---|---|
| | A ($n$ = 2) | P ($n$ = 0) | A ($n$ = 4) | P ($n$ = 1) | A ($n$ = 16) | P ($n$ = 4) |
| Heterozygous | 2 | 0 | 4 | 1 | 12 | 1 |
| Homozygous | 0 | 0 | 0 | 0 | 4 | 3 |

| c.1249dupC | GTCA | | Adult onset IGE | | Unclassified IGE | |
|---|---|---|---|---|---|---|
| | A($n$ = 4) | P | A($n$ = 2) | P | A($n$ = 2) | P |
| Heterozygous | 3 | N/A | 2 | N/A | 2 | N/A |
| Homozygous | 1 | N/A | 0 | N/A | 0 | N/A |

CAE: Childhood absence epilepsy; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; GTCA: IGE with tonic-clonic seizures alone; IGE: idiopathic generalized epilepsy; A: affected individual; P: parent; N/A: not available. Data are the number of patients.

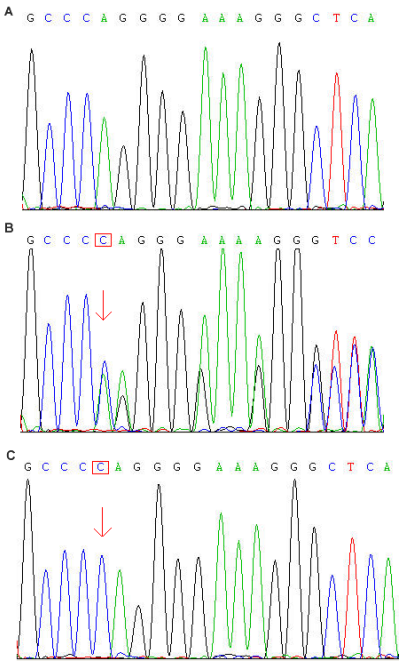


Figure 1 c.1249dupC sequencing results of human seizure-related gene 6.

(A) Wild-type DNA sequence.

(B) Heterozygous form (the double peak; arrow) of this mutation; the inserted base C (red box) is indicated.

(C) Homozygous form of this mutation (arrow).

### *p.Thr546Ala*

The second most frequent mutation was a missense mutation within exon 7, c.1636A > G (p.Thr546Ala). In the majority of patients, this mutation is concomitantly present in the same patients with the c.1249dupC variant, considering as compound mutations (Figure 2). Eleven patients (including two cases of childhood absence epilepsy, two of juvenile absence epilepsy, six of juvenile myoclonic epilepsy, and one of IGE with tonic-clonic seizures alone) carried the heterozygous form of this variant. There was only one exception in which the homozygotic form occurred in the parental DNA of a juvenile myoclonic epilepsy patient (Figure 2C). The frequencies in the patients and asymptomatic relatives were 11.2% (11/98) and 26.9% (7/26), respectively. In addition, the heterozygous form of c.1636A > G was identified in five controls (5%).

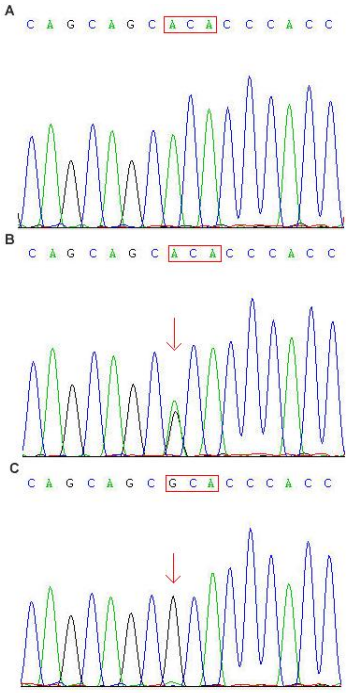


Figure 2 DNA sequencing results for mutation c.1636A > G of human seizure-related gene 6.

(A) Control. ACA (red box) indicates the normal codon.

(B) Heterozygous form (the double peak. arrow) of this mutation from a male juvenile myoclonic epilepsy patient.

(C) Homozygous form of this mutation from the juvenile myoclonic epilepsy patient's first-degree relative. Codon ACA was substituted by GCA (red box), which resulted in an amino acid change from threonine to alanine.

### *c.1807G > A*

A novel missense mutation c.1807G > A within exon 8, resulting in the substitution of methionine for valine at codon 603 (p.Val603Met), was found in an adult-onset IGE. Amino acid alignment of this mutation showed that it affected a highly conserved domain of SEZ-6 protein in other organisms (cow, mouse and Xenopus) and the *SEZ-6* gene family (*SEZ-L1* and *SEZ-L2*; Figure 3). DNA samples of 100 controls were screened for this mutation, successfully excluding the hypothesis of a genetic polymorphism.

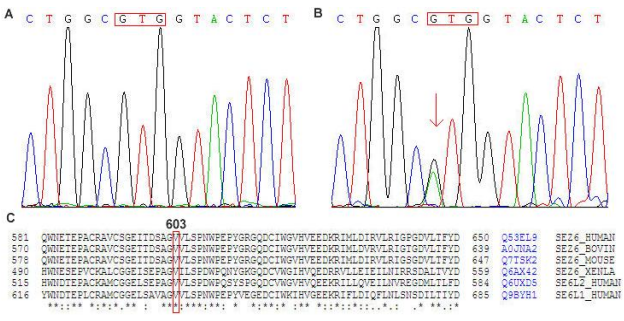


Figure 3 DNA sequencing results for mutation c.1807G > A within exon 8 of human seizure-related gene 6.

(A) Control. GTG (red box) indicates the normal codon.

(B) A heterozygous missense mutation G→A (the double peak, arrow) was identified at position 1807 in a late-onset IGE patient, which resulted in an amino acid change from valine to methionine.

(C) Valine 603 is an evolutionarily invariant in the paralogous human seizure-related gene 6 family and in homologous from other species (cow, mouse and Xenopus).

There was no significant difference in frequency of the above three mutations among different IGE subgroups and controls.

## DISCUSSION

Since the homologous *SEZ-6* gene was cloned by homologous screening, the possible molecular mechanisms of its function and association with epilepsy are gradually being investigated. Human *SEZ-6* gene is located on chromosome 17q12, encoding at least three alternative splice variants, SEZ-6 types I, II and III[16]. SEZ-6 types I and II appear to be transmembrane proteins with long extracellular domains and short C-terminal cytoplasmic domains, whereas the type III isoform appears to be a secreted protein. Expression analysis shows highly restricted and stage-specific expression of *SEZ-6* mRNA in the developing forebrain. *SEZ-6* mRNA is expressed strongly in the cortical plate of the fetal brain, and is moderately expressed in the adult mouse brain, except for strong expression in the hippocampus, piriform cortex, and olfactory tubercle[10, 12, 17-18]. Recently, a new anti-SEZ-6 antibody has been used to show spatiotemporal changes in SEZ-6 distribution during the postnatal period, which suggests developmental regulation of the expression of *SEZ-6* mRNA and implies that SEZ-6 plays crucial roles in the development of the forebrain and in cognitive function in the adult mouse brain[10]. Although *SEZ-6*-deficient mice only show moderate signs of impaired spatial memory, motor deficits, and decreased anxiety, this is not discouraging, because complex conditions like epilepsy are probably caused by abnormal expression of multiple genes, not

just by mutation or deletion of a single gene[17]. The heritability of epilepsy on a population basis is logistically complex and driven by polygenic susceptibility loci[19-20]. In addition, reduced numbers of excitatory synapses and unaltered inhibitory inputs, along with greater seizure resistance in *SEZ-6* null mice suggest to some extent that levels of SEZ-6 play a role in determining excitability and therefore may be indirectly involved in seizure disorders[21-22].

IGE is considered to be caused by a genetic predisposition with no other evident etiology[2-3, 23]. Patients with one of the four IGE sub-syndromes usually have seizure onset during childhood or adolescence, which used to be defined as the classic age at onset[24]. However, IGE cases with a later-than-usual onset have been regularly described, with an incidence less rare than the previously reported[25-32]. It has been suggested that IGE with late onset shares biological determinants common with IGE, while etiological factors and relations between each IGE syndrome are still under investigation.

In this study, we performed genetic screening focusing on *SEZ-6* mutations in a small cohort of various Chinese IGE patients. To the best of our knowledge, this is the first report on the correlation between *SEZ-6* and IGE. Thirty-eight sequence variants were identified in the 34 mutation-positive patients, while four affected children each had two changes. We described two frequent variants, c.1249dupC and c.1636A > G, in almost all types of IGE patients with no significant difference in occurrence among them. In addition, a small proportion of first-degree relatives of patients were found to be carriers of these mutations. Many reasonable causes could account for this phenomenon; for example, these two variants could be non-pathogenic, or certain individuals in the population could be tolerant of these mutations. What is more, a novel *SEZ-6* mutation, c.1807G > A, was found in a late-onset IGE patient, which seemed to be pathogenic, because it was located in a highly conserved domain of SEZ-6. The patient carrying this unique mutation was a 48-year old man, who was referred to the clinic after his first tonic-clonic seizure at the age of 26 years. No evidence of an underlying cause was found upon clinical and electroencephalographic examination. Only eight patients were defined as adult-onset IGE in our study, with a broad age of seizure onset ranging from 21 to 58 years. Further analysis of a larger population might reveal interactions between *SEZ-6* mutations and adult-onset IGE. Here, we cannot yet confirm the assumption that *SEZ-6* is a susceptibility gene for IGE with various sub-syndromes.

## SUBJECTS AND METHODS

### Design

A case-control study focused on gene mutations or polymorphisms.

### Time and setting

The study was performed at the Morbid Genomics Laboratory, School of Medicine, Zhejiang University, China, between April 2010 and May 2011.

### Subjects

#### *IGE group*

A total of 98 Southern Chinese Han patients (56 males and 42 females) from Shanghai, Zhejiang Province, Wuxi of Jiangsu Province and Jiangxi Province in China with different types of IGE, were enrolled. The mean age of the patients was 26.5 years (range: 7–78 years). All affected individuals were inpatients at the Department of Neurology, Changhai Hospital, Shanghai, China. The forms of epilepsy were subdivided into clinical syndromes on the basis of age of onset, seizure pattern and other clinical, electroencephalography and imaging features according to the International League Against Epilepsy classification of epileptic syndromes[4]. Patients were evaluated by three neurologists independently. The epilepsy phenotypes of the 98 patients are shown in Table 1.

Inclusion criteria: (1) electroencephalography with generalized spike-wave and normal background; (2) compatible clinical history; (3) no pre-existing known neurological deficit; or (4) normal brain neuroimaging unless abnormality due to an acquired unrelated condition.

Exclusion criteria: (1) evidence for structural lesions, metabolic or degenerative diseases of the brain; (2) atonic/astatic or tonic seizures; (3) complex partial seizures; (4) epilepsy with myoclonic absences; (5) exclusively stimulus induced seizures.

#### *First-degree relatives group*

Twenty-six IGE patients' parents were available as a first-degree relatives group. Exclusion criteria comprised the presence of any abnormal neurological finding, mental retardation, and morphological or metabolic brain disorders.

#### *Control group*

One hundred biologically unrelated healthy controls, including 55 men and 45 women, aged 20–79 years, with a similar ethnic background, were enrolled as the control group.

This study was conducted according to the 33rd Rule of Hospital Administration Regulation of China[33], and was approved by the *Second Military Medical University of Chinese PLA Review Board*, Shanghai, China. Informed consent was given by all participants.

### Methods

#### *Genotyping of SEZ-6 gene and mutation analysis*

Genomic DNA was extracted from the peripheral blood sample by standard extraction protocols. PCR was carried out to amplify the target DNA frames of the *SEZ-6* gene as previously described[13]. PCR products were sequenced directionally with an automated sequencer (ABI 3770; Applied Biosystems, Foster City, CA, USA) and analyzed by the DNA Assist 2.0 analysis software package (http://www.dnassist.com)[34]. Mutated sites

were identified through comparison with the normal sequences of the exons of the *SEZ-6* gene. All mutation sites were expressed with reference to *SEZ-6* cDNA (GenBank accession number GI: 20143984)[13].

### *Statistical analysis*

All data were entered into a database and analyzed by standard statistical methodology with SPSS 10.0 software (SPSS, Chicago, IL, USA). Comparison of mutation incidences among the IGE, first-degree relatives and control groups were carried out using a chi-square test. Statistical significance was accepted at $P < 0.05$.

**Author contributions:** Jianming Jiang and Xiaoling Chen designed the study, analyzed experimental data, wrote the article, and are responsible for the foundation. Jianming Jiang, Yangtai Guan, Yan Han, Feng Wang, and Zhiliang Yu analyzed the clinical data. Wenting Liu, Yan Zhao, Jiajun Lu and Zhenfang Du analyzed experimental data. Xianning Zhang designed and wrote the paper, and provided instruction for this study.

**Conflict of interest:** None declared.

**Funding:** The study was supported by Shanghai Natural Science Foundation, China, No. ZR1404500.

**Ethical approval:** The experiment complied with the Ethics Committee of the Second Military Medical University of Chinese PLA, Shanghai, China.

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(Edited by Zhao R, Shi J/Yang Y/Wang L)