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Novel heterozygous mutation of *CACNA2D1* gene in a Chinese family with arrhythmia

Qian Wang[1,2,3,4†], Yong Deng[3†], Liang-Liang Fan[1,4], Yi Dong[4], Ai-Qian Zhang[1*] and Yu-Xing Liu[2,3,4*]

Abstract

Background Primary electrical disorders (PEDs) are a group of cardiac rhythm abnormalities that occur in the absence of detectable structural heart disease and are a significant cause of sudden cardiac death (SCD). The initiation of cardiac muscle contraction and relaxation is orchestrated by the action potential (AP), generated through ionic changes across the membrane. Mutations in the AP-related gene *CACNA2D1* have been identified as a causative factor for PED.

Methods We recruited a Chinese family with a history of arrhythmia. The proband has experienced palpitations and chest tightness for over 40 years, with symptoms worsening over the past year. Whole exome sequencing (WES) was used to determine the genetic etiologies in this family.

Results A novel heterozygous missense mutation (NM_000722.3: c.1685G > C;p.G562A) of *CACNA2D1* gene was detected. Genotyping of the proband's parents indicated that the arrhythmia phenotype in the proband was caused by a de novo mutation.

Conclusions WES was utilized to explore the genetic etiology in a family with arrhythmia, leading to the identification of a novel mutation in the *CACNA2D1* gene. This study not only expands the mutation spectrum of the *CACNA2D1* gene but also contributes to genetic counseling and clinical diagnosis for this family.

Keywords Arrhythmia, PED, *CACNA2D1*, Mutation

Introduction

Primary electrical disorders (PEDs) constitute a category of cardiac rhythm abnormalities characterized by arrhythmias in the absence of detectable structural heart disease [1]. This encompasses various inherited syndromes, including but not limited to early repolarization syndrome (ERS), long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and arrhythmogenic right ventricular cardiomyopathy (ARVC) [1, 2]. Sudden cardiac death (SCD), characterized by the abrupt cessation of cardiac function, is often linked to PED, especially in individuals under the age of 35 [3, 4]. About 25% of unexplained sudden deaths may be attributed to inherited cardiac diseases such as BrS,

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idiopathic ventricular fibrillation (IVF), and LQTS, highlighting the critical role of PED in the occurrence of SCD [5–8].

Mutations in ion channel genes play a crucial role in the development of PED [9]. The action potential (AP) represents an electrical signal that triggers cardiomyocyte contraction through a series of ion movements across the cell membrane. The initiation of action potentials, which regulates cardiac muscle contraction and relaxation, depends on the coordinated activation and inactivation of voltage-gated ion channels, such as those for sodium, potassium, and calcium [7, 10]. Molecular abnormalities, especially within these channels, can lead to PED [9]. Since the identification of the first ion channel-causative gene, *SCN5A*, by George et al. (1995), numerous arrhythmia-causative/candidate genes, such as *SCN3B*, *KCNE1*, *CACNA2D1* and *RYR2*, have been reported [11–13]. While some genes have been identified with pathogenic mutations causing PEDs, their detection has been relatively limited, and their specific pathological mechanisms remain unclear.

Here, we described a Chinese family with arrhythmia. The proband has experienced palpitations and chest tightness for over 40 years, with exacerbation over the past year. Employing whole exome sequencing (WES) and bioinformatics strategies, we identified a novel mutation in *CACNA2D1* gene.

Methods

Subjects

A Chinese family with arrhythmia was encountered. Blood was collected from all members in this family. A total of 200 unrelated healthy individuals from the general population of Hunan, China, were included as control subjects to exclude polymorphisms, as described in our previous studies [14]. The Review Board of the Second Xiangya Hospital of Central South University approved this research. Written informed consent was obtained from all subjects participate in this study.

WES

The central part of the WES was provided by the BerryGenomics (Bei Jing, China). The exomes were captured using Agilent SureSelect Human All Exon V6 kits, and high-throughput sequencing was performed using Illumina HiSeq X-10. The data filtering was performed as described in our previously studies [14, 15]. The general steps are as follows: (**A**) exclusion of variants in intergenic, intronic, UTR regions, and synonymous mutations; (**B**) filtering out variants present in Genome Aggregation Database (gnomAD, http://www.gnomad-sg.org/), the 1000 Genomes project (1000G,www.1000genomes.org), and in-house controls; (**C**) using SIFT (http://sift.bii.astar.edu.sg/), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), MutationTaster (https://www.mutationtaster.org/), and CADD (https://cadd.gs.washington.edu/score) to predict variant impacts; (**D**) screening for potential causative variants using an arrhythmia gene panel (Table S1); and (**E**) validating family segregation of variants through Sanger sequencing.

Sanger sequencing

All filtered mutations in the patient were validated by Sanger sequencing. Primer pairs were designed using DNASTAR and the primer sequences have been shown in Table S2. Sequences of the polymerase chain reaction (PCR) products were determined using an ABI 3100 Genetic Analyzer (ABI, Foster City, CA, USA).

Bioinformatics analysis

The necessary bioinformatics analyses including conservation analysis (ConSurf Server software, https://consurf.tau.ac.il/), tolerance analysis (MetaDome software, https://stuart.radboudumc.nl/metadome/dashboard) and mutant modeling (SWISS-MODEL software, https://swissmodel.expasy.org/interactive) were performed as described in our previously studies [14, 15].

Results

Clinical features

The proband (II-1) was a 49-year-old man from the central south region of China (Hunan Province) (Fig. 1A). The proband began experiencing recurrent palpitations without apparent triggers since the age of 9. The episodes lasted for a few seconds and spontaneously resolved without chest tightness or dyspnea. The frequency of episodes did not exceed 6 times per year, hence not deemed significant. Over the past year, the proband's palpitations have become more frequent, with significantly prolonged duration ranging from seconds to 2 h. Episodes lasting over half an hour were associated with chest tightness, chest pain, dyspnea, diaphoresis, and dizziness. The proband experienced syncope after palpitations lasting over half an hour, similar to previous episodes, sought medical attention at a local hospital, and was discharged after improvement, with specific treatment details unknown. Seeking further treatment, the proband presented to our hospital (Fig. 1B). The electrocardiogram (ECG) examination of the proband indicates cardiac arrhythmia and paroxysmal supraventricular tachycardia (PVST) (Fig. 1C). The cardiac echocardiography results suggest the proband has a slightly enlarged left atrium, while the right atrium is within normal high values (LV: 48 mm; LA: 37 mm; RV: 31 mm; RA: 35 mm; EF: 60%). Results of serum and urine laboratory investigations in various measurements in the proband have been shown in Table 1. Family history investigation revealed the proband's eldest daughter (III-1) has a history of palpitations.

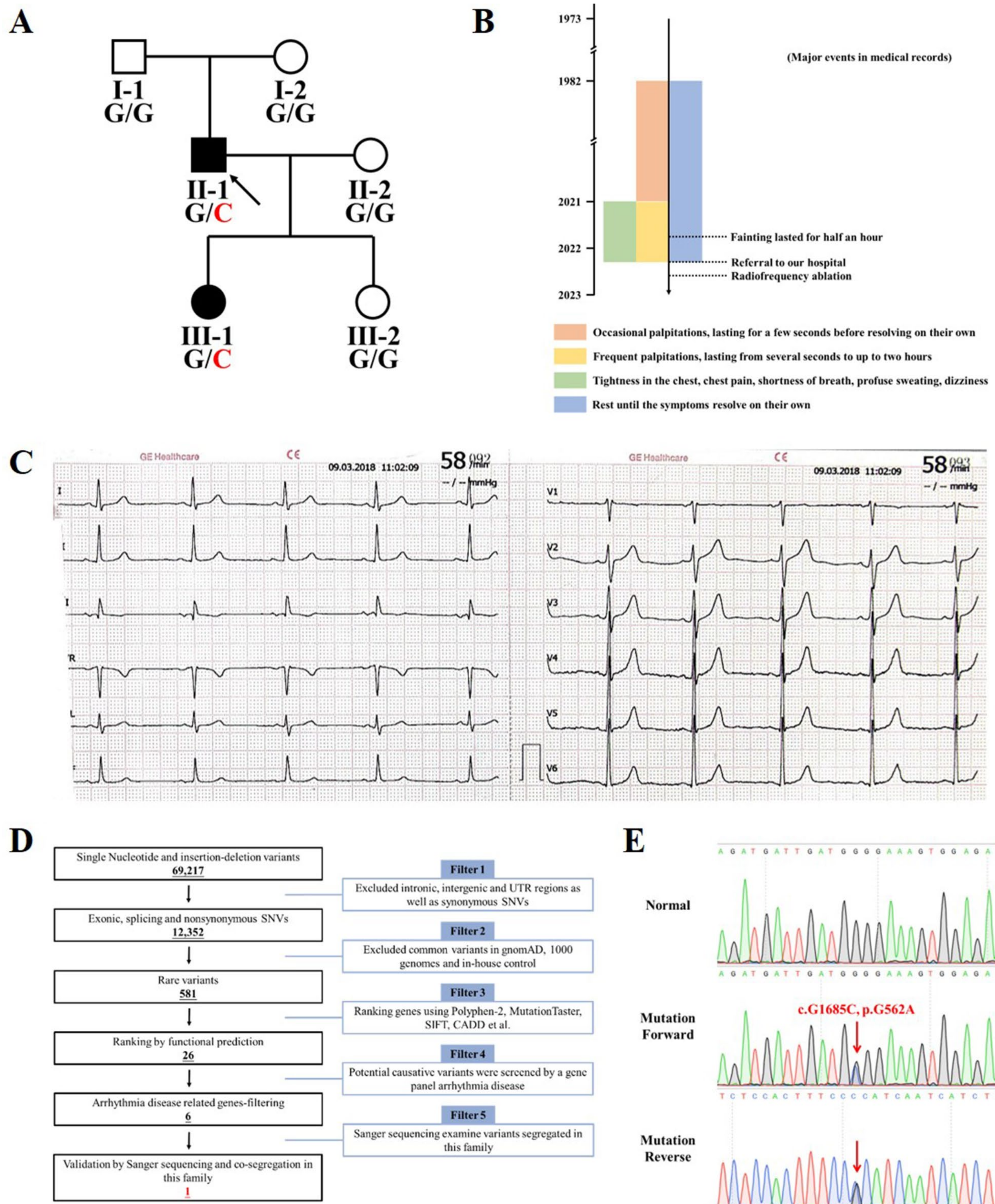

Fig. 1 (**A**) Pedigrees of the family with segregation analysis. The black symbols represent affected members and arrows indicate the proband. Genotypes are identified by letters and a slash, with red representing mutations. (**B**) Major events in the medical record of the proband. (**C**) Baseline 12-lead electrocardiographs of the proband. The results show that the proband had arrhythmia. (**D**) Schematic of the filter strategies used in our study. (**E**) Sequencing results of the mutations in *CACNA2D1* (c.1685G > C, p.G562A). The sequence chromatograms indicate heterozygous mutations in the proband

Table 1 Results of serum and urine laboratory investigations in various measurements in the proband

Laboratory values	Observed values	Normal values (range)
Hematocrit (%)	46	42–49
Serum sodium (mEq/L)	143	140–145
Serum potassium (mEq/L)	4.1	3.5–4.6
Serum calcium (mg/dL)	10.1	8.2–10.5
Serum phosphorous (mg/dL)	**1.1**	2.5–4.2
Serum parathormone (pg/mL)	19	10–65
Arterial pH	7.41	7.35–7.45
D-dimer (ng/mL)	207	0-500
PT (sec)	12	10–14
FDP (μg/mL)	1.66	0–5.00
N-terminal pro BNP (pg/mL)	10.7	0-250.0
Hypersensitive troponin T (pg/mL)	1.9	<40
Creatine kinase (U/L)	95.7	50.0-310.0
Creatine kinase isoenzyme (U/L)	16.1	0–24.0
Cysteine protease inhibitor C (mg/L)	0.77	0.54–1.25
Serum creatinine (umol/L)	90	53–106
Serum uric acid (μmol/L)	419.1	208.0-428.0
Serum renin (mIU/L)	42	5–47
Serum aldosterone (pmol/L)	66	20–130
ALB (g/L)	**30.9**	35–50
ALT (U/L)	12.6	9.0–50.0
AST (U/L)	15.2	15.0–40.0
DBIL (μmol/L)	2.4	0–6.0
TBIL (μmol/L)	9.8	3.4–17.1
TBA (μmol/L)	2.0	0–10.0
GLO (g/L)	28.1	20.0–40.0
TG (mmol/L)	**2.69**	1.70 ~ 2.25
Total cholesterol (mmol/L)	**5.32**	<5.18
HDL-C (mmol/L)	**0.91**	>1.04
LDL-C (mmol/L)	**3.39**	≤ 3.37
Apolipoprotein A1 (g/L)	1.01	1.00-1.60
Apolipoprotein B (g/L)	0.9	0.6-1.0
CRP (mg/L)	4.55	0.06 ~ 8.20
hs-CRP (mg/L)	**4.03**	≤ 3.00
ESR (mm/h)	7	≤ 15
Urine sodium (mmol/day)	210	130 ~ 260
Urine potassium (mmol/day)	101	25-125mmol/24 h
Urine chloride (mmol/day)	189	170–255
Urine calcium (mmol/day)	5.2	2.7 ~ 7.5
Urine phosphorous (g/day)	1.0	0.5–1.3
Urine uric acid (mmol/day)	5.1	2.4–5.9
Urine creatinine (mmol/day)	10	7–18
Urine protein (g/day)	0.11	<0.15
Urine Oxalate (μmol/day)	230	91–456μmol
Urine β2-microglobulin (mg/L)	0.35	0-0.65

ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CRP, C-reactive protein; DBIL, direct bilirubin; ESR, erythrocyte sedimentation rate; FDP, fibrin degradation products; GLO, globulin; HDL-C, high density lipoprotein cholesterol; hs-CRP, hypersensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PT, prothrombin time; TBA, total bilirubin; TBIL, total bilirubin; TG, triglyceride; the bold indicates outliers

Other family members denied having related symptoms (Fig. 1A).

Genetic analysis

WES yielded 10.1 Gb of data with 99.2% coverage of the target region and 98.5% of the target regions were covered over 10×. After alignment and single-nucleotide variant calling, 69,217 variants were identified in the proband. Data filtering was performed as shown in Fig. 1D. After filtering the data, a set of six variants in six genes was identified in the proband (Table 2). Sanger sequencing validated that only the *CACNA2D1* mutation (NM_000722.3: c.1685G>C, p.G562A) was segregation within the family (Fig. 1A and E). The newly identified mutation was absent in our 200 healthy controls. Alignment of CACNA2D1 amino acid sequences revealed that G562 is conserved in different species (Fig. 2A). Similarly, ConSurf Server software predicted that G562 amino acid is located in the conserved region of CACNA2D1 protein (Fig. 2B). SWISS-MODEL software was used to explore the spatial configuration of the mutation. Mutant CACNA2D1 modeling showed that a glycine was substitution by alanine, and the hydrophobic index was altered (Fig. 2C). Also, ProtScale software predicted that the G562A mutation raised local hydrophobicity compared with WT protein (Fig. 2D). Furthermore, MetaDome software predicted that G562 amino acid is located in the intolerant region of CACNA2D1 protein (Fig. 2E). Thus, we thought that the *CACNA2D1* mutations were disease-causing.

Discussion

In this study, we recruited a Chinese family with arrhythmia. The proband has experienced palpitations and chest tightness for over 40 years, with a worsening trend observed over the last year. Following an ECG examination, cardiac arrhythmia and PVST were diagnosed. Family history investigation revealed that the proband's eldest daughter (III-1) had a history of palpitations, while other family members reported no symptoms of dizziness, palpitations, or other arrhythmia-related issues and were considered healthy. Due to transportation and financial constraints, all family members except the proband declined long-term arrhythmia monitoring. As a result, the current findings cannot determine whether there are other undetected arrhythmia manifestations within the family. Through WES, a mutation (c.1685G>C, p.G562A) in the *CACNA2D1* gene was identified. Results of genotype-phenotype co-segregation analysis showed that both the proband (II-1) and his daughter (III:1) had arrhythmia-related issues and carried this mutation, while unaffected family members did not, indicating segregation within the family. Of note, medical history and genetic screening in the proband's parents revealed

Table 2 The whole exome sequencing results of the proband

Gene	Mutation	Mutation Taster	PolyPhen-2	SIFT	1000G	ExAC	gnomAD	OMIM clinical phenotype	ACMG classification
NEB	c.1435T > C, p.Y479H	D	D	D	-	-	-	AR, Nemaline myopathy 2	PM2, PP3, BS4, BP5
LMCD1	c.22G > A, p.V8M	D	B	D	-	0.00002	0.00006	-	PS2, BP5
SYNE1	c.17867G > A, p.R5956H	D	D	D	0.00100	0.00035	0.00032	AR, Arthrogryposis multiplex congenita, myogenic type; AD, Emery-Dreifuss muscular dystrophy 4; AR, Spinocerebellar ataxia	PP3, BS4, BP5
CACNA2D1	c.1685G > C, p.G562A	D	D	T	-	0.00003	0.00003	-	PS2, PP1, PP3
DNM1L	c.550 C > A, p.L184I	D	B	D	-	0.00001	0.00001	AD/AR, Encephalopathy, lethal, due to defective mitochondrial peroxisomal fission 1; AD, Optic atrophy 5	BS4, BP5
UNC45B	c.325 C > T, p.R109W	D	D	D	-	0.00003	0.00016	AD, Cataract 43; AR, Myofibrillar myopathy 11	PS2, PP3, BP5

Red words, mutations identified in this study; D, disease causing; T, tolerated; P, polymorphism; B, benign; AR, autosomal recessive; AD, autosomal dominant

that none of them was *CACNA2D1* mutation carriers (c.1685G>C, p.G562A), suggesting that the de novo mutation, and not an inherited mutation, contributed to the manifestation of arrhythmia in the proband (Fig. 1A). The proband underwent radiofrequency ablation therapy [16, 17], resulting in postoperative improvement and subsequent discharge. The proband was advised to rest, avoid excessive exertion, severe colds, or emotional stress, and to attend regular follow-up appointments. Given the proband's eldest daughter's (III-1) history of palpitations and her carriage of this mutation, we recommend prompt medical evaluation for relevant examinations to facilitate early intervention.

Typically, PED refers to malignant arrhythmias without clear structural cardiac abnormalities and could lead to SCD [7]. The major representatives include LQTS, SQTS, BrS, CPVT. Additional arrhythmias such as ERS and PVST have recently been identified as potential PED [18]. The proband in this study experienced recurrent palpitations and chest tightness for over 40 years without giving it due attention. It wasn't until the exacerbation of symptoms and the occurrence of syncope in the past year that he sought further medical evaluation, thereby posing a significant risk to his own life safety. Considering that patients with PED often remain unaware of their condition, and SCD might be the initial symptom [7], we believe it is necessary to screen adolescents with arrhythmias or related symptoms for mutations in PED-related genes. This approach will help provide intervention or preventive strategies for carriers before their first cardiac event.

CACNA2D1 is part of the CACNA gene family, which plays a key role in calcium signaling across various physiological processes, including neuronal excitability, muscle contraction, and hormone secretion. Upon membrane depolarization, these channels activate, allowing Ca^{2+} influx into the cell. This triggers downstream signaling crucial for neuronal communication and synaptic transmission. Investigating mutations in members of the CACNA gene family holds promise for advancing our understanding of genetic neurological disorders [19]. Recent studies have identified some members of the CACNA gene family such as *CACNA1C*, *CACNB2*, and *CACNA2D1* as novel arrhythmias susceptibility genes [5]. Similarly, we identified a novel heterozygous missense mutation (c.1685G>C, p.G562A) of *CACNA2D1* gene in a Chinese family with arrhythmia. Our study added to the literature and could help for personalized medicine care with precision genomics.

CACNA2D1 is post-translationally processed into two peptides, an alpha-2 subunit and a delta-1 subunit, that are entirely extracellular and held together by a disulfide bond [19]. They play a role in Ca^{2+} inflows in AP, as an auxiliary protein modulator of Ca^{2+} channels. Thus far, there are at least five known *CACNA2D1* missense mutations, including one (D550Y) in the Cache 2 domain and two (S709N and S755T) in the Cache 3 domain of alpha-2 subunit [20]. Mutation p.G562A in Patient 6 occurred in the Cache 2 domain, and p.D550Y was located in the same domain and detected in a BrS family [19]. Both may have the analogous pathogenic mechanism, altering the Ca^{2+} channel and affecting AP. Previous *CACNA2D1* mutations were identified in neurodevelopmental disorder and PED/SCD patients [19]. The reports on *CACNA2D1* gene mutation are scarce, only 12 mutations are identified in PED/SCD patients so far. We've compiled these reported phenotypes based on HGMD (http://www.hgmd.cf.ac.uk/ac/validate.php), aiding in genotype-phenotype correlation analysis (Fig. 3). Of note, the mutation (c.1685G>C, p.G562A) reported in this study has not been documented in previous literature, thus, considered novel. Our study expanded the

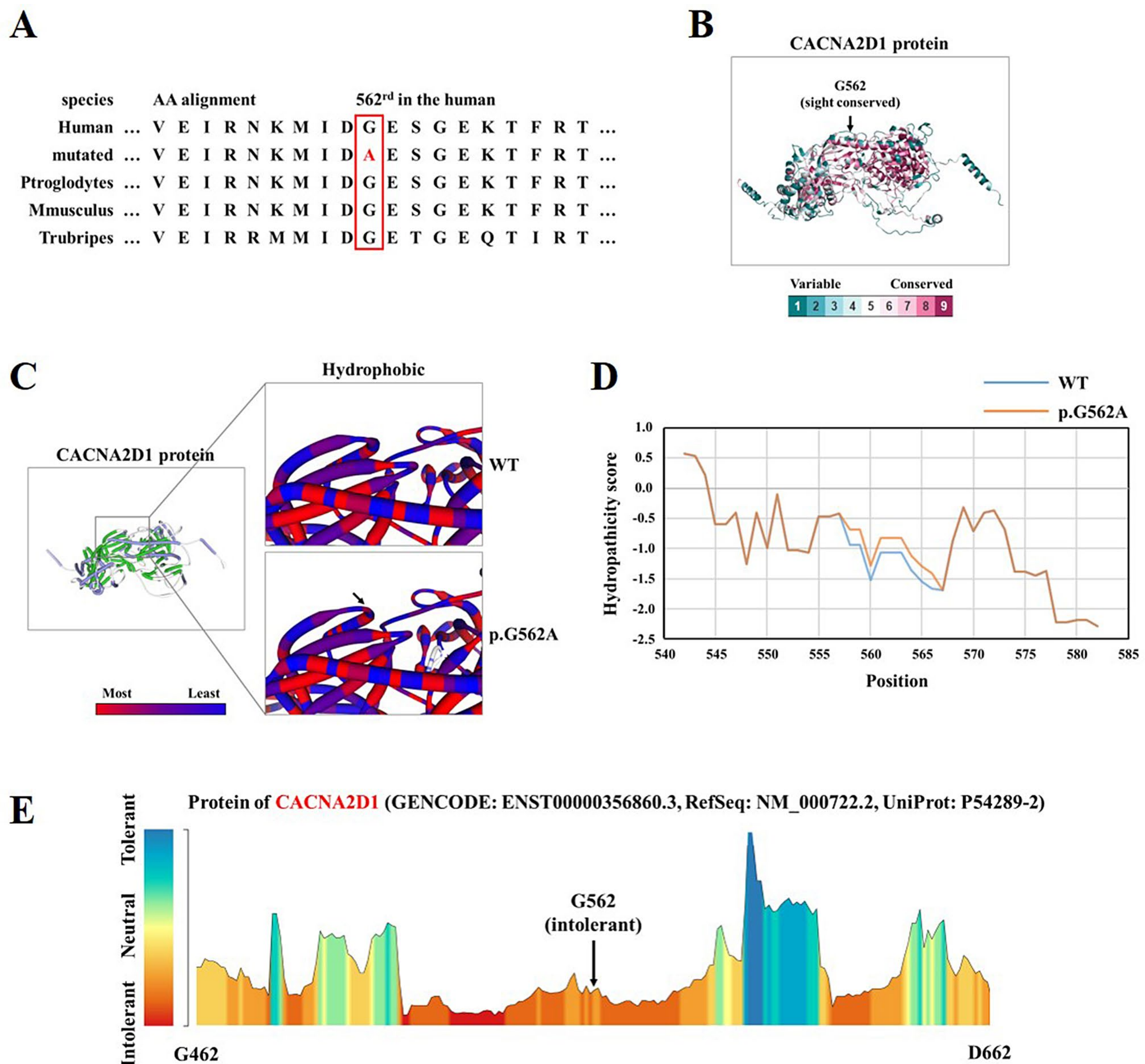

Fig. 2 (**A**) Alignment of multiple CACNA2D1 protein sequences across species are showed respectively. Letters in red show affected sites are evolutionarily conserved. (**B**) The conservation analysis of mutant amino acid sites of CACNA2D1 was predicted by ConSurf Server software. (**C**) Protein models of CACNA2D1 with or without mutants were predicted by SWISS-MODEL online software. Black arrows show the changes altered by mutation. (**D**) The Protscale online software predict the hydrophobicity of wild type and p.G562A mutant CACNA2D1 protein. The blue curve showed the hydrophobicity score of each amino acid of wild type CACNA2D1. The yellow curve showed the p. G562A mutant CACNA2D1. (**E**) The tolerance analysis of mutant amino acid sites of CACNA2D1 was predicted by MetaDome software

pathogenic mutant spectrum of *CACNA2D1* gene and further supported the association between *CACNA2D1* mutations and PED. Additionally, different from missense mutations, copy number variations (CNVs) and small deletions/insertions (del/ins) of *CACNA2D1* can lead to epilepsy and other neurodevelopmental diseases [21]. This phenomenon demonstrates the phenotypic heterogeneity of CACNA2D1 defects. This is probably because CNVs and del/ins cause more severe destruction to CACNA2D1.

Conclusions

In summary, this study detected a novel mutation (c.1685G>C, p.G562A) of *CACNA2D1* gene in a Chinese family with arrhythmia. Our identification contributed to the genetic counseling and clinical diagnosis of this family and expanded the mutation spectrum of PED-related genes.

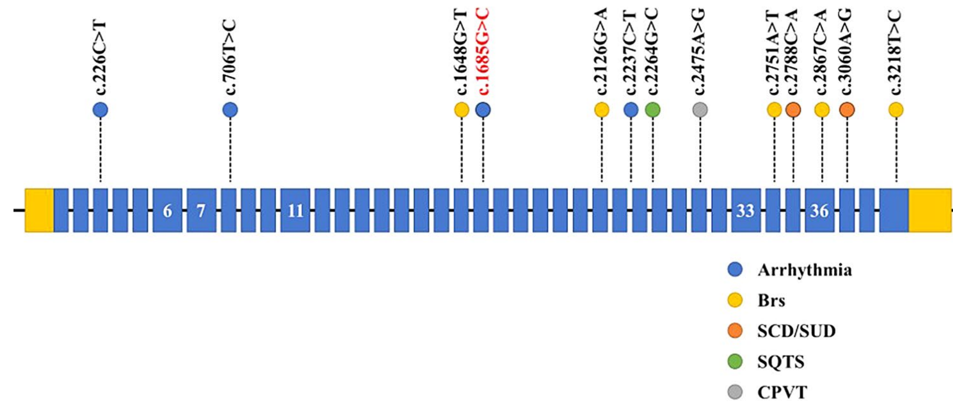

Fig. 3 Overview of all reported PED/SCD cases caused by *CACNA2D1* gene mutations. SQTS, Short QT syndrome; BrS, Brugada syndrome; CPVT, Catecholaminergic polymorphic ventricular tachycardia; SCD, Sudden cardiac death; SUD, Sudden unexplained death

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04204-3.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Yong Deng collected and provided clinical information. Qian Wang carried out whole exome sequencing and data analysis. Yi Dong performed DNA isolation and Sanger sequencing. Liang-Liang Fan performed genetic analysis. Yu-Xing Liu and Qian Wang wrote the manuscript. Yu-Xing Liu and Ai-Qian Zhang supported the project. All authors reviewed the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Data availability

The data presented in the study are deposited in the GSE-Human repository, accession number HRA007742 (https://ngdc.cncb.ac.cn/gsa-human/browse/HRA007742).

Declarations

Ethical approval

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (Approval number: 2022111617), Changsha, China. Written informed consent was obtained from all adult participants and legal guardians of minor participants.

Consent for publication

The patient provided written informed consent for publication.

Competing interests

The authors declare no competing interests.

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