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Role of glyoxalase I gene polymorphisms in late-onset epilepsy and drug-resistant epilepsy

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ABSTRACT

Background: Recent studies indicate that increased expression of glyoxalase I (GLO1) could result in epileptic seizures; thus, this study further explored the association of GLO1 with epilepsy from the perspective of molecular genetics.

Material and methods: GLO1 single nucleotide polymorphisms (SNPs; rs1130534, rs4746 and rs1049346) were investigated in cohort I (the initial samples: 249 cases and 289 controls). A replication study designed to confirm the positive findings in cohort I was performed in cohorts II (the additional samples: 130 cases and 191 controls) and I + II.

Results: In cohorts I, II and I + II, the CC genotype at rs1049346 T > C exerts a protective effect against both late-onset epilepsy (odds ratio [OR] = 2.437, $p = 0.013$; OR = 2.844, $p = 0.008$; OR = 2.645, $p = 0.000$, $q = 0.003$, respectively) and drug-resistant epilepsy (DRE) (OR = 2.985, $p = 0.020$; OR = 2.943, $p = 0.014$; OR = 3.049, $p = 0.001$, $q = 0.006$, respectively). Further analyses in cohort I + II indicate that the presence of the TAC/AAT haplotypes (rs1130534–rs4746–rs1049346) may be used as a marker of predisposition to/protection against DRE ($p = 0.002$, $q = 0.010$; $p = 0.000$, $q = 0.002$, respectively).

Conclusions: This study is the first to demonstrate that the GLO1 SNPs are significantly associated with epilepsy. In particular, the rs1049346 T > C SNPs are potentially useful for risk assessment of late-onset epilepsy and DRE.

1. Introduction

Epilepsy is a chronic disease of the brain that is characterized by spontaneous recurrent seizures and that affects approximately 60 million people of different ages and ethnic backgrounds worldwide. Currently, nearly one-third of patients with epilepsy do not respond to antiepileptic drugs, underlining the need to explore innovative targets for treatment [1]. Methylglyoxal (MG), an endogenous neurotransmitter, plays an inhibitory role in the process of synaptic transmission by competitively activating γ-aminobutyric acid type A ($GABA_A$) receptors and functions in seizure control [2]. Because the glyoxalase system is essentially responsible for the clearance of MG, its role in epilepsy has gradually become evident.

Glyoxalase I (GLO1) is a key enzyme in the glyoxalase system that detoxifies MG and then limits the conversion of MG to advanced glycation end products (AGEs). AGEs are toxic mediators of a number of diseases, including, but not limited to, diabetic complications [3]. Recent studies suggest that increased GLO1 expression results in neurological and psychiatric disorders due to aberrant detoxification of MG [4,5]. Palmer and colleagues discovered a correlation between increased GLO1 expression and susceptibility to epilepsy by analyzing epileptic phenotypes in BXD recombinant inbred mice with various copies of the GLO1 gene [2]. Moreover, the administration of a GLO1 inhibitor increased MG concentrations and attenuated pilocarpine-induced seizures in mice [2,6], suggesting that inhibition of GLO1 activity reduces epileptic seizures by increasing MG expression. Notably, the concentration of MG required to activate $GABA_A$ receptors is in the physiological range [4], implying that fine-tuning MG expression for seizure control

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Table 1
Participant information.

	Cohort I			Cohort II		
	Cases	Controls	*p* value	Cases	Controls	*p* value
Gender (male/female, n)	137/112	157/132	0.872	60/70	101/90	0.237
Age (mean ± SD, years)	26.51 ± 15.25	27.32 ± 21.24	0.325	34.77 ± 15.27	35.27 ± 8.91	0.710
Age of onset (n)						
Early-onset epilepsy	145			–		
Late-onset epilepsy	104			95		
DRE (n)	67			81		

should not result in pathological accumulation of AGEs. Thus, GLO1 may be a promising target for antiepileptic treatment.

Currently, single nucleotide polymorphisms (SNPs) are the most common genetic determinant of predisposition to human diseases. The GLO1 gene, which is located at 6p21.3–p21.1 in the human genome, contains hundreds of polymorphic sites. Several studies have reported the association of GLO1 SNPs with disease susceptibility. The A allele at rs1130534 T > A, which causes a synonymous substitution at codon 124 (GGA to GGT, Gly to Gly), is correlated with reduced MG concentrations in human whole blood cell lysates, implying that the A allele could serve as a marker for susceptibility to GLO1-related diseases [7]. Meanwhile, the C allele at rs4746 A > C, which results in a missense mutation at codon 111 (GAG to GCG, Glu to Ala), exerts a protective effect against autism through genotyping, proteomic measurements and western blot analyses of brain tissues [8,9]. Additionally, the CC genotype at rs1049346 T > C is significantly associated with diabetic retinopathy/nephropathy, and luciferase reporter assays indicate that the activity of the GLO1 promoter was decreased with the C allele compared with the T allele, implying that the toxic AGEs involved in diabetic complications likely result from insufficient expression of the GLO1 gene [10]. Nevertheless, the role of GLO1 polymorphisms in epilepsy remains undetermined.

To determine whether GLO1 SNPs are associated with epilepsy, this study selected the three aforementioned SNPs of the GLO1 gene (rs1049346, rs1130534 and rs4746) and assessed their association with epilepsy.

2. Material and methods

2.1. Ethics statement

This study protocol was approved by the Ethics Committees of the First Affiliated Hospital of Harbin Medical University, Affiliated Hospital of Guangdong Medical University and Beijing Tongren Hospital, Capital Medical University. Written informed consent was obtained from each participant, and all experiments involving human participants were conducted according to the Declaration of Helsinki.

2.2. Participant enrollment

In cohort I, a total of 249 epileptic patients and 289 healthy individuals were enrolled in the case and control groups, respectively. All participants were Han Chinese recruited from the First Affiliated Hospital of Harbin Medical University in northern China or from the Affiliated Hospital of Guangdong Medical University in southern China. Patients with epilepsy were selected in accordance with the definition of epilepsy proposed by the International League Against Epilepsy (ILAE) [11]. All of these patients were further stratified by age at onset (early-onset epilepsy, <18 years old; late-onset epilepsy, ≥18 years old) and drug-resistant epilepsy (DRE). In light of the consensus raised by the ILAE [12], DRE was defined as the absence of a change or a reduction in seizure frequency (<60%) after at least a one-year treatment with two or more tolerated, appropriately selected and used antiepileptic drugs. Notably, 3 patients with epilepsy and 8 healthy volunteers that failed to be genotyped for the GLO1 SNPs were excluded from the study, as well as 11 cases with extrinsic factors, including intracranial infections, tumors and brain trauma.

More importantly, additional participants were recruited from Beijing Tongren Hospital in northern China into cohort II according to inclusion and exclusion criteria similar to those used for cohort I. Cohort II was composed of 130 epileptic patients (late-onset epilepsy, 95 cases; DRE, 81 cases) and 191 healthy individuals. Then, a replication study designed to confirm the positive findings in cohort I (the initial samples: 249 cases and 289 controls) was performed in cohorts II and I + II. In particular, the analyses in cohort I + II were further adjusted using Bonferroni correction, expecting to enhance the reliability of the findings in the present study.

Table 2
Alleles and genotypes of the GLO1 SNPs between all cases and the controls.

	All cases n (%)	Controls n (%)	OR (95% CI)	*p* value
rs1130534 T > A				
T/A	385 (77.31)/113 (22.69)	456 (78.89)/122 (21.11)	0.903 (0.675–1.207)	0.490
TT/TA/AA	147 (59.04)/91 (36.55)/11 (4.42)	178 (61.59)/100 (34.60)/11 (3.81)	0.898 (0.666–1.210)	0.479
TT/TA + AA	147 (59.04)/102 (40.96)	178 (61.59)/111 (38.41)	0.884 (0.622–1.255)	0.489
TT + TA/AA	238 (95.58)/11 (4.42)	278 (96.19)/11 (3.81)	0.861 (0.361–2.024)	0.732
rs4746 A > C				
A/C	437 (87.75)/61 (12.25)	501 (86.68)/77 (13.32)	1.105 (0.771–1.584)	0.587
AA/AC/CC	188 (75.50)/61 (24.50)/0 (0)	214 (74.05)/73 (25.26)/2 (0.69)	1.119 (0.764–1.641)	0.563
AA/AC + CC	188 (75.50)/61 (24.50)	214 (74.05)/75 (25.95)	1.084 (0.733–1.603)	0.687
AA + AC/CC	249 (100.00)/0 (0)	287 (99.31)/2 (0.69)	1.494E9	0.999
rs1049346 T > C				
T/C	289 (58.03)/209 (41.97)	328 (56.75)/250 (43.25)	1.059 (0.830–1.351)	0.644
TT/TC/CC	79 (31.73)/131 (52.61)/39 (15.66)	101 (34.95)/126 (43.60)/62 (21.45)	1.058 (0.831–1.347)	0.647
TT/TC + CC	79 (31.73)/170 (68.27)	101 (34.95)/188 (65.05)	0.870 (0.605–1.253)	0.454
TT + TC/CC	210 (84.34)/39 (15.66)	227 (78.55)/62 (21.45)	1.472 (0.946–2.292)	0.087

Remarks: ORs and *p* values have been adjusted for gender and age.