



# Functional characterization of a *KCNAB3* genetic epilepsy with febrile seizures plus adult mouse model

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**Background:** Genetic epilepsy with febrile seizures plus (GEFS+) is a type of epileptic syndrome closely related to heredity factors, which can be caused by gene mutations. However, it still remains unclear how these mutations result in seizures. Previously, we identified a new heterozygous missense mutation of the *KCNAB3* gene, H258R, in the GEFS+ family; the electric currents of the human embryonic kidney 293 (HEK293) cells co-expressing Kv $\beta$ 3 (H258R) and Kv1.1 showed obvious inactivation. This study sought to examine the effects of this mutation on the potassium channels in the mammalian brain.

**Methods:** Mutant mice were generated by introducing the human H258R missense mutation within exon 10 at an equivalent position in the mouse *KCNAB3* gene via CRISPR/Cas9 and homologous recombination. A patch clamp was used to detect the potassium currents in the pyramidal cells of the hippocampal CA1 region of the mutant mice. The total potassium currents of the pyramidal cells in the hippocampal CA1 region of *KCNAB3* [wild-type (WT)] and *KCNAB3* (H258R) adult mice were recorded with increased voltage.

**Results:** We found a decreased total potassium current in the H258R group but no significant differences at a maximum voltage (+80 mV;  $P > 0.05$ ).

**Conclusions:** These results suggest that the *KCNAB3* mutation reduced hippocampal potassium currents in this mouse model.

**Keywords:** Genetic epilepsy with febrile seizures plus (GEFS+); *KCNAB3* gene; mutation; potassium channel; mouse model

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## Introduction

Genetic epilepsy with febrile seizures plus (GEFS+), previously known as generalized epilepsy with febrile seizures (FS) plus, was first reported in a large Australian family by Scheffer and Berkovic (1) in 1997. Later, focal epilepsy phenotypes, such as temporal lobe and frontal lobe

epilepsy, were observed in GEFS+ families. Thus, Scheffer and Berkovic (2) proposed the current denomination of GEFS+. In 2001, this disease was identified as a new epileptic syndrome by the International League Against Epilepsy and is characterized by phenotypic and genetic heterogeneity. GEFS+ is a genetic epilepsy syndrome with a broad phenotypic spectrum (3). Different members of the

same family may have phenotypes ranging from slight FS to serious epileptic encephalopathy, such as Dravet syndrome (4-7). The etiopathology of GEFS+ is complex, and there is strong evidence that it has a genetic predisposition (8). GEFS+ is a complex autosomal dominant disorder (9). According to family analysis, most GEFS+ can be attributed to autosomal dominant inheritance with incomplete dominance, the GEFS+ phenotypic penetrance has been reported to range from 62–76%, a study has found double inheritance in GEFS+ families, GEFS+ may have complex inheritance modes, such as polygenic inheritance (10). Mutations in a variety of pathogenic genes are involved in the pathogenesis of GEFS+, usually caused by mutations in gene encoding voltage-gated sodium channel protein subunit *SCN1A* (9). *SCN2A*, *SCN1B*, *GABRG2*, and *GABRD* are also common pathogenic genes associated with GEFS+. Other genes such as *SCN9A*, *STX1B*, and *Fgf13* may also be involved in the pathogenesis of GEFS+.

Previously, we identified a new missense mutation in the *KCNAB3* gene H258R (HR) in a GEFS+ family. This mutation was first reported by our team. There are 18 members in this family, 4 were affected with GEFS+. Whole-exome sequencing was performed to assess for genetic mutations. *KCNAB3*<sup>HR</sup> was shared by three affected and one unaffected family member. This mutation was thought to affect protein function by the bioinformatics tools. For patients with genetic epilepsy, the connection between a specific mutation and their behavioral symptoms is largely unknown (11). To clarify the relationship between the *KCNAB3* gene mutation (H258R) and GEFS+, wild and mutant plasmids were constructed and transfected into human embryonic kidney 293 (HEK293) cells for patch-clamp detection. The whole cell patch-clamp detection results suggested that this mutation caused the inactivation of potassium channels, reduced potassium outflow, increased cell excitability, and promoted convulsion (12). In the present study, to examine the effects of this mutation on potassium channels in the mammalian brain, we introduced the H258R mutation into the mouse *KCNAB3* gene using CRISPR/Cas9. A patch clamp was then used to detect potassium currents in the pyramidal cells of the hippocampal CA1 region. Hippocampal sclerosis (HS) is considered to be an important pathological change of epilepsy, especially temporal lobe epilepsy (TLE). Many TLE patients with HS have a history of FS in childhood. The clinical manifestations of GEFS+ are mainly heat-related convulsions, therefore, hippocampal cells were selected as the research objects in this study (13). A protocol was

prepared before the study without registration. We present the following article in accordance with the ARRIVE reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-436/rc>).

## Methods

### Generation of *KCNAB3*<sup>HR</sup> mice

CRISPR/Cas9 technology was used to knock-in the human *KCNAB3* exon 10 (H258R) expression frame at exon 10 of the mouse *KCNAB3* gene through homologous recombination. Briefly, Cas9 messenger RNA (mRNA) and guide RNA (gRNA) were obtained by *in-vitro* transcription. In-fusion cloning was used to construct a donor vector comprising 3.0 kb 5'homologous arms, human *KCNAB3* exon10 (H258R) and 3.0 kb 3'homologous arms. Cas9 mRNA, gRNA, and the donor vector were microinjected into the fertilized eggs of C57BL/6J mice (Bought from Shanghai Model Organisms Center, Inc., Shanghai, China) to obtain the F0 generation mice. The mice confirmed to be positive by polymerase chain reaction (PCR) amplification and sequencing were mated with C57BL/6J mice to obtain the F1 generation.

Animal experiments were performed under a project license (No. KY-D-2021-120-06) granted by the ethics committee of Guangdong Provincial People's Hospital, in compliance with Guangdong Provincial People's Hospital guidelines for the care and use of animals.

### PCR

To screen for mice with the *KCNAB3*<sup>HR</sup> mutation, the DNA was amplified using a *KCNAB3*-specific forward primer and a reverse primer. PCR amplification was performed for 35 cycles at 98 °C for 15 s, 61 °C for 15 s, and 68 °C for 30 min. The reaction mixture consisted of 13.2 µL of ddH<sub>2</sub>O, 2 µL of GXL PCR buffer, 2 µL of 2.5-mM dNTP, 0.8 µL of GXL DNA polymerase, 0.5 µL of forward primer, 0.5 µL of reverse primer, and 1 µL of genomic DNA.

### Cell separation

The hippocampal CA1 region was dissected from brain slices from the experimental mice and placed in protease [Hanks' Balanced Salt Solution (HBSS) configuration] for digestion at 33.3 °C for 30 min. The whole digestion process was treated with high purity oxygen. After digestion, 3 mL

of oxygen-saturated HBSS Na<sup>+</sup> solution was added to each tube of enzyme solution to terminate the protease action. This was repeated 3 times; then, 2 mL of oxygen-saturated low Ca<sup>2+</sup> N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) solution was added. The tissue was sequentially agitated with large, medium, and small caliber Pasteur pipettes and left to stand for 2 min. After agitation with the large and medium caliber pipettes, the supernatant was removed and placed in a new 15-mL centrifuge tube. Next, the tissue was agitated with a small caliber Pasteur pipette and left to stand for 2 min. The supernatant was then sucked out and mixed with the 1st supernatant. Mixed cell suspensions were inoculated in a 3.5-cm cell culture dish treated with polylysine at 2 mL per dish. After standing for 10 min, the cells had adhered to the wall and were ready for the patch clamp.

### Patch clamp

A capillary glass tube (BF150-86-10, Sutter Instruments) was drawn into the recording electrode with a microelectrode drawing instrument (P97, Sutter Instruments). The microelectrode manipulator (MP225, Butter Instrument) was operated under an inverted microscope (MF53, micro-shot). The recording electrode contacted the cell, and negative pressure was pumped to form a GΩ seal. After achieving the GΩ seal, rapid capacitive compensation was performed. Continuous negative pressure served to absorb the membrane and achieve the whole cell recording mode. Next, the slow capacitance was compensated, and the membrane capacitance and series resistance were recorded. The experimental data were collected using an EPC-10 amplifier (HEKA) and stored with PatchMaster (HEKA) software. All the experiments were performed at room temperature. The following fluids were used for the recording: extracellular fluid: 140 mM of NaCl, 3.5 mM of KCl, 2 mM of CaCl<sub>2</sub>·2H<sub>2</sub>O, 1 mM of MgCl<sub>2</sub>·6H<sub>2</sub>O, 10 mM of HEPES, 10 mM of D-glucose, and 1.25 mM of NaH<sub>2</sub>PO<sub>4</sub>, with a NaOH adjusted pH of 7.4. The following intracellular fluids were used: 20 mM of KCl, 115 mM of K-aspartic, 1 mM of MgCl<sub>2</sub>·6H<sub>2</sub>O, 5 mM of EGTA, 10 mM of HEPES, and 2 mM of Na<sub>2</sub>-ATP, with a KOH adjusted pH of 7.2.

### Statistical analysis

After exporting the current diagram recorded by PatchMaster, the original current data were output by Igor

Pro software and saved in Excel. The current density was calculated using the I-V curve, and a collaboration diagram was then prepared with GraphPad Prism 8.0 software, and the current obtained under the maximum activated voltage was subsequently compared. The *t*-test was used for the statistical analysis, and a P value <0.05 was considered statistically significant.

## Results

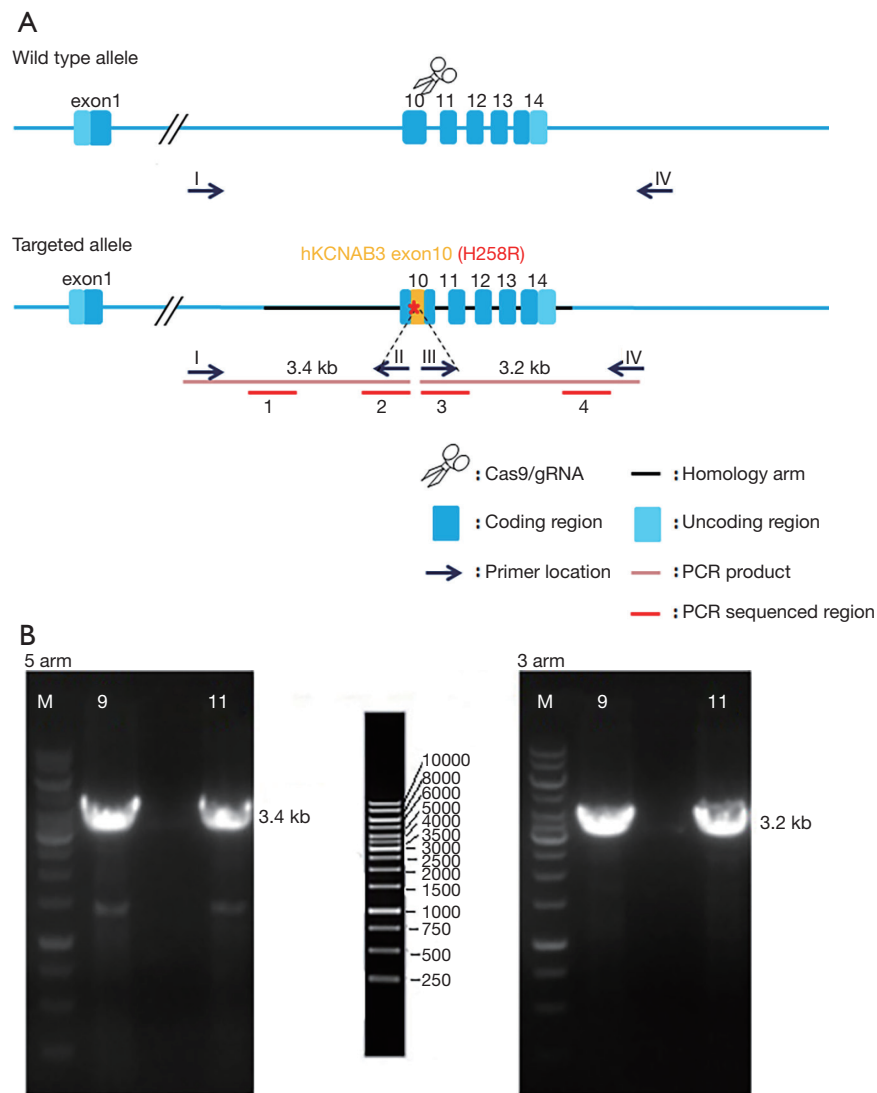
### Generation of *KCNAB3<sup>HR</sup>* mutant mice

The injected fertilized eggs were transplanted into pseudo-pregnant female mice. The F0-generation mice were born at about 20 days and identified by PCR amplification. Positive 5' arm homologous recombination with 5'CTGACCTCATCAACGTGCCT'3 as the forward primer and 5'CGCTCCGCTTGTTCACACAC'3 as the reverse primer resulted in an amplification that produced a 3.4 kb fragment, while positive 3' arm homologous recombination with 5'GAGCGCCATCTGTTTCAGA'3 as the forward primer and 5'CTGGCCTTTTGTGGTTTCC'3 as the reverse primer resulted in an amplification that produced a 3.2 kb fragment (see *Figure 1*). Due to the rapid cleavage rate of the fertilized eggs in the early stages, the obtained F0-generation mice were chimeras, which may not have a stable inheritance. Thus, the passage was required to obtain stable inheriting F1 mouse generations.

The F0-generation positive mice were mated with wild-type (WT) C57BL/6J mice to obtain F1-generation mice. The F1-generation mice were identified by PCR and sequencing; 4 sequencing reactions were performed (see *Figure 2*). The F1-generation mice genotypes were amplified using the primer pairs (P1: 5'GAGCAAGCGGAGAACCACT'3, P2: 5'AAACAGAGCTGACACCCTCG'3) and (P3: 5'GCGGAGCGCCATCTGTTTCA'3, P4: 5'TGGCTTGTGCTTCTTGCCT'3). The genotypes were as follows: WT, only (P1, P2) amplified 673 bp band, (P3, P4) no band; heterozygous type: (P1, P2) amplified 673 bp band and (P3, P4) amplified 413 bp band; homozygous type: (P1, P2) no band, (P3, P4) amplified 413 bp band (see *Figure 3*).

### Potassium current of CA1 pyramidal neurons in *KCNAB3<sup>HR</sup>* mice

A patch clamp was used to detect the total potassium



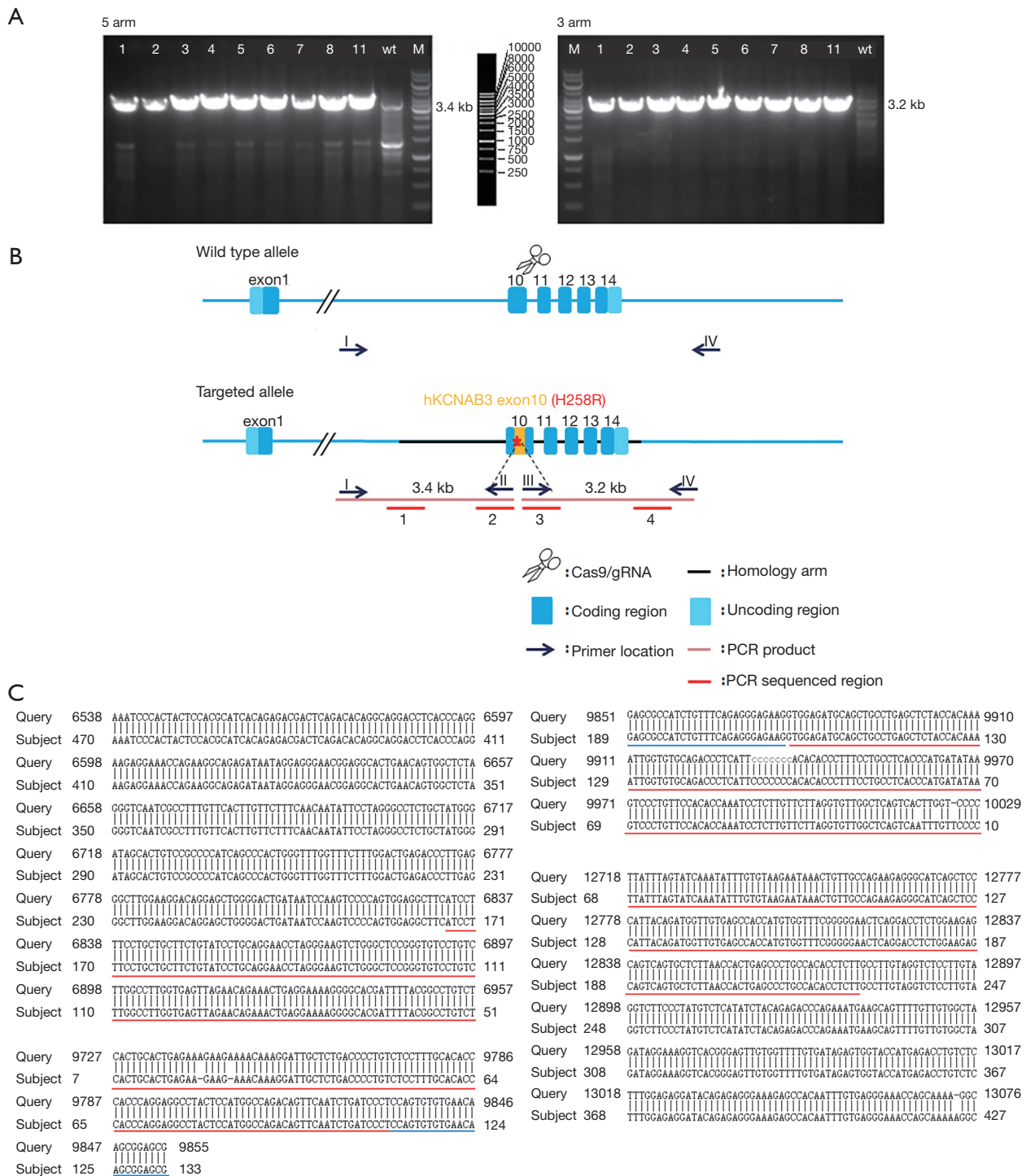
**Figure 1** PCR identification of F0 generation mice. (A) Schematic diagram of identification strategy of F0 generation mice. (B) The electrophoretic map of F0 generation mice was identified by PCR. (Number: number of F0 generation mice; M: 1 kb DNA ladder). Red star symbol indicates knock-in site. PCR, polymerase chain reaction.

current of the pyramidal cells ( $n=10$ ) in the hippocampal CA1 region of the *KCNAB3* (WT) and *KCNAB3* (H258R) adult mice; changes in the current were recorded as voltage increased. The current stimulus programme was as follows: after forming the whole cell seal, the cell membrane voltage was clamped at  $-80$  mV and maintained for 50 ms. The cell membrane voltage was stimulated from  $-80$  mV to  $+80$  mV with 10 mV steps and maintained for 200 ms. Finally, it was

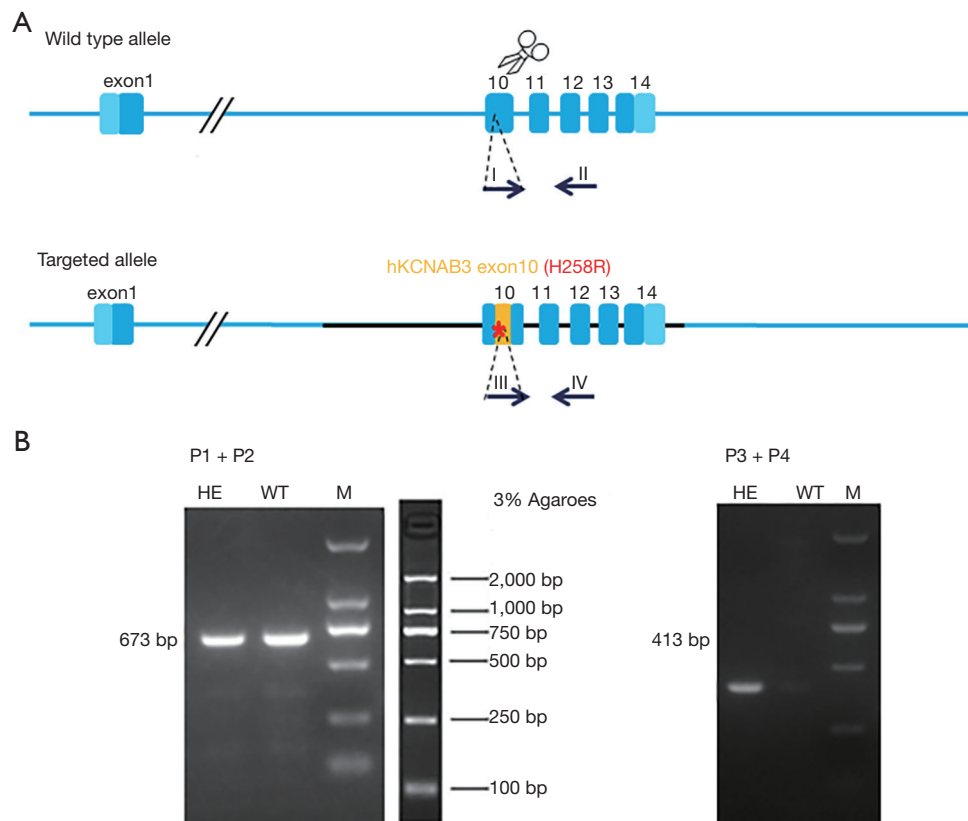
recovered to  $-80$  mV and maintained for 50 ms. The original current diagram showed that the total potassium current of the H258R group decreased as voltage increased (see *Figure 4*).

We plotted an I-V curve and compared the current difference at the maximum voltage. The result showed that the total potassium current decreased in the H258R group, but there were no significant differences in the current at the maximum voltage ( $+80$  mV) ( $P>0.05$ ; see *Figure 5*).

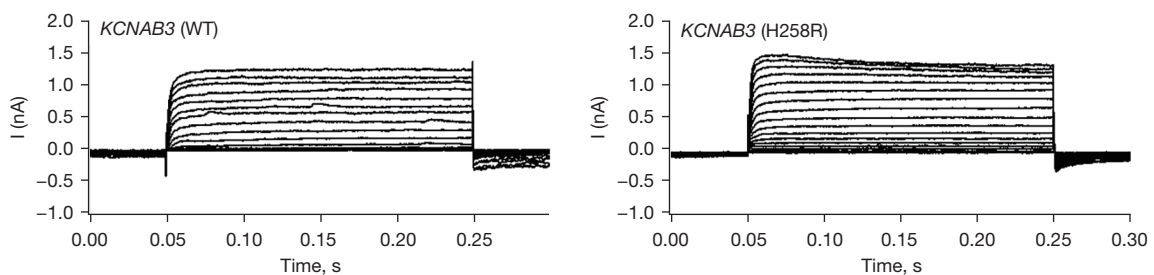




**Figure 2** PCR and sequencing identification of F1 generation mice. (A) The electrophoretic map of F1 generation mice was identified by PCR. (Number: number of F1 generation mice; WT: wild-type control; M: 1 kb DNA ladder). (B) Schematic diagram of sequencing identification of F1 generation mice (5’homologous arm identification: PCR products were sequenced in 2 reactions, labeled as 1 and 2; 3’homologous arm identification: PCR products were sequenced in 2 reactions, labeled as 3 and 4). (C) Comparison of PCR product sequence and target sequence in F1 generation mice (“Query” is the target sequence; “Subject” is the sequencing result; the red underlining is the homologous arm sequence; the blue underlining is the knock-in sequence). Red star symbol indicates knock-in site. PCR, polymerase chain reaction.



**Figure 3** Identification of F1 generation mice genotypes. (A) Primer location diagram of PCR identification. (B) Electrophoretic map of F1 generation mice genotypes identified by PCR (wild: amplified 673 bp band; heterozygous: amplified 673 bp band and amplified 413 bp band; homozygous: amplified 413 bp band). (HE: heterozygote; WT: wild-type control; M: 1 kb DNA ladder). Red star symbol indicates knock-in site. PCR, polymerase chain reaction.

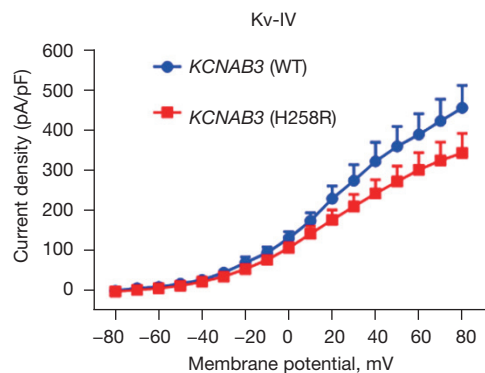


**Figure 4** Original current diagram of the patch-clamp experiment. WT, wild-type.

## Discussion

At present, the genetic research of GEFS+ mainly focuses on pathogenic genes. The pathogenic genes related to GEFS+ are mainly divided into two categories: (I) genes encoding voltage-gated sodium channel protein subunits

(*SCN1A*, *SCN2A*, *SCN1B*, *SCN9A*); (II) genes encoding ligand-gated chloride channel GABA<sub>A</sub> subunits (*GABRG2*, *GABRD*). Voltage-gated sodium channels (Nav) exist in the membrane of most excitable tissues and play an important role in the generation and propagation of action potentials. GABA is the most important inhibitory transmitter in



**Figure 5** I-V curve of *KCNAB3*. The data shows that: the total potassium current decreased in the H258R group. WT, wild-type.

the central nervous system. It is mainly located in the postsynaptic membrane of neurons in the central nervous system. It inhibits the excitability of neurons and is the target of neuroexcitatory inhibitory drugs such as benzodiazepines, barbiturates, and steroids. Others include *STX1B*, which encodes synapse fusion protein 1B, and *Fgf13*, which encodes fibroblast growth factor protein.

The potassium channel is the most complex ion channel and has the most known subtypes. It is widely expressed in the body and plays a role in maintaining neuron membrane potential, regulating excitability, and participating in cardiac myocyte repolarization. Further, it is associated with neurological and cardiac diseases. Recently, several cases of GEFS+ caused by mutations in potassium channel genes have been reported. Notably, Zou *et al.* (14) reported the heterozygous missense mutation P537S of *KCNQ4* in a GEFS+ family. Yu *et al.* (15) found a *KCNQ3* mutation (c.2128T > C) related to GEFS+. Tian *et al.* (16) summarized the clinical characteristics of a GEFS+ family caused by a *KCNT2* gene mutation and theorized that GEFS+ induced by this mutation may be insensitive to antiepileptic drugs. In a previous study, we identified the heterozygous missense mutation p.H258R of the *KCNAB3* gene encoding the voltage-gated potassium channel  $\beta 3$  subunit (Kv $\beta 3$ ) in a GEFS+ family.

Kv $\beta 3$  is primarily expressed in the rat brain (17). Human Kv $\beta 3$  mRNA is expressed in the brain and predominantly detected in the cerebellum (18). Kv $\beta 3$  subunits have an N-terminal inactivating domain that confers rapid N-type inactivation to Kv channels (19). The co-expression of rat Kv $\beta 3$  in *Xenopus* oocytes leads to the rapid inactivation of Kv1.4 channels but not of other Kv1 $\alpha$  channels (17). However, the co-expression of Kv1.5 and Kv $\beta 3$  in a

mammalian cell line yields rapidly inactivating A-type channels (18). In contrast to findings on the *Xenopus* oocyte expression system, Kv $\beta 3$  confers rapid inactivation to all Kv1 channels except Kv1.3 channels in Chinese hamster ovary cells (20).

In previous studies, HEK293 cells expressing human Kv1.1 and Kv $\beta 3$  were detected by the patch clamp. The present results showed that the current of cells expressing only Kv1.1 exhibited no inactivation, while the current of cells co-expressing Kv $\beta 3$  was inactivated; the inactivation characteristics were more obvious in cells co-expressing Kv $\beta 3$  (H258R). Together, these findings indicate that the Kv $\beta 3$  subunit promotes potassium channel inactivation and that the H258R mutation further accelerates this inactivation. In the present study, we induced the expression of the human *KCNAB3* gene in mice using a knock-in technique and then used a patch clamp to detect potassium currents in the pyramidal cells in the hippocampal CA1 region of the mouse brain. Our results showed that the total potassium current decreased in the H258R group but was not significantly different from the current at the maximum voltage (+80 mV). This may be explained by the different inactivation activity of Kv $\beta 3$  in various expression systems. Compared to cell-line expression systems, animal expression systems are more complex, and potassium currents are affected by other genes in addition to *KCNAB3*. Additionally, the function of human Kv $\beta 3$  might not be fully expressed in the heterologous expression system.

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## Footnote

**Reporting Checklist:** The authors have completed the ARRIVE reporting checklist. Available at <https://>

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tp.amegroups.com/article/view/10.21037/tp-22-436/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Animal experiments were performed under a project license (No. KY-D-2021-120-06) granted by the ethics committee of Guangdong Provincial People's Hospital, in compliance with Guangdong Provincial People's Hospital guidelines for the care and use of animals.

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