Role of t-PA and PAI-1 variants in temporal lobe epilepsy in Chinese Han population

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Abstract

Background: Epilepsy is one of the most common chronic disabling neurologic diseases. The purpose of our study was to investigate whether there is an association between t-PA (tissue plasminogen activator, rs2020918 and rs4646972), PAI-1 (plasminogen activator inhibitor 1, rs1799768) polymorphisms and susceptibility to temporal lobe epilepsy (TLE) in Chinese Han population.

Method: One hundred and twenty-one cases of patients who were diagnosed as TLE and 146 normal controls were enrolled and the genotypes of t-PA and PAI-1 were detected by polymerase chain reaction-ligase detection reaction (PCR-LDR) method after the genomic DNA being extracted from peripheral blood.

Result: There were significant differences for the genotypic frequencies at the two polymorphic sites in t-PA gene between TLE patients and controls (P = 0.019; P = 0.001). Furthermore, the frequency of rs2020918 (C>T) with T (CT + TT) and rs4646972 (311 bp insertion/−) with 311 bp deletion (311 bp/− + /−) was significantly higher among TLE patients relative to controls respectively (P = 0.006; P = 0.001). However, no significant difference in genotypic and allelic frequency was found at the polymorphic site in PAI-1 gene between TLE patients and controls (P = 0.735).

Conclusion: We reported for the first time to our knowledge the significant role of the two SNPs in t-PA gene (rs2020918 and rs4646972) in developing susceptibility to TLE in Chinese Han population.

Keywords: t-PA; PAI-1, Temporal lobe epilepsy, Polymorphism

Background

Epilepsy is a chronic disorder characterized by recurrent seizures, which affects 8 in 1000 children and children are more frequently affected than adults (children to adult ratio is 2:1) [1–3]. As one of the most common forms of epilepsy, partial seizure is initially focused in just one part of the brain. Among them, more than 1/3 of patients manifested as temporal lobe epilepsy (TLE) [4]. Genetic factors together with environmental factors may contribute to the occurrence, development and prognosis of TLE. Most of the clinical TLE cases are sporadic and may be affected by a combination of multiple pathogenic genes. Emerging evidence suggests that several genetic defects in Interleukin-1β (IL-1β) [5], Interleukin −1 receptor antibody (IL-1 RA) [6], γ-Aminobutyric acid B receptor 1(GABBR1) [7], prodynorphin (PYDN) [8], ApolipoproteinE (ApoE) [9] and prion protein (PRNP) [10] have been associated with TLE.

In addition to the well-known ion channels and signaling pathways involved in TLE etiology, tissue plasminogen activator (t-PA) is responsible for the activation of plasminogen to plasmin, which then degrades extracellular matrix (ECM) components, promoting synaptic plasticity and influencing neurite sprouting and extension [11]. Abnormalities including the nature and quantity in t-PA may be involved in the synaptic plasticity alterations and abnormal neurite extension, leading to the susceptibility of epilepsy. As a member of the serpin family proteinase inhibitors, plasminogen activator inhibitors (PAI-1) can specifically bind to t-PA and terminate the t-PA enzymatic activity in the extracellular space [12], which also may be involved in epileptic seizures. Studies have shown that t-PA is highly enriched in all
kinds of types of neurons in the human central nervous system (CNS), including neocortex, pyramidal neurons, and hippocampus, and thus is involved in several physiological and pathological processes in the CNS, such as learning and memory, anxiety, epilepsy, stroke, Alzheimer's disease, and spinal cord injuries [13, 14]. As expected, elevated t-PA mRNA levels were found in the hippocampus [15] and entorhinal cortex [16] of animal models of epilepsy induced by electricity. Consistent with the findings above, elevated t-PA mRNA levels were also detected in epilepsy patients [17], which identified a role for t-PA in the mechanisms of underlying seizure activity. In addition, PAI-1 becomes a key factor in epileptic seizures due to its high affinity for t-PA. Increased levels of PAI-1 mRNA have also been observed in human TLE with hippocampal sclerosis and focal cortical dysplasia [17]. Based on the above background, we aimed to investigate the association between t-PA (rs2020918, rs4646972), PAI-1 SNPs (rs1799768) and susceptibility to TLE in Chinese Han population.

Methods

Study population
A total of 121 (70 boys and 51 girls, sex ratio 1.37:1.0, mean age at seizure onset 6.4 ± 3.27 y) cases of TLE patients were enrolled in our study. All the patients were recruited at the outpatient clinic of the Second Xiangya Hospital in Hunan Province. The TLE was diagnosed by comprehensive evaluation of characteristic partial seizure symptoms. Criteria for the diagnosis and exclusion of the TLE patients have been described previously [18, 19]. Briefly, since electroencephalography (EEG) and magnetic resonance imaging (MRI) criteria are considered to be reliable interictal indicators of TLE, the diagnosis of TLE was mainly based on typical temporal auras or ictal and interictal EEG discharges over the temporal lobes in the presence of focal spikes or sharp waves followed by slow waves. Patients with any mass lesion such as tumor, cortical dysgenesis, vascular lesion, malformation, or posttraumatic scars detected by MRI were excluded. None had mental retardation, psychiatric malformation, or posttraumatic scars detected by MRI.

Results

Genomic DNA was extracted from peripheral blood using TIANamp Blood DNA Kit (TIANGEN, China), according to the manufacturer's recommendations. Polymerase chain reaction-ligase detection reaction (PCR-LDR) method was used to identify the genotypes. All primers for both PCR and LDR reaction were designed by online software Primer 3 (shown in Table 1). These PCR products and the LDR probes were then subjected to a multiplex ligase detection reaction, with a DNA sequencer used to detect the products. In addition, not less than 10% of DNA samples were randomly selected and genotyped again for the purpose of quality control of the genotyping.

Statistical analysis
The Hardy–Weinberg Equilibrium test was performed for every single-nucleotide polymorphism in controls. The Person χ2 test was used to compare the statistical differences in genotype distributions and allele frequencies between TLE patients and controls. Moreover, Bonferroni adjustment was performed to correct for multiple comparisons. The odds ratio (OR) and 95% confidence intervals (95%CI) were also calculated. A P value < 0.05 was considered as significant. All analyses were conducted using statistical software package SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Table 1 Primers of Target Gene Used in the PCR

| SNP         | Ancestor allele | Primer sequence                                                                 | Product size (bp) |
|-------------|-----------------|--------------------------------------------------------------------------------|-------------------|
| rs2020918   | C               | 5′-CAGATAATTCCTTCTTGACCC-3′(forward) 5′-TGAATAGGGCTTTGGCCGCT-3′(reverse)          | 117               |
| rs4646972   | not available   | 5′-AGTAAAGGTCCTGGCCTGT-3′(forward) 5′-TCATCTTGACCTTGCAGCAC-3′(reverse)           | 219               |
| rs1799768   | T               | 5′-CAACCTCAGCGCAACAAGT-3′(forward) 5′-CAAGCCACGTGATTGTCTAGG-3′(reverse)           | 192               |
patients and healthy controls; however, the significance of this result was not confirmed after the strict Bonferroni adjustment ($P = 0.057$). When subdividing these samples into CC and CT+ TT groups, an obvious difference between cases and controls was found ($\chi^2 = 7.670$, $P = 0.006$, OR = 2.008, 95% CI = 1.223–3.298). Moreover, the T allele showed a significant association with TLE patients group ($\chi^2 = 8.098$, $P = 0.004$, OR = 1.789, 95% CI = 1.195–2.678). Similarly, for rs4646972, the genotypic and allelic distributions between two groups were statistically different after the strict Bonferroni adjustment ($\chi^2 = 13.366$, $P = 0.003$ by genotype; $\chi^2 = 15.630$, $P = 0.000$, OR = 2.007, 95% CI = 1.418–2.840 by allele). The frequency of genotype with 311 bp deletion (311 bp/− + −/−) was significantly more frequent among the TLE patients and the controls ($\chi^2 = 10.517$, $P = 0.001$, OR = 0.422, 95% CI = 0.250–0.715).

### PAI-1 polymorphism

The results of genotypic and allelic frequencies in rs1799768 of PAI-1 gene were presented in Tables 2 and 3. No significant differences were observed at the polymorphic sites between the two groups in terms of genotypic distributions ($\chi^2 = 0.616$, $P = 0.735$), nor for allelic frequencies ($\chi^2 = 0.01$, $P = 0.919$, OR = 1.018, 95% CI = 0.721–1.437).

### Discussion

The human gene t-PA (PLAT) spanning more than 30 kb is located on chromosome 8p11.21 and consists of 14 exons, encoding tissue plasminogen activator [20]. As a key protease of the fibrinolytic system, t-PA is localized broad regions including cortex, cerebellum, amygdala, and hippocampus, and thus has essential physiological and pathological functions in CNS. As the specific inhibitor of t-PA in plasma, plasminogen activator inhibitor-1 (PAI-1) plays a crucial role in the regulation of t-PA activity.

### Table 2 Genotypic distribution of the t-PA and PAI-1 gene between TLE patients and controls

| Gene  | SNP     | Genotype | Cases (242 alleles across 121 subjects) n (% of population) | Controls (292 alleles across 146 subjects) n (% of population) | OR(95%CI) | $\chi^2$ | p-value<sup>a</sup> | p-value<sup>b</sup> |
|-------|---------|----------|-------------------------------------------------------------|---------------------------------------------------------------|-----------|--------|-----------------|-----------------|
| t-PA  | rs2020918 | CC       | 61(50.4)                                                    | 98(67.1)                                                      |           |        |                 |                 |
|       |         | CT       | 49(40.5)                                                    | 41(28.1)                                                      |           |        |                 |                 |
|       |         | TT       | 11(9.1)                                                     | 7(4.8)                                                        | 7.939     | 0.019  | 0.057<sup>b</sup> |                 |
|       |         | CT + TT  | 60(49.6)                                                    | 48(32.9)                                                      | 2.008(1.223–3.298) | 7.670   | 0.006           |                 |
|       | rs4646972 | 311 bp/311 bp | 30(24.8)                                                | 64(43.8)                                                      |           |        |                 |                 |
|       |         | 311 bp/− | 52(43.0)                                                    | 57(39.1)                                                      |           |        |                 |                 |
|       |         | −/−      | 39(32.2)                                                    | 25(17.1)                                                      | 13.366    | 0.001  | 0.003<sup>b</sup> |                 |
|       |         | 311 bp/−− | 91(75.2)                                                   | 82(56.2)                                                      | 0.422(0.250–0.715) | 10.517  | 0.001           |                 |
| PAI-1 | rs1799768 | GG       | 20(16.5)                                                    | 27(18.5)                                                      |           |        |                 |                 |
|       |         | −/G      | 63(52.1)                                                    | 69(47.3)                                                      |           |        |                 |                 |
|       |         | −/−      | 38(31.4)                                                    | 50(34.2)                                                      | 0.616     | 0.735  |                 |                 |

*CT + TT: the sum of CT and TT genotype
*311 bp/−− + −/−: the sum of 311 bp/− and −/− genotype
*<sup>a</sup>p-value without adjustment
*<sup>b</sup>p-value after Bonferroni adjustment for multiple comparisons

### Table 3 Allelic distribution of the t-PA and PAI-1 gene between TLE patients and controls

| Gene  | SNP     | Allele | Cases (242 alleles across 121 subjects) n (% of population) | Controls (292 alleles across 146 subjects) n (% of population) | OR(95%CI) | $\chi^2$ | p-value |
|-------|---------|--------|-------------------------------------------------------------|---------------------------------------------------------------|-----------|--------|---------|
| t-PA  | rs2020918 | C      | 171(70.7)                                                  | 237(81.2)                                                    |           |        |         |
|       |         | T      | 71(29.3)                                                    | 55(18.9)                                                      | 1.789(1.195–2.678) | 8.098   | 0.004  |
|       | rs4646972 | 311 bp | 112(46.3)                                                  | 185(63.4)                                                    |           |        |         |
|       |         | −      | 130(53.7)                                                  | 107(36.6)                                                    | 2.007(1.418–2.840) | 15.630  | 0.000  |
| PAI-1 | rs1799768 | −      | 139(57.4)                                                  | 169(57.9)                                                    |           |        |         |
|       |         | G      | 103(42.6)                                                  | 123(42.1)                                                    | 1.018(0.721–1.437) | 0.01    | 0.919  |
inhibitor type-1 (PAI-1) is encoded by PAI-1 (also known as SERPINEL1) gene, which is located at 7q21.1 and consists of 9 exons and 8 introns [21]. Genetic variations have been shown to play a vital role in regulating the level of t-PA and the three mostly studied SNPs (rs2020918, rs4646972 in t-PA and rs1799768 in PAI-1) have been associated with the occurrence of a variety of diseases [20, 22, 23]. Specifically, the C-T transition at −7351 (rs2020918, -7351C>T) within the t-PA enhancer can cause a potential weakening of the enhancement, which may affect the regulation of t-PA expression. Likewise, an Insertion/Deletion of 311 bp sequence polymorphism (rs4646972) identified in the 8th intron of the t-PA gene may affect the splicing of mRNA, resulting in the alterations of t-PA function. Interestingly, both of these two SNPs above have been shown to be strongly correlated to t-PA release [22]. As accumulated evidences identified its pivotal role in the mature of pro-neurotrophins [24, 25] and activation of receptors [26], altered t-PA level may be associated with a series of neurological diseases such as epilepsy [27]. In addition, another single guanine nucleotide Insertion/Deletion polymorphism (−/G) is located in the promoter region of the PAI-1 gene, which was claimed to influence the expression of PAI-1 [22]. Although previous data showed that these SNPs were not only associated with multiple thrombotic disorders, such as strokes [20, 22, 28], myocardial infarction [29–31], but also with the severity of bacterial infections, such as meningitis [32, 33], it remains blank concerning the relationship between t-PA, PAI-1 polymorphisms and TLE.

First data linking t-PA to epilepsy were provided by Qian [34] who has shown increased t-PA mRNA expression in the rat cortex and hippocampus following by pentylenetetrazol (PTZ) inducement. Then, the increase not only in t-PA mRNA expression but also in t-PA enzymatic activity has been observed in subsequent mice models [35]. Involvement of t-PA in seizure induction has been demonstrated for the first time by Tsirka who indicated that seizures should be induced by higher injection of either KA or PTZ in t-PA deficiency mice compared with controls [34]. In addition, t-PA knock-out mice did not induce seizures even though injecting highest dose of kainic acid (KA) [27], which indicated that the expression of t-PA may be associated with the susceptibility of epilepsy. Fillla [36] and Hagen [37] reported that mutation in neuroserpin had been associated with neurological disorders characterized by the presence of seizures, and the anti-epileptic function of neuroserpin had been proved by the fact that application of neuroserpin can diminish progression of seizures during SE induced by KA injection to the amygdala. As a form of neuroserpin, increased expression of PAI-1 mRNA has also been observed in human TLE with hippocampal sclerosis and focal cortical dysplasia. Previous studies have reported that t-PA and PAI-1 levels can be affected by their gene polymorphisms [38, 39], and thus we speculated that t-PA and PAI-1 gene polymorphisms may be an associated with the occurrence of TLE.

In this context, we adopted a case-control study to investigate the association between the SNPs in t-PA (rs2020918, rs4646972) and PAI-1 (rs1799768) and susceptibility to TLE in Han Chinese population in terms of genetic perspective. Our study of 121 TLE patients and 146 controls found significant differences in genotypic and allelic frequencies of polymorphic sites (rs2020918, rs4646972) between TLE patients and control groups. However, the significant difference of the rs2020918 results was not confirmed after Bonferroni adjustment. To further study the association between t-PA polymorphism and the clinical phenotypes, for rs2020918, the TLE patients were divided into two groups according to whether they carried T allele or not (CC and CT+ TT groups). The results showed an obvious difference between cases and controls, which indicated that genotypes carrying T (mutant allele) may be more susceptible to TLE compared with wild-genotype. Moreover, the T allele was higher in TLE patients than that in normal controls, which indicated that T allele may play a risky role in the development of TLE. Likewise, for rs4646972, when subdividing these samples into 311 bp/311 bp and 311 bp/311 bp/311 bp groups, we also observed an obvious difference between cases and controls, which indicated that genotypes with 311 bp deletion carriers seem to be more susceptible to TLE compared with wild-genotype. Furthermore, a statistical difference in 311 bp deletion allele was found between TLE patients and normal controls and 311 bp deletion allele may be a risky factor to the occurrence of TLE according to the value of OR.

However, we failed to find a significant difference in genotypic and allelic frequencies of polymorphic site PAI-1 rs1799768 between TLE and control groups, which suggested that rs1799768 polymorphism may not be associated with the pathogenesis and progression of TLE. The negative results can be explained by many reasons. Firstly, TLE is a complex polygenetic hereditary disease which can be influenced by environmental factors rather than several genetic defects only. Moreover, our results may be affected by regional and racial biases to some extent. One limitation of our study is that most subjects are from Hunan province. Additionally, the effects of environmental risk factors and comorbidity are not taken into consideration as we only investigated one SNP of PAI-1. To ensure the replicability of our finding, the independent group of patients should be included in further study.
Conclusion
In conclusion, the obtained results suggested an apparent association between the t-PA polymorphisms and increased TLE susceptibility in the analyzed Chinese Han population, which can enrich the understanding of sporadic TLE susceptibility genes. In order to provide a molecular genetic evidence for clinically seizure risk prediction and individual treatment, larger-scale functional and genetic studies investigating different genes are necessary to be carried out in patients from multiple regions to discover new TLE susceptibility genes and gain further insights into its pathogenesis.

Abbreviations
ApoE: Apolipoprotein E; CNS: Central nervous system; GABBR1: γ-aminobutyric acid B receptor 1; IL-1 RA: Interleukin-1 receptor antibody; IL-1β: Interleukin-1β; KA: Kainic acid; PAI-1: Plasminogen activator inhibitor 1; PCR-LDR: Polymerase chain reaction-ligase detection reaction; PRNP: Prion protein; PTZ: Pentylentetrazol; PYDN: Prodynorphin; TLE: Temporal lobe epilepsy; t-PA: Tissue plasminogen activator

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
GQY and PJ designed the study and wrote the protocol; YJG, GYL, XH and YJG were involved in the interpretation of the results and undertook critical revision of the manuscript. WXH and PJ contributed equally to the work. All authors have read and approved the final version of the manuscript, and ensured that this is the case.

Ethics approval and consent to participate
Our study was approved by the medical ethics committee of the Second Xiangya Hospital of Central South University. Written informed consent was signed by each participant or their parents/legal guardians before they participated in the study.

Consent for publication
Not Applicable.

Competing interests
The authors declare that they have no competing interests.

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