BMC Medical Genomics

CASE REPORT

Open Access

Torsades de Pointes electrical storm in children with *KCNH2* mutations

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Abstract

Congenital long QT syndrome (LQTS) is a genetic heart disorder, which may lead to life-threatening arrhythmias, especially in children. Here, we reported two children who were initially misdiagnosed with epilepsy and experienced Torsades de Pointes (TdP) cardiac electrical storm (ES). Through whole exome sequencing (WES), we identified two Potassium voltage-gated channel subfamily H member 2 (*KCHN2*) mutations (c.1841 C>T and c.1838 C>T) respectively in a 6-year-old boy and a 13-year-old girl. Clinical data indicated that the QT interval was significantly prolonged, the T-wave pattern of chest V5-V6 leads and limb leads were inverted. Our study suggests that patients with epilepsy, especially those refractory epilepsy with atypical features, need comprehensive evaluation of cardiovascular function. *KCNH2* mutation in pore region, QT interval prolongation and T wave inversion are high risk factors for ES. For LQT2 patients with ES, Nadolol and left cardiac sympathetic denervation are indicated, sometimes with an ICD.

Keywords Congenital long QT syndrome, *KCHN2*, Electrical storm, QT interval, T wave morphology

Introduction

Congenital long QT syndrome (LQTS) is one of the important hereditary cardiac diseases. It is characterized by abnormal cardiac repolarization, which can lead to prolonged QT interval and increase the probability of life-threatening polymorphic ventricular tachycardia called Torsades de Pointes (TdP) [1]. The diagnostic criteria for LQTS are based on the Schwartz criteria [2], and it is recommended to use genetic testing to detect pathogenic mutations of relevant ion channels. Recently, more than 170 mutations have been identified in the genes (such as *KCNQ1*, *KCNH2*, *SCN5A*) for 17 different forms of LQTS (LQTS 1–17). LQTS type 1–3 are the three main genotypes of LQTS, accounting for about 80%. It is reported that the incidence of cardiac malignant events in LQT2 patients is higher than those with LQT1 and LQT3 [3]. However, the clinical presentation of LQT2 in children varies greatly. Some are asymptomatic, while others have recurrent cardiovascular events. Therefore, it is particularly important to have risk stratification in children with LQT2.

Nearly 500 *KCNH2* mutations have been linked to LQT2, which is characterized by a prolonged time duration from ventricular depolarization to repolarization (QT interval on an ECG) and increased risk for sudden cardiac death. The *KCNH2* encodes the Kv11.1 channel α subunit, which underlies the rapid delayed-rectifier K(+)-current (IKr) in the heart during phases 2 and 3 of the cardiac action potential, thus playing an important role in cardiac repolarization. Kv11.1 channel α-subunits contain cytosolic amino (NH2), carboxyl (COOH) termini and six transmembrane segments (S1-S6). S1-S4

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contribute to the voltage sensor domain and S5-S6 along with the intervening pore loop contribute to the pore domain [4]. Electrical storm (ES) is a type of cardiac electrical instability characterized by recurrent ventricular arrhythmias (VAs) within a short period, which can lead to high mortality.

In this study, we report two cases of *LQT2* children who were initially misdiagnosed with epilepsy and experienced TdP ES. Whole exome sequencing (WES) was utilized to identify possible disease-causing genes or variants. Paired end reading was aligned with the GRCh37/hg19 human reference sequence. Through comprehensive ClinVar software and GATK analyses, BAM and VCF files were produced. *KCHN2* gene heterozygous mutation p.Ala614Val in a 6-year-old boy and p.Thr613Met in a 13-year-old girl with LQT2 were identified. Our results indicate that patients with epilepsy, especially those refractory epilepsy with atypical features, need comprehensive evaluation of cardiovascular function. Long QT2 syndrome presents significant challenges in terms of treatment, and determining the most appropriate therapeutic approach has become a complex issue that requires careful consideration. Our research provides reliable evidence that supports the effectiveness of the treatment, demonstrating its potential to significantly improve patient outcomes.

Materials and methods

Clinical manifestation and examination

Case one, a 6-year-old boy, had first syncope during physical training at age 5. The patient suffered with syncope characterized by eyes turn, trismus, oral cyanosis, accompanied with stiffness for a few seconds to 1 min, occurred frequently. The family history was unremarkable. He went to a local hospital and was diagnosed with epilepsy due to the electroencephalogram (EEG) change. Antiepileptic therapy was given for 4 months, but it was ineffective. He had syncope attack once a few months at the beginning and once a few days in recent two months. The episodes were the same as before. He went to a provincial hospital for further treatment. EEG, brain magnetic resonance imaging (MRI), echocardiography, ECG, and electrolyte analysis were performed and only ECG was abnormal. ECG showed that he had prolonged QT interval with Bazett's correction (QTc=540 ms), ventricular tachycardia and ST-T changes. 24-hour ECG revealed that he had sinus bradycardia, prolonged QT (QTc=680ms), premature ventricular contractions (visible RonT), and TdP. Magnesium sulfate, propranolol (2 mg/Kg/d), and mexiletine (10 mg/Kg/d) were applied to control arrhythmia, but attacks still repeated and became frequent. There were syncopes every 3–4 days at night, while no seizure during the day. He was transferred to the cardiac department of our hospital and was performed monitoring. ECG exhibited that he had prolonged QT (QTc=590 ms), inverted T waves in leads II, III, aVF, and V4 to V6 (Fig. 1A). On the day of being transferred to hospital, the child had five syncope attacks within 24 h. The onset time was at night and in the early morning. ECG monitoring showed TdP during the attack and the longest TdP lasted for 72 s at about 4:00 a.m (Fig. 1B). Temporary pacemaker was placed immediately because of the critical condition. Pacing rate was set to 100 bpm, and no attack afterwards. Five days later, Implantable Cardioverter Defibrillator (ICD) (Medtronic, model: DVBC3D4) was implanted, together treated with Nadolol. The patient has remained event-free for two years.

Case two, a 13-year-old girl, experienced serial syncope attacks at age11 and was diagnosed as epilepsy. Despite antiepileptic therapy, she still experienced recurrent episodes of syncope. The family history was unremarkable. At the age of 13 years old, she underwent a series of relevant examination in the neurology department of four hospitals for further evaluation. Craniocerebral CT and EEG were normal. ECG showed prolonged QT interval (QTc=500 ms), inverted T waves in leads II, III, aVF and V4-V6 (Fig. 2A). She had 24-hour video electroencephalogram (VEEG) examination and her mother complained that there were 4 times similar to previous attacks at night and in the morning awakening stage during the test. By playing back the video, attacks were characterized by limb stiffness, loss of consciousness, lip-blue mouth, accompanied by urinary incontinence for 1–2 min to relieve and two times with vomiting. No abnormal discharge was found in the synchronous monitoring VEEG, but ventricular fibrillation was observed in the synchronous monitoring ECG (Fig. 2B). It was considered that the onset of malignant arrhythmia. Continuous monitoring of electrocardiogram showed prolonged QT interval, with the longest QTc of 636 ms. Considering that the child had long QT syndrome and recurrent ventricular tachycardia or ventricular fibrillation, temporary pacemaker was placed to prevent malignant arrhythmia. Four days later, ICD (Medtronic, model: DVMD3D1) was implanted. TdP occurred repeatedly during the multilayer suture (Fig. 2C). Meanwhile, in the process of resuscitation of anesthesia, shocks occurred three times. After interrogating the pacemaker, TdP was confirmed and was terminated by automatically defibrillation converting of ICD (Fig. 2D). Nadolol was given, together with potassium magnesium aspartate tablet. The girl has remained event-free for one year follow-up.

Whole exome sequencing and the filtering process

DNA libraries of constructs and WES assay were carried out according to the manufacturer's instructions. Briefly, a whole-blood genomic DNA extraction kit (Tiangen,

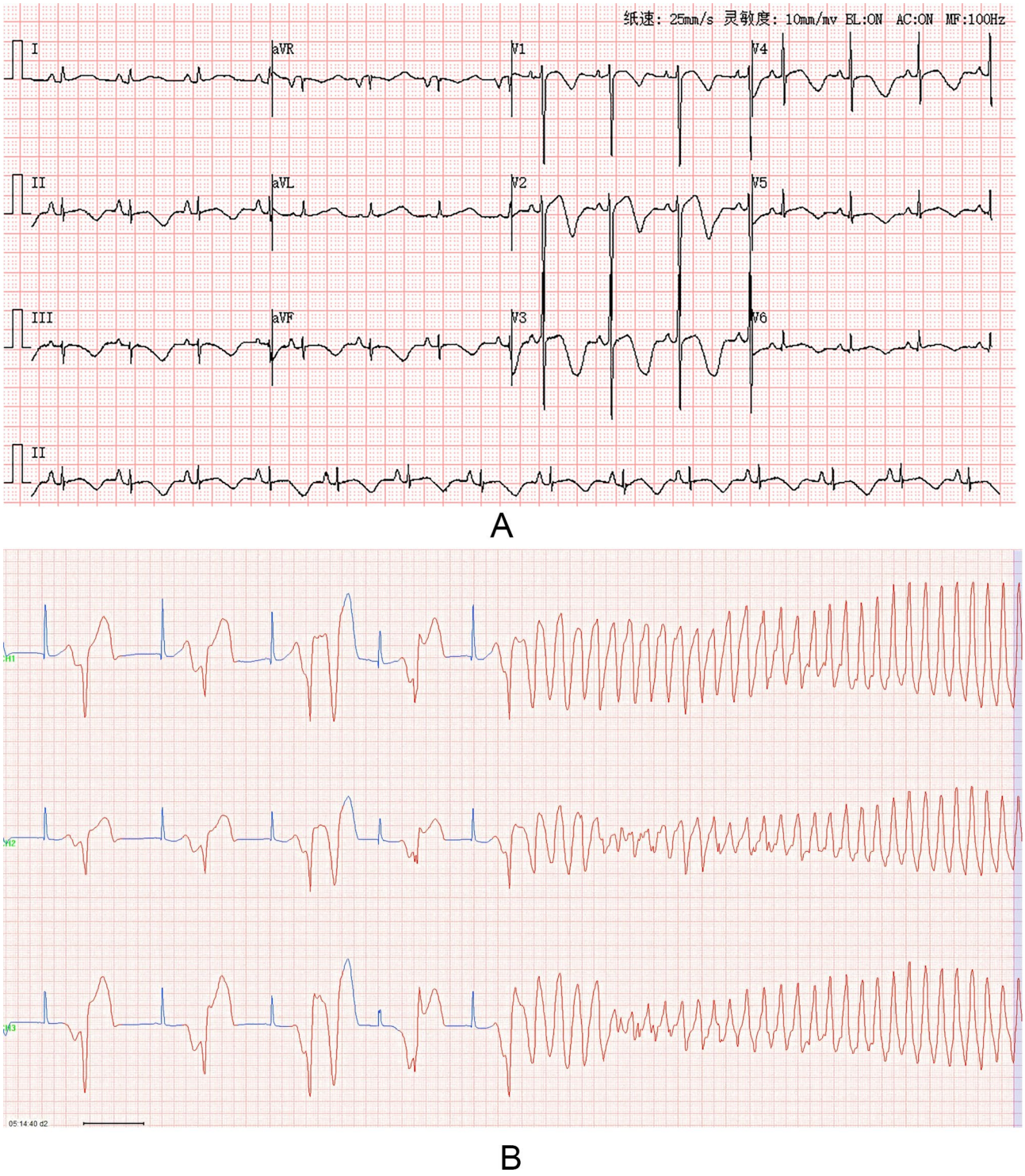

Fig. 1 Clinical data of Case one : (**A**) ECG showed sinus bradycardia, prolonged Q-T interval (QTc = 589ms), inverted T waves in leadsII, III, aVF, and V4-V6. (**B**) Dynamic ECG showed Torsades de Pointes when one of the episodes occurred

China) was utilized to isolate genomic DNA, 1 μg DNA was used for WES assay. Specific experimental procedures and experimental instruments are detailed in previous publications [5]. The data were filtered and analyzed in our previous study [5]. Briefly, BWA-0.710 software was utilized to compare with human genome database (GRCh 37/hg 19). Then promising data were filtered and further compared with the 1,000 Genomes Project (http://www.1000genomes.org), Exome Variant Server, Exome Aggregation Consortium databases (http://exac.

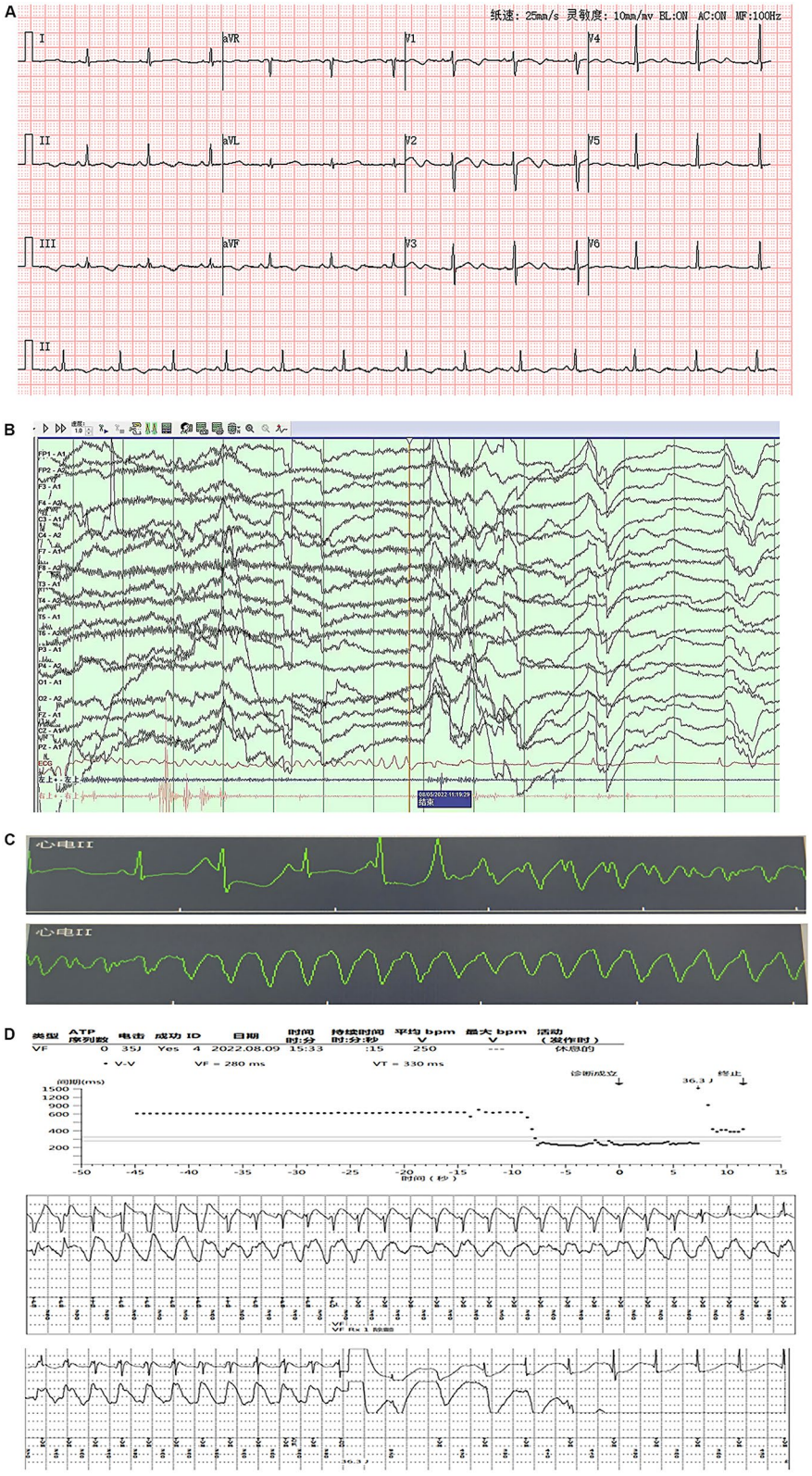

Fig. 2 Clinical data of Case two: (**A**) ECG: It showed prolonged QT interval (QTc = 500ms), inverted T waves in leads II, III, aVF, and V4-V6. (**B**) VEEG: When the girl had a attack, no abnormal discharge was found in the synchronous monitoring VEEG, but ventricular fibrillation was observed in the synchronous monitoring ECG. (**C**) ECG monitor revealed RonT and TdP when multilayer suture during ICD implantation. (**D**) The display of pacemaker program controller: After interrogating the pacemaker, TdP was confirmed and was terminated by automatically defibrillation converting of ICD in the process of resuscitation of anesthesia

broadinstitute.org), gnomAD (https://gnomad.broadinstitute.org/), Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/ac/index.php), Clinvar (http://www.ncbi.nlm.nih.gov/clinvar), and Online Mendelian Inheritance in Man (OMIM) (https://omim.org/).

Sanger sequencing and data analysis

KCNH2 mutations were confirmed via Sanger sequencing. Primers were designed using Primer 5 software to cover the known mutation sequence. The sequence of the forward primer was 5′-TGACCTCTGATGCTCGCTCTGA-3′, and that of the reverse primer was 5′-TGACTGTGACCGCCTGAGACT′. PCR products were resolved and purified using the QIAquick kit (Qiagen, Germantown, MD USA). Sanger sequencing was carried out at Suzhou Hong Xun Biotechnology Co., Ltd. In addition, protein stability was confirmed by a number of web-based prediction tools such as SIFT and MutPred.

Results

Next generation gene sequencing was performed after medical ethics review and parental informed consent. As Fig. 3A showed, 15,231variants were detected and further annotated and filtered by Ingenuity Variant Analysis in Case one. According to Exome Aggregation Consortium, 1000 Genomes Project, Exome Sequencing Project, or genomAD, 322 common variants were filtered and eliminated from their frequencies (minor allele frequency (MAF) < 0.005). Two variants in four genes were determined and identified through a thorough analysis. Finally, *KCNH2* (c.1841 C > T) mutation was detected and selected after rigorous analysis, which was linked to the long QT phenotypes (Fig. 3A). The same filtration process was undertaken with the other case, and *KCNH2* (c.1838 C > T) mutation was also linked to the long QT phenotype (Fig. 3B).

A heterozygous variant c.1841 C > T (p.Ala614Val) in the *KCNH2* gene was confirmed by Sanger sequencing in Case one (Fig. 4A). P.Ala614Val is a missense mutation. Secondary structure analysis showed that after the mutation occurred, the secondary structure of some amino acids near the mutation changed, from "α helix" to "irregular curling", "peptide chain extension", and from "peptide chain extension" to "irregular curling" (Fig. 4C). Three-dimensional structure analysis of protein showed: After the mutation of *KCNH2* gene p.Ala614Val, the h-bonds between 614 amino acids and 611 amino acids could not be formed, and the h-bonds between 614 amino acids and 618 amino acids were reduced, suggesting that this mutation would lead to a weakening of the interaction between amino acid residues and may affect the three-dimensional structure of the protein (Fig. 4E). In addition, protein stability was confirmed by a number of web-based prediction tools such as MutPred and SIFT, which also showed that the mutation affected its protein stability (Table 1). The above data indicate that *KCNH2* heterozygous variants p.Ala614Val may disrupt its protein structure and ability.

The genetic cardiac arrhythmia panel revealed a missense mutation of *KCNH2* gene in Case two: c.1838 C > T (p.Thr613Met) and confirmed with Sanger sequencing (Fig. 4B). Secondary structure analysis showed that the secondary structure of some amino acids near the mutation changed from "irregular curling" and "peptide chain extension" to "α helix" and "irregular curling", respectively, after the occurrence of missense mutation (Fig. 4D). Protein three-dimensional structure analysis showed that after the mutation of *KCNH2* gene

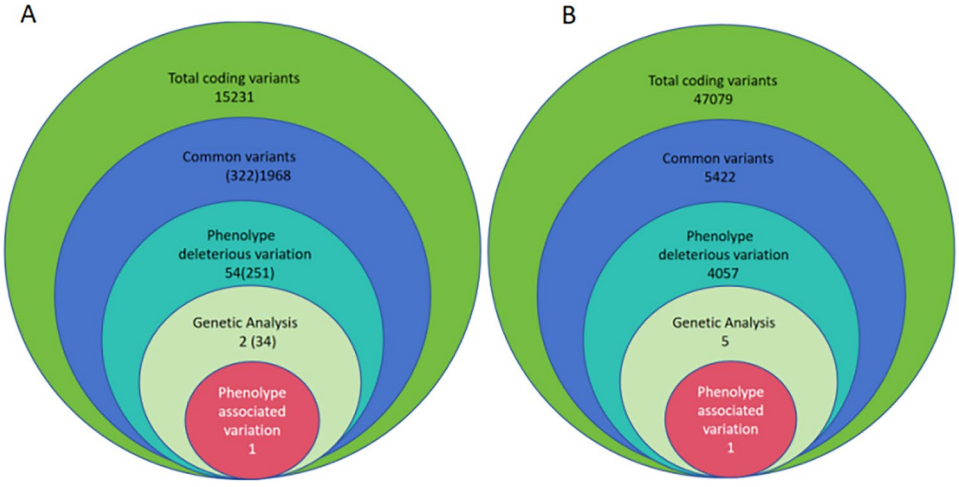

Fig. 3 The filtering process for WES data. (**A**) Case one: It contains 15,231 total coding variants. Then, 322 common variants, 54 deleterious variations, 2 genetic analyses, and final 1 associated with this phenotype variation were filtered: *KCNH2*(c.1841 C > T). (**B**) Case two: It contains 47,079 total coding variants. Then, 5, 422 common variants, 4057 deleterious variations, 5 genetic analyses, final 1 associated with this phenotype variation were filtered: *KCNH2*(c.1838 C > T)

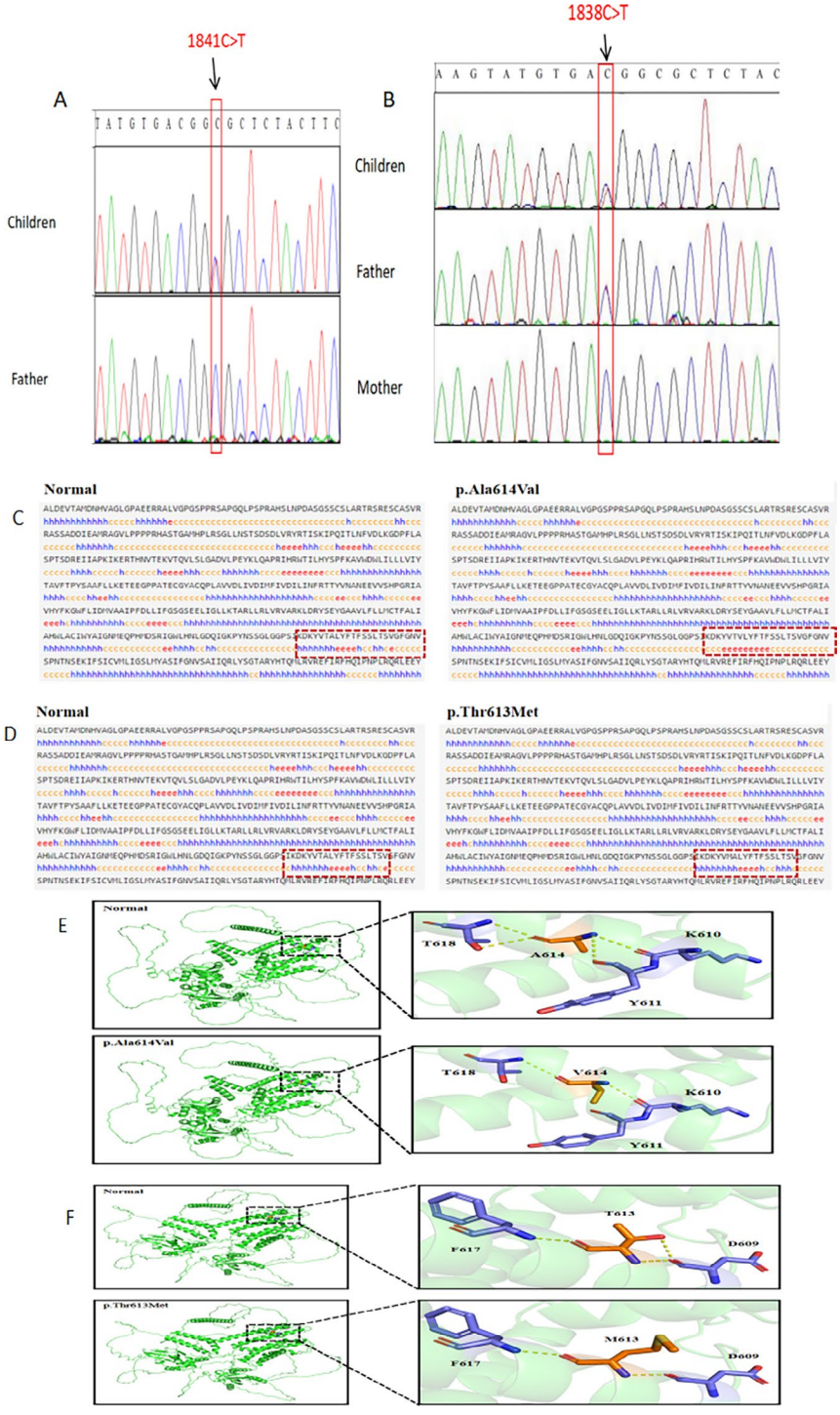

Fig. 4 Sanger sequencing and data analysis: (**A**) Heterozygous variant c.1841 C > T (p.Ala614Val) in the *KCNH2* gene was detected in the whole blood genomic DNA of Case one. (**B**) The genetic cardiac arrhythmia panel revealed a missense mutation of *KCNH2* gene in Case two: c.1838 C > T (p.Thr613Met). (**C**) Secondary structure analysis showed that some amino acids near the mutation changed, from "α helix" to "irregular curling", "peptide chain extension", and from "peptide chain extension" to "irregular curling" after the p.Ala614Val missense mutation occurred. (**D**) Secondary structure analysis showed that some amino acids near the mutation changed from "irregular curling" and "peptide chain extension" to "α helix" and "irregular curling", respectively, after the occurrence of missense mutation *KCNH2*: p.Thr613Met. (**E**) Three-dimensional structure analysis of protein showed that p.Ala614Val missense mutation would lead to a weakening of the interaction between amino acid residues and may affect the three-dimensional structure of the protein. (**F**) Protein three-dimensional structure analysis showed that after the mutation of *KCNH2* gene p.Thr613Met may affect the three-dimensional structure of the protein

Table 1 Prediction using web-based tools (p.Ala614Val)

Web-server	Score	Effect
SIFT	0.0001	Damaging
MutPred	0.931	Deleterious

Table 2 Prediction using web-based tools (p.Thr613Met)

Web-server	Score	Effect
SIFT	0.000	Damaging
MutPred	0.881	Deleterious

p.Thr613Met h-bonds between 613 amino acids and 609 amino acids were reduced, suggesting that this mutation would lead to a weakening of the interaction between amino acid residues, which may affect the three-dimensional structure of the protein (Fig. 4F). In addition, protein stability was confirmed by a number of web-based prediction tools, which also showed that the mutation affected protein stability (Table 2). The above data indicate that *KCNH2* heterozygous variants (p.Thr613Met) may disrupt its protein structure and ability.

Discussion

Life-threatening events occur more frequently in patients with LQT2, accounting for 35–45% of congenital LQTS incidents [6]. Our cases highlight three aspects: We should conduct a comprehensive assessment of the cardiovascular aspects in patients with epilepsy, especially in refractory epilepsy cases with atypical features; LQT2 patients with significantly prolonged QTc interval, T wave inversion, and *KCNH2* mutations in pore region had a higher risk of ES; Temporary ventricular pacing is one of the safest and most effective treatments for ES in emergency. ICD in combination with Nadolol implantation is optional and effective for LQT2 patients with ES.

LQT2 usually develops cardiac events after rest and being startle (noise, thunder, et al.) at night [7]. Some are often misdiagnosed as epilepsy [8], although recent reports suggest that related potassium channel mutations may be co-expressed as concomitant epilepsy and LQTS [9]. Two of our patients, initially misdiagnosed as epilepsy, were diagnosed as LQT2 based on the prolonged QT interval and *KCNH2* mutation. Arrhythmia is one of the key factors in the differential diagnosis between syncope and epilepsy.

ES is defined as three or more discrete episodes of VA within 24 h, or incessant VA for more than 12 h. Our two cases suffered from ES according to the clinical episodes combined with ECG manifestations. A meta-analysis of the available evidence reported a 2.5-fold increase in mortality in patients with ES compared with patients with unclustered sustained VA, and a 3.3-fold increase in mortality compared with patients with no sustained VA [10, 11].To reduce cardiac arrest or sudden cardiac death, risk stratification of patients with LQT2 is very important. The common characteristics of QTc duration, T-Wave morphology, mutation type and location in both patients may be helpful to identify patients at high risk for ES. Both cases had markedly prolonged QT interval, with the Max QTc duration greater than 630ms. A markedly prolongation of QTc interval has been reported to be associated with an increased risk of sudden death [12]. Changes in T-wave morphology may reflect penetrance of LQTS mutations [13]. Patients with LQT2 typically present low amplitude and often bifid T-waves. However, the T wave morphology of the two patients showed deeply inverted in chest V5-V6 leads and limb leads. Combined with our cases of ES, it is speculated that the continuous T-wave inversion is an independent risk factor for recurrent Tdp in patients with LQT2. In addition, intragenic risk stratification has been realized for LQTS based upon mutation type, location, and cellular function. The mutation locations of the two cases were at the pore region. Missense variation in this region may lead to *KCNH2* protein transport and channels form defects, or lead to impaired protein function [14]. These *KCNH2* variants had already been assessed in some electrophysiological studies [15–17]. Evidence shows that LQT2 patients with pore region *KCNH2* mutations have a longer QTc, a more severe clinical manifestation of the disorder, and more arrhythmia-related cardiac events occurring at a younger age than those LQT2 patients with non-pore mutations in *KCNH2* [18, 19]. In LQT2 patient, TdP could occur due to not only main genetic background but some modifiers, e.g. sex hormones, drugs, hypokalemia, et al. [20].

ES is a clinical emergency and has a very high lethality. Electrical defibrillation and cardioversion as soon as possible during the ES attack are the primary measures to restore the stability of hemodynamics [10]. Left cardiac sympathetic denervation (LCSD) is recognized as an effective treatment in the prevention of genetically mediated life-threatening ventricular arrhythmias [21]. Due to insufficient experience with LCSD, we did not use it. LCSD is very effective but does not always guarantee complete protection [22–24] and sometimes should be complemented by an ICD.

It is reported that ICD implantation is an effective and safe method both of primary and secondary prevention of sudden cardiac death in children with LQTS [25, 26]. However, excessive and frequent use of electric defibrillation and cardioversion can easily lead to myocardial injury, make patients (especially children) in a state of extreme fear to activate the sympathetic nervous system [27]. Therefore, repeated ventricular fibrillation and electric defibrillation may cause patients to develop secondary ES, forming a vicious circle [28, 29]. To our experience, temporary transvenous ventricular pacing is one of the most safe and effective treatments for ES. The pacing rate is usually set to 100-120 bpm to avoid repeated

attacks of malignant VA by stabling rhythm, shortening QT interval and reducing QT dispersion [30, 31]. The second case had ES at the multilayer suture stage and the recovery stage of anesthesia during the procedure of ICD implantation. It reminds us to strengthen local anesthesia to reduce pain stimulation. Few reports describe LQTS genotype-specific considerations for anesthesia. KumakuraM, et al. noted that patients with LQT2 be more susceptible to volatile anesthetics than those with other major genotypes [32]. It may suggest us, besides strengthening anesthesia management, set higher heart rate to pacemaker in advance for suppressing malignant VA to avoid unnecessary ICD discharge.

Even after ICD implantation, optimized antiarrhythmic drug therapy is required. Both our two patients had ICD implantation and were treated with Nadolol. They have been event-free for two years and one year separately. Beta-blockers (BB), are first-line therapy in patients with congenital LQTS [33]. Because Nadolol is a hydrophilic long-acting nonselective drug with the longest elimination half-life of BBs and also has sodium channel blocking effects to shorten QTc intervals, it is superior to other BBs in the treating of LQT2 patients to reduce cardiac events [34, 35]. We failed to control malignant arrhythmias with mexiletine in one child, but it is reported that mexiletine have antiarrhythmic efficacy in the majority of patients with LQT2 [36].

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-024-02025-z.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Author contributions

Conceptualization, Li Zhang, Meng Xu; methodology, Li Zhang; validation, Yan Han, Xunwen Jiang; literature review, Tingting Xiao; writing-original draft preparation, Li Zhang, Meng Xu, Zhen Yan; writing-review and editing, Yun Li, Cuilan Hou; supervision, Cuilan Hou, Yun Li; All authors have read and agreed to the published version of the manuscript.

Funding

This work is supported by Shanghai Jiao Tong University medical technology crossing project (YG2021ZD26), National Natural Science Foundation of China (NSFC) (no. 81900437), and Shanghai Children's hospital (2019YQ06).

Data availability

Data is provided within the manuscript or supplementary information files. (Table S1-S5) were deposited in Figshare.com and can be accessed (https://figshare.com/s/456f3d30e4360588ccf7).

Declarations

Ethical approval

Human participants in the study were approved by the Ethics Review Committee of Shanghai Children's Hospital, Shanghai Jiao Tong University School of Medicine (no.2019R002-E03).

Informed consent

Informed consent was obtained from the subjects involved in the study.

Competing interests

The authors declare no competing interests.

Received: 26 November 2023 / Accepted: 7 October 2024
Published online: 11 October 2024

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