



Integrative Analyses Identify *KCNJ15* as a Candidate Gene in Patients with Epilepsy

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ABSTRACT

Introduction: Although there is accumulating evidence that genetic factors play a vital role in the pathogenesis of epilepsy, few epilepsy-associated genes have been identified. Additionally, the role of *KCNJ15* in epilepsy has not been evaluated so far.

Methods: Here, we performed differentially expressed gene analysis, expression quantitative trait loci analysis, gene co-expression analysis, and protein–protein interaction analysis to evaluate the role of *KCNJ15* in epilepsy.

Results: Analysis of gene expression and expression quantitative trait loci data revealed

that *KCNJ15* was significantly downregulated in patients with epilepsy (adjusted $P = 0.0146$ and \log_2 Fold change = -1.0025), and an epilepsy-associated polymorphism (rs2833098) was linked to altered *KCNJ15* expression level in human temporal lobe brain tissue ($P = 0.0036$). Gene co-expression analysis revealed that *KCNJ15* was co-expressed with genes that have been reported to be associated with epilepsy in human brain tissue. Furthermore, protein–protein interaction analysis revealed strong supportive evidence for the role of *KCNJ15* in epilepsy.

Conclusion: Our results show that *KCNJ15* may be a candidate target for epilepsy. Functional analysis of *KCNJ15* may provide novel insights for epilepsy treatment.

Keywords: Epilepsy; Gene; *KCNJ15*; Therapy

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Key Summary Points

Epilepsy is one of the nervous system diseases with complex inheritance. However, the role of *KCNJ15* in epilepsy remains unknown.

About 30% of patients do not respond well to current antiepileptic drugs. Furthermore, current antiepileptic drugs are often correlated with multiple adverse reactions. Considering the limitations of current therapeutic strategies, gene therapy may be a promising option.

The protein encoded by *KCNJ15*, ATP-sensitive inward rectifier potassium channel 15, is an integral membrane protein. Its physiological function is to act as an inward potassium channel that allows potassium to flow into the cell through the cell membrane.

By an integrative analysis with data on *KCNJ15* expression, expression quantitative trait locus (eQTL), gene co-expression, and protein–protein interaction (PPI), we hypothesize that *KCNJ15* has an active role in epilepsy.

INTRODUCTION

Epilepsy is the most prevalent nervous system disease [1], and it is characterized by episodes of excessive synchronized neuronal activity. About 30% of patients do not respond well to current antiepileptic drugs [2, 3]. Furthermore, these drugs often have multiple adverse side effects [4, 5]. Although surgery is an effective option for drug-resistant epilepsy, it is suitable only for a few patients [6] and might also affect other brain tissues surrounding the epileptic focus [7]. Considering the limitations of current therapeutic strategies, gene therapy may be a promising option [8]

K⁺ channels play an important role in membrane repolarization of active

neurons. Therefore, K⁺ channels may be potential targets for epilepsy treatment [9]. The protein encoded by *KCNJ15*, ATP-sensitive inward rectifier potassium channel 15, is an integral membrane protein. Its physiological function is to act as an inward potassium channel that allows potassium to flow into the cell through the cell membrane. The expression of *KCNJ15* has been observed in glial cells [10]. Knockdown of *KCNJ15* can result in compromised electro-taxis [11]. *KCNJ15* is associated with Parkinson's disease [12], and it also plays a vital role in Alzheimer's disease pathogenesis [13], suggesting that it is involved in the pathogenesis of central nervous system diseases more broadly. However, the association between *KCNJ15* and epilepsy has not been evaluated so far. Therefore, we conducted a study including differentially expressed gene (DEG) analysis, expression quantitative trait locus (eQTL) analysis, gene co-expression analysis, and protein–protein interaction (PPI) analysis, to systematically investigate the role of *KCNJ15* in epilepsy.

METHODS

Differentially Expressed Genes Identified in Human Brain Tissue

The GSE6834 data set was downloaded from NCBI (<https://www.ncbi.nlm.nih.gov>), and R software was used to screen the DEGs between epilepsy and controls. The GSE6834 data set is divided into temporal lobe brain tissue samples from patients with epilepsy and temporal lobe brain tissue samples from the control group. Specifically, ten epilepsy temporal lobe brain tissue samples were obtained from patients undergoing therapeutic surgery for drug-resistant mesial temporal lobe epilepsy according to routine clinical protocols and controls from ten nonepileptic temporal lobe samples. Patients in the case group were between 18 and 60 years old, and those in the control group were between 56 and 90 years old. An adjusted $P \leq 0.05$ and $|\log_2 \text{Fold change}| \geq 1$ were considered statistically significant.

This article is based on previously conducted studies and does not contain any new studies

with human participants or animals performed by any of the authors.

Expression Quantitative Trait Locus Analysis in Human Brain Tissue

Rs2833098 has been reported to be associated with the risk of epilepsy [14]. To explore if rs2833098 regulates the expression level of *KCNJ15* in human temporal lobe brain tissue, we conducted eQTL analysis in the BRAINEAC database (<http://www.braineac.org/>), which provides gene expression values across ten brain tissues. *KCNJ15* expression was measured using RNA sequencing, and a linear regression analysis under an additive model was used to explore the association of rs2833098 with *KCNJ15* expression levels.

Gene Co-expression Analysis in Human Brain Tissue

We queried the Coexpedia database (<https://www.coexpedia.org/>), a database for studying gene co-expression in mice and humans, to evaluate the co-expression network of *KCNJ15* for genes with co-expression scores greater than 1 with *KCNJ15* in the brain. This database was supported by the National Research Foundation of Korea.

Protein–Protein Interaction Analysis

PPI networks can be used to develop new drugs and discover novel drug targets. To explore the association between *KCNJ15* and epilepsy drug therapy, we identified 115 genes (Table 1) targeted by approved antiepileptic drugs from two databases, Therapeutic Target Database 2020 and DrugBank 5.0 [15, 16]. These drug databases include molecular information about drugs, as well as their mechanisms, interactions, and targets. The PPI analysis was conducted using the STRING database (<https://string-db.org/cgi/input.pl>) [17]. Finally, the PPI network was built using Cytoscape software [18].

Table 1 The 115 identified genes whose encoded proteins are targeted by epilepsy drugs

Drug	Gene
Phenobarbital	NR1I2, GRIA2, GABRA1, CHRNA4, CHRNA7, GRIK2, GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A, GRIN3B
Primidone	CHRNA4, GRIK2, GABRA1, GABRA3, GABRA6, GABRA2, GABRA4, GABRA5, CHRNA7, GRIA2, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ
Phenytoin	SCN5A, SCN3A, CACNA1C, CACNA1D, CACNA1F, CACNA1S, CACNB1, CACNB2, CACNB3, CACNB4, CACNA1A, SCN8A, KCNH2, SCN1A, NR1I2, SCN1B, SCN2A, GABRA1, GABRA3, GABRA6, GABRA2, GABRA4, GABRA5, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ, SCN5A
Carbamazepine	SCN1A, SCN2A, SCN3A, SCN4A, SCN5A, SCN7A, SCN8A, SCN9A, SCN10A, SCN11A, CHRNA4, NR1I2
Valproate	ALDH5A1, HDAC2, PPARA, PPARD, OGDH, SCN1A, SCN2A, SCN3A, SCN4A, SCN5A, SCN7A, SCN8A, SCN9A, SCN10A, SCN11A, SCN1B, SCN2B, SCN3B, SCN4B, PPARG, HDAC9, ACADSB, GSK3A, ABAT
Clonazepam	TSPO, NR1I2, GABRA1, GABRA3, GABRA6, GABRA2, GABRA4, GABRA5, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ

Table 1 continued

Drug	Gene
Clobazam	GABRA1, GABRA3, GABRA6, GABRA2, GABRA4, GABRA5, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ
Gabapentin	CACNA2D1, KCNQ5, ADORA1, CACNA1B, CACNA1B, CACNA2D2, KCNQ3, CACNA2D1, CACNA2D2, GABBR1, GABBR2, SLC5A6
Lamotrigine	HTR3A, CACNA1E, ADRA2A, HRH1, OPRK1, ADORA1, ADORA2A, ADRA1A, DRD2, GABRA1, GABRA3, GABRA6, GABRA2, GABRA4, GABRA5, GABRG1, GABRG2, GABRG3, SCN2A, ADRB1, DRD1, DRD5, GABRA1, GABRA3, GABRA6, GABRA2, GABRA4, GABRA5, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, HTR2A, SCN11A
Topiramate	CA2, GRIK1, GRIK2, GRIK3, GRIK4, GRIK5, CA3, CA4, CA1, CACNA1E, GABRA1, SCN1A, SCN2A, SCN3A, SCN4A, SCN5A, SCN7A, SCN8A, SCN9A, SCN10A, SCN11A, CACNA1C, CACNA1D, CACNA1F, CACNA1S, CACNB1, CACNB2, CACNB3, CACNB4
Oxcarbazepine	SCN1A, SCN2A, SCN3A, SCN4A, SCN5A, SCN7A, SCN8A, SCN9A, SCN10A, SCN11A, SCN1B, SCN2B, SCN3B, SCN4B
Tiagabine	SLC6A1
Levetiracetam	SV2A, CACNA1B

Table 1 continued

Drug	Gene
Zonisamide	CA5B, CA10, CA11, CA12, CA13, SCN3A, SCN4A, SCN3B, MAOB, CA2, CA4, CA7, CA9, CACNA1H, SCN9A, SCN1B, SCN2B, SCN1A, CA1, CACNA1G, CA3, CA5A, CA6, CA8, CA14, CACNA1I, SCN2A, SCN5A, SCN11A, SCN4B, MAOA
Felbamate	GRIN3A, GRIN2A, GRIN2B
Pregabalin	CACNA2D1
Vigabatrin	ABAT, GABBR1

RESULTS

Differentially Expressed Genes Identified in Human Brain Tissue

On the basis of the DEG analysis, *KCNJ15* was identified as differentially expressed in one microarray data set (GSE6834). As shown in the volcano plot (Fig. 1), the results showed that the expression level of *KCNJ15* in epileptic temporal lobe brain tissue was significantly downregulated compared with that in controls (adjusted $P = 0.0146$ and \log_2 Fold change = -1.0025) (Table 2).

Expression Quantitative Trait Locus Analysis in Human Brain Tissue

eQTL analysis in the BRAINEAC database indicated that rs2833098 is associated with *KCNJ15* expression level in human temporal lobe brain tissue ($P = 0.0036$), providing evidence that this polymorphism is involved in modifying *KCNJ15* expression in human temporal lobe brain tissue. Specifically, the AA genotype is associated with downregulated *KCNJ15* expression compared with that of the GG and GA genotypes in the human temporal lobe (Fig. 2).

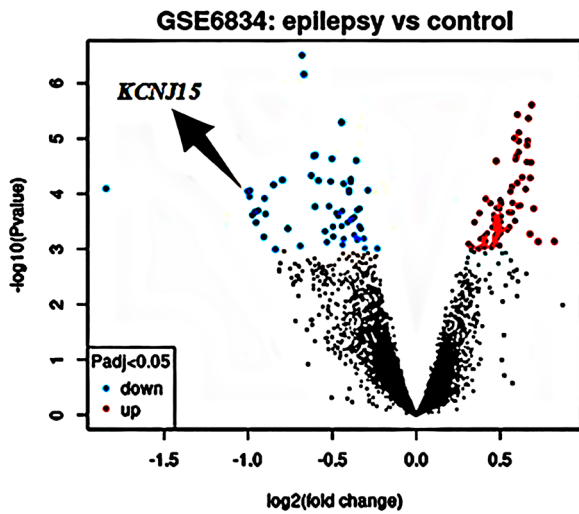


Fig. 1 Volcano plot illustrating differentially expressed genes (DEGs) between controls and patients with epilepsy in the analysis of the GSE6834 data set

Table 2 Comparison of the expression of *KCNJ15* in the brain tissue of the epilepsy group and the control group

Adjusted <i>P</i> value	<i>P</i> value	<i>t</i>	<i>B</i>	log ₂ FC value
0.0146	9.00E-05	—	1.5103	—
		4.7501		1.0025

FC fold change

Gene Co-expression Analysis in Human Brain Tissue

As shown in the co-expression network map (Fig. 3), the genes with co-expression scores greater than 1 with *KCNJ15* in brain tissue are *A1CF*, *RABAC1*, *CYP2A6*, *SIGLEC6*, and *CRHR2*. Thus, these genes are likely to be functionally associated with *KCNJ15*.

Protein–Protein Interaction Analysis

PPI analysis was performed for 115 genes targeted by epilepsy drugs and *KCNJ15*. The PPI network indicated that the protein encoded by *KCNJ15* directly interacts with two epilepsy drug targets encoded by *GABBR1* and *GABBR2* (Fig. 4). *GABBR1* is the target of vigabatrin and

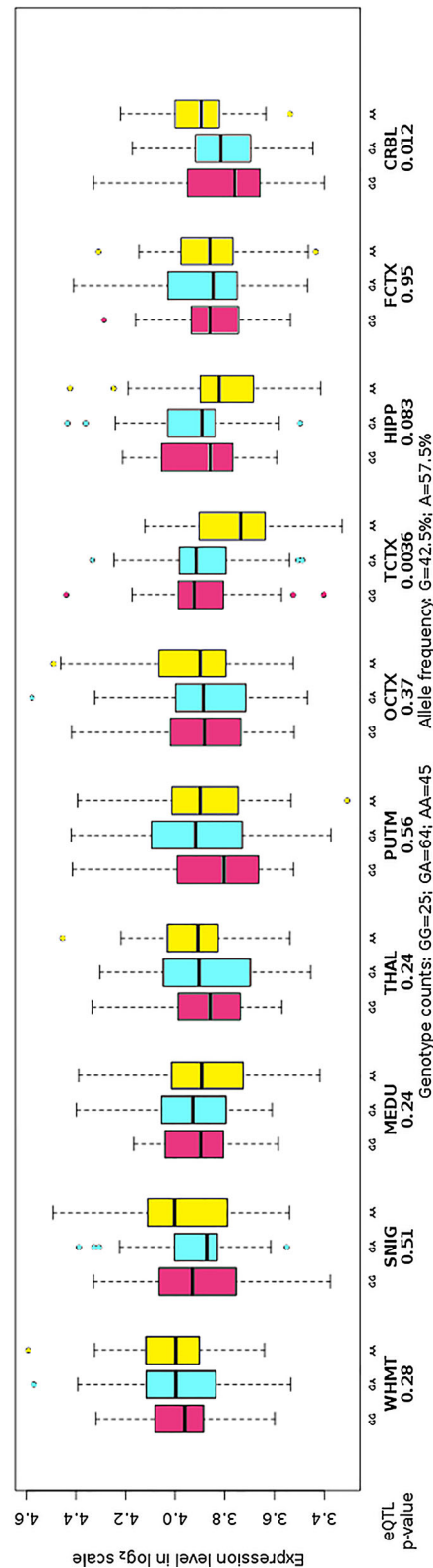


Fig. 2 rs2833098 is associated with *KCNJ15* expression in human brain tissues ($P = 0.0036$). The data were retrieved from the BRAINEAC database: *CRBL* cerebellum, *PUTM* putamen, *HIPP* hippocampus, *TCTX* temporal cortex, *OCTX* occipital cortex, *FCTX* frontal cortex, *THAL* thalamus, *SNIG* substantia nigra, *MEDU* medulla, *WHMT* white matter

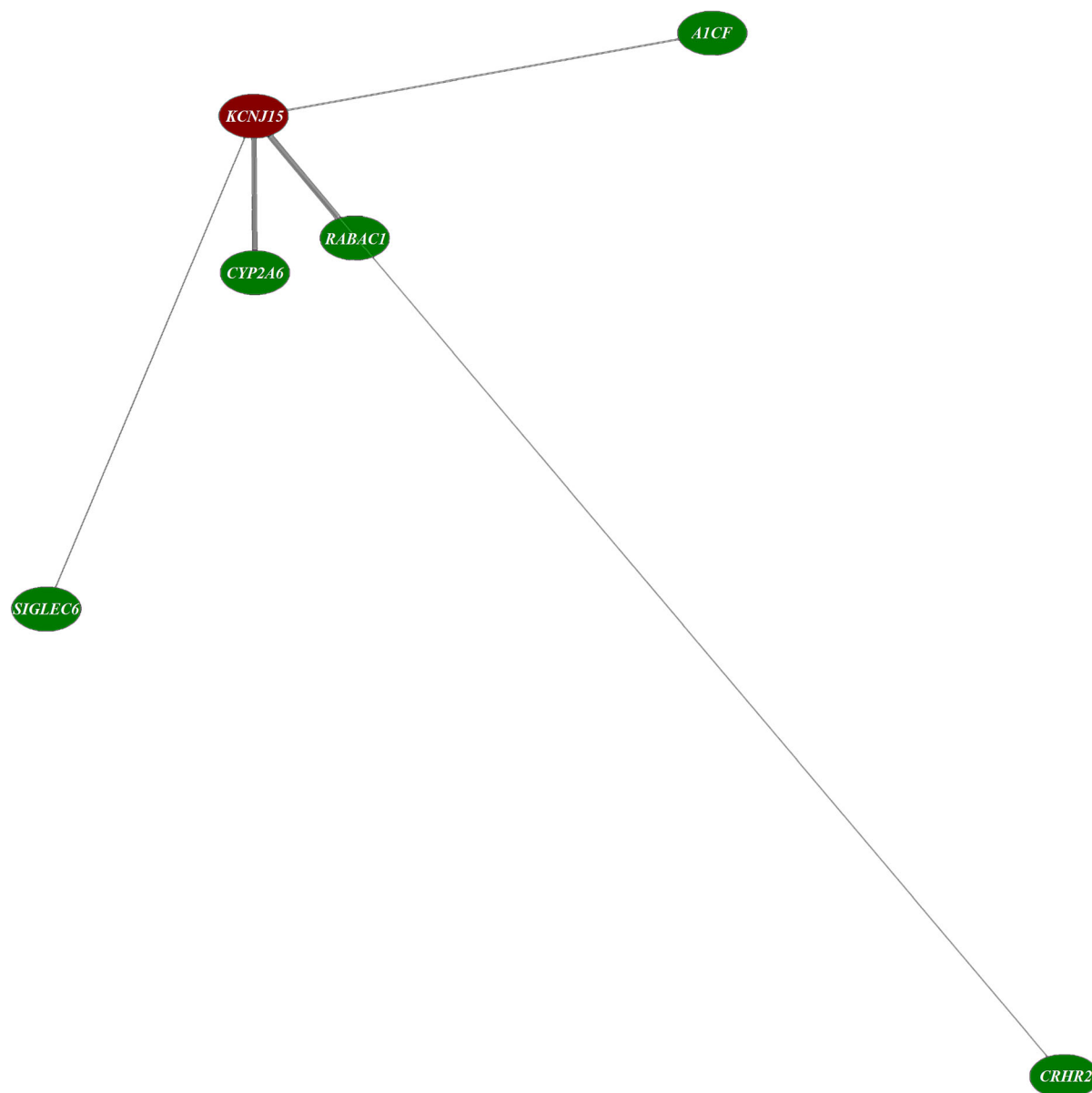


Fig. 3 Gene co-expression analysis. Genes with a co-expression score greater than 1 with *KCNJ15* in brain tissue are *AICF*, *RABAC1*, *CYP2A6*, *SIGLEC6*, and

CRHR2. These genes are highly likely to be functionally associated with *KCNJ15*. Data were retrieved from the Coexpedia database (<https://www.coexpedia.org/>)

gabapentin, and *GABBR2* is the target of gabapentin.

DISCUSSION

Although genetic factors play a vital role in the pathogenesis of epilepsy [19], the genetic

association between polymorphisms of *KCNJ15* and epilepsy has not yet been evaluated. Here, we conducted an association study to explore the role of *KCNJ15* in contributing genetic risk to epilepsy. By an integrative analysis with data on *KCNJ15* expression, eQTLs, gene co-expression, and PPI, we hypothesize that *KCNJ15* has an active role in epilepsy. To our knowledge,

temporal lobe brain tissue. Rs2833098, which is located in a noncoding region, was previously associated with the risk of epilepsy in a genome-wide meta-analysis [14]. Additionally, eQTL analysis showed that the AA genotype of rs2833098 is associated with decreased *KCNJ15* mRNA level in human temporal lobe brain tissue (Fig. 2). SNPs in non-coding regions often confer risk of disease by regulating the expression of their target genes [26]. Furthermore, we also found that *KCNJ15* was significantly downregulated in the temporal lobe brain tissue of patients with epilepsy. Therefore, we speculate that rs2833098 may be a marker of epilepsy risk by regulating the expression level of *KCNJ15* in human temporal lobe brain tissue.

Gene co-expression networks can be used to identify regulatory genes [27]. Gene expression and regulation are highly tissue-specific, and most disease-related genes have different expression levels in different tissues [28, 29]. Gene co-expression analysis revealed that *KCNJ15* is co-expressed with multiple genes, including *A1CF*, *RABAC1*, *CYP2A6*, *SIGLEC6*, and *CRHR2*, in human brain tissue (Fig. 3), suggesting that these genes are functionally associated. Previous studies have identified that *CYP2A6* is associated with the efficacy of antiepileptic drug treatment in patients with epilepsy [30, 31], so we speculate that *CYP2A6* may play an important role in epilepsy, and *KCNJ15* may be a candidate target for epilepsy treatment. However, *CYP2A6* has many substrates and interactors, not only antiepileptic drugs, so the role of *KCNJ15* in epilepsy still needs further verification.

Considering the limitations of current therapeutic strategies, it is necessary to discover new targets for epilepsy treatment. Understanding the association between genes and drug targets will facilitate the translation of clinical utility in the future. The PPI network is an effective tool to discover drug targets and drugs [32]. Our study demonstrated that *KCNJ15* is more likely to interact with targets of approved epilepsy drugs, including *GABBR1* and *GABBR2* (Fig. 4), indicating that these proteins may be functionally associated. By querying the DrugBank database and the Therapeutic Target Database, we found that *GABBR1* is the target of

vigabatrin and gabapentin, and *GABBR2* is the target of gabapentin, further supporting a role of *KCNJ15* in epilepsy.

Although no patients with epileptic syndrome with de novo mutations in this gene have yet been found, we found that a SNP associated with the risk of epilepsy is associated with the expression level of *KCNJ15* in brain tissue. Therefore, we speculate that *KCNJ15* may not affect the risk of epilepsy through mutations in the amino acid sequence, but through altered expression level in human brain tissue, thereby affecting the risk of epilepsy. Therefore, this study may contribute to the discovery of new targets for epilepsy treatment. However, this is a future prospect that requires further in-depth studies. Knockdown or overexpression of the gene in epilepsy animal models can help to further validate the role of the gene in epilepsy, and epilepsy pharmacogenomics can help translate genetic findings into clinical treatment.

Although we identified *KCNJ15* as a potential biological target by integrative analysis, some limitations of our study should be acknowledged. First, the sample size of the temporal lobe brain tissue samples in our study is relatively small. Second, we did not validate our conclusions with animal models, so more investigations are necessary to confirm our findings. Third, the association of *KCNJ15* with epilepsy has not been evaluated by other studies, so it is important to validate our results in different populations.

CONCLUSIONS

Our study suggests that *KCNJ15* may be a potential therapeutic target for epilepsy. Additional functional analysis of *KCNJ15* may provide novel insights for epilepsy treatment.

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Disclosures. Shitao Wang, Zongyou Li, Xiangqian Ding, Zongyou Zhao, Menggen Zhang, Hui Xu, Jinghong Lu, and Lili Dai declare that they do not have any personal, financial, commercial, or academic conflicts of interest.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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