Association of mutation in the PRKAG2 with familial left ventricular non-compaction cardiomyopathy

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Research Article

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Abstract

Left ventricular non-compaction cardiomyopathy (LVNC) is one of the most common inherited cardiovascular diseases. The genetic backgrounds of most LVNC patients are not fully understood. We collected clinical data, family histories, and blood samples and performed genetic analysis using next-generation sequencing (NGS) from a Chinese family of 15 subjects. Clinically LVNC affected subjects showed marked cardiac phenotype heterogeneity. We found that these subjects with LVNC carried a missense heterozygous genetic mutation c.905G□A(p. R302Q) in γ2 subunit of AMP-activated protein kinase (PRKAG2) gene through NGS. Individuals without this mutation showed no symptoms or cardiac structural abnormalities related to LVNC. One subject was the victim of sudden cardiac death. To sum up, PRKAG2 mutation [c.905G□A (p. R302Q)] caused familial LVNC. Our results described a potentially pathogenic mutation associated with LVNC, which may further extend the spectrum of LVNC phenotypes related to PRKAG2 gene mutations.

Background

Left ventricular non-compaction cardiomyopathy (LVNC) is a rare disease caused by abnormalities in the normal myocardial compaction process. Both sporadic and familial LVNC have been described[1, 2]. In familial disease, LVNC is a genetically heterogeneous disorder [1]. Mutations in the γ2 subunit of AMP-activated protein kinase (PRKAG2) gene are known to cause an energetic disease affecting the myocardium [3] and previous studies have confirmed that they can cause Wolff-Parkinson-White (WPW) syndrome, hypertrophic cardiomyopathy (HCM), ventricular pre-excitation and very few symptoms of myopathy [3–5]. The PRKAG2 gene encodes the γ_2 subunit of the AMP-activated protein kinase (AMPK)[6] which may be involved in cardiac development, particularly in the development of the atrioventricular (AV) annulus fibrosus[7–10]. AMPK is a highly conserved kinase responsible for the control of the cellular energetic balance[11]. In the cardiomyocyte, AMPK is implicated in promoting myocardial fatty acid uptake[12], oxidation[13], glucose uptake[14], glycolysis[15, 16], and possibly glycogen storage or exercise[17, 18], all of which may contribute to the maintenance of an adequate supply of ATP necessary for normal cardiac function. The main feature of myocardial histopathology in PRKAG2 cardiomyopathy is extensive intracellular vacuoles filled with glycogen[3, 19, 20].

In the present study, we used next-generation sequencing(NGS)and Sanger sequencing in a Chinese family with LNVC and confirmed for the first time that PRKAG2 mutation (c.905G□A [p. R302Q]), previously proposed to be associated with HCM and WPW syndrome 3–5, was associated with LVNC.

Methods

Clinical evaluation

Available detailed clinical evaluation of the proband and her relatives was performed, including an accurate medical history, physical examination, 12-lead electrocardiogram (ECG) and cardiac magnetic

resonance (CMR). Due to the distance from the hospital or their young age, several sujects did not visit the hospital for clinical examination. CMR exams have been performed on a 1.5 Tesla scanner. The images were transferred to a workstation (Siemens Medical Systems) for analysis. A 17-segment model was made from three short axis sections. All CMR data were analyzed using Argus post-processing software (Siemens Medical Systems). The left ventricular (LV) ejection fraction and ventricular volumes were measured on the SAX cine images. According to American Heart Association criteria[21], the presence or absence of non-compaction and was qualitatively assessed using the 17 segment model. The ratio of non-compacted to compacted (NC/C) myocardium was measured for each involved myocardial segment in diastole, on three long-axis views, and the maximum ratio was then used for analysis. Noncompaction was defined as a ratio of NC/C > 2.3[22]. Sinus bradycardia was defined as a heart rate less than 60 beats per minute, and short PR interval was defined as a PR interval< 120 ms on electrocardiogram.

Samples

Blood samples were collected from the preexisting witnesses and their families. Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood using a QIAmp DNA blood mini kit (Qiagen, Limburg, NL) according to the standard procedures. Qubit was used for accurate quantification of DNA concentration.

Next generation sequencing and analysis

Genomic DNA were randomly broken into 150-200bp fragments by Bioruptor Pico ultrasound, and fragmented DNA was end-repaired and "A" added at the 3' end. splice ligation. Next, sample labeling and enrichment of DNA were performed by PCR amplification. Libraries with specific indexes were further mixed for capturing using TargetSeq® liquid chip capture sequencing kits with Biotin-labeled RNA probe, and then using stranded affinity-labeled magnetic spheres to obtain target gene exons, followed by PCR amplification for target gene enrichment. Library quantification was performed using Qubit 3.0, and concentration >25ng/ul was considered as qualified library. The main peak of the library should be around 220-320bp with no spurious peaks before and after the main peak by Agilent 2100 assay. Illumina NextSeq 500 sequencing platform was used for sequencing after the quantification of qualified libraries. The raw image data files obtained from high-throughput sequencing were transformed into raw sequenced sequences (Sequenced reads). The Sequenced reads were then aligned to the reference sequences or reference genomes (GRCh37/hgl9). Clean reads were obtained by preliminary filtering of the Sequenced reads. The Burrows-Wheeler Aligner tool was used to compare the clean reads with the reference genome, and the sequencing work was performed to obtain the bam result file, and the average library length, comparison rate, coverage rate, capture rate, sequencing depth, homogeneity and other indicators were analyzed. All the mutations were compared with databases such as dbSNP, ExAC or 1000 genome projects. All the mutations found that can potentially cause cardiac ion channelopathies and cardiomyopathy were subject to Sanger sequencing (ABI3730xl) for verification.

Conservation analysis and bioinformatics prediction

The homologs of the region including Arg302 in homosapiens were detected (HomoloGene, http://www.ncbi.nlm.nih.gov/homologene). The potential pathogenicity of the identified missense mutation was evaluated by combining different methods: PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2), SIFT (http://sift.jcvi.org), and Mutation Taster (http://www.mutationtaster.org). The reference protein ID of PRKAG2 was 'Q9UGJ0 ' and the Ensembl transcript ID was 'ENSG00000106617'.

Results

Clinical features of the proband

The proband of this family was a 36-year-old female (II-2, Table and Figure 1). She had paroxysmal palpitations and chest distress for about 6 months, without angina pectoris, dyspnea or syncope. Physical examination revealed a grade II /III systolic murmur heard best over the left lower sternal border. The proband's ECG showed sinus bradycardia, short PR interval and LV hypertrophy with nonspecific ST-T wave changes (Figure 2A). The echocardiogram showed septal hypertrophy (Figure 2B) and prominent left ventricular apical trabeculations (Figure 2C). The cardiac magnetic resonance image indicated abundant trabeculation overlying a very thin compacted myocardial layer in the lateral left ventricular wall (Figure 2D) and the layer of non-compact myocardium (Figure 2E).

Pedigree analysis

The proband's brother (II-3) died of sudden cardiac death (SCD) suddenly at age 24. Unfortunately, the records of her brother were not available to us. Her mother (□-2) was hospitalized 10 years ago for sinus bradycardia, complete right bundle branch block, left anterior branch block, Lown-Ganong-Levine (LGL) syndrome and underwent radiofrequency ablation of the atrioventricular node bypass. Unfortunately, she developed third degree AV block after the procedure, so she underwent a double-chamber pacemaker implantation. She was readmitted 6 years ago for atrial flutter and had a repeat ECG for atrial flutter and complete right bundle branch block. Her young sister (II-4) had varying degrees of palpitations and chest distress. Her ECG showed Sinus bradycardia, short PR interval and LV hypertrophy. Her echocardiogram and CMR showed LVNC. The proband's son (□-1) had no clinically significant symptoms. His ECG showed normal, but the echocardiogram and CMR showed LVNC. Subject □-3 was too young to cooperate with CMR test. Subjects II-6, II-7, □-5, □-6, □-4 did not present at our hospital due to the long distance to the hospital, so their blood samples and clinical documents could not be obtained (Table and Figure 1).

Mutation identification

To identify the genetic basis of the LVNC suffered by this family, a custom-made NGS panel consisting of 675 genes previously associated with cardiomyopathies and related striated muscle disorders was used (Supplemental Table). Genetic sequencing was performed in the proband using this NGS panel. Mutation c.905G>A was found in PRKAG2 (RefSeq: NM_016203), corresponding to a nonsynonymous amino acid change from arginine to glutamine at position 302 (p.R302Q) (Figure 3). Next, the above mutation was

sequenced in all family members. The PRKAG2 mutation [c.905G□A (p.R302Q)] was confirmed in the subjects with LVNC manifestations (□-2, II-2, II-4, III-1 and III-3) and was not seen in other asymptomatic family members. The proband's nephew (III-3) who had no clinical symptoms currently was also found to carry the mutation.

Discussion

In the present study, we studied the family in which the proband presented with the LVNC. We performed NGS on the family members and identified a missense heterozygous genetic mutation in PRKAG2 (c.905G□A [p. R302Q]) which might to be the potentially pathogenic mutation. To our knowledge, this is the first study to describe the association of this mutation with LVNC.

LVNC, first described by Grant in 1926[23], is a heterogeneous myocardial disease characterized by prominent trabeculae, intratrabecular recesses, and two distinct layers of left ventricular myocardium: compaction and non-compaction[24, 25]. There is continuity between the left ventricular cavity and the deep intratrabecular recesses[2]. Assessment of imaging and pathologic changes shows that the disease is characterized by spongy left ventricular myocardium with abnormal trabeculae, usually most pronounced at the left ventricular apex[26]. The development of LVNC, is associated with cessation of end-stage myocardial compaction and morphogenesis[2, 27–29]. The American Heart Association (AHA) classifies LVNC as a separate genetic cardiomyopathy, but the European Society of Cardiology (ESC) defines it as an unclassified entity[30]. Currently, the incidence of LVNC is increasing, which may be due to greater awareness and more sensitive diagnostic tools such as modern ultrasound techniques and cardiac magnetic resonance (CMR) [31–34]. CMR has improved cardiac imaging, which has allowed for a more detailed understanding of the disease[26]. More importantly, genetics and genetic analysis play an important role in the prediction and management of LVNC [35].

The PRKAG2 mutation have been already described previously in HCM and WPW syndrome[4]. However, our study found that the PRKAG2 mutation [c.905G□A (p.R302Q)] was associated with LVNC. Previous studies have described a heterogeneous phenotypic presentation of LVNC[26, 36], such as hypertrophic LVNC, dilated LVNC, restrictive LVNC, arrhythmogenic LVNC and benign LVNC with preserved systolic and diastolic function[37]. Of those, the hypertrophic subtype was characterized by left ventricular hypertrophy, usually with asymmetric septal hypertrophy, usually accompanied by diastolic or systolic dysfunction. In families expressing both HCM and LVNC phenotypes, genotypes may overlap and both diseases can occur simultaneously [6]. Previous trials have collected a total of 242 children diagnosed with isolated LVNC, and 66 patients (27%) presented with hypertrophic[38].

The proband and her young sister presented with LVNC combined with short PR and sinus bradycardia. Previous studies confirmed that the association of WPW syndrome with LVNC was widely recognized and has been described in 17% of pediatric patients with LVNC. Sinus bradycardia is also associated with LVNC[24, 39], with a lower incidence than WPW syndrome. Previous studies have confirmed that patients

misdiagnosed with HCM were definitively LVNC by autopsy, and eight of nine patients had arrhythmias, in most cases sinus bradycardia, confirming that ventricular muscle dyssynchrony was often associated with conduction defects[40–42]. It has been proposed that fibrosis might be a possible cause of AV in patients with LVNC[43, 44]and defective local myocardial angiogenesis may be a potential cause of conduction abnormalities. Patients with progressive sinus bradycardia are associated with an abnormal vascular supply near the sinus node. Our study indicated that except for one SCD victim (II-5), the most LVNC survivors were about more than 30 years old. The mechanisms of how this missense mutation interferes with the PRKAG2 function and then leads to LVNC are not clear yet. Further biochemical and cell biological studies are needed to determine the consequence of this missense mutation.

The proband's sister and son (II-4 and III-1) manifesting with LVNC carried the mutation. The proband's brother (II-5) died of SCD, thus we concluded that the proband's brother may have suffered from LVNC and carried the same mutation. Our predictive genetic testing identified an asymptomatic individual (III-3) who was 6 years old and carried the disease-causing mutation, but unfortunately, he was so young that he could not cooperate to complete the CMR. His associated clinical symptoms have not yet expressed. Therefore, on the basis of our genetic diagnosis of LVNC in this family, we have been able to identify this young mutation carrier without phenotypic expression, which will facilitate better disease management and follow-up by clinicians before the appearance of symptoms. Bioinformatic prediction can provide us with some useful information about the pathogenicity of the PRKAG2 mutation [c.905G□A (p.R302Q)]. However, our experiments do not reflect the true pathology of this mutant in cardiac myocytes. Due to the inaccessibility of human heart tissues, we were unable to obtain sufficient numbers of patient heart tissues. The creation of mutant mice using CRISPR/Cas9 gene editing methods or the use of patient-specific induced pluripotent stem cell (iPSC) derived cardiomyocytes are state-of-the-art methods to directly and reproducibly study the pathogenicity of human mutants. In the future, we will further investigate the pathogenic role of the mutation using cardiomyocytes derived from patient-specific iPSCs.

Conclusions

We reported a missense heterozygous mutation of PRKAG2 [c.905G□A (p. R302Q)] in a Chinese family that presented with LVNC. The present study confirmed the genotype-phenotype correlation of the PRKAG2 mutation and provided further insight into the genetic factors underlying LVNC pathology. In addition, our findings demonstrate that CMR and NGS assays are effective methods for identifying pathogenic mutations associated with hereditary cardiomyopathies.

Declarations

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Authors Contribution

JZ: Data collection, experimental genetic work, manuscript preparation. XH and QL: Data analysis, including clinical data analysis. TW: Review and supervision. AM: Review, study design.

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Availability of data and materials

All data generated or analyzed in this study are included in this manuscript. Meanwhile, data supporting the manuscript is available from any of the two corresponding authors on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, and all methods were carried out in accordance with its guidelines and regulations. Written informed consent was obtained from all subjects.

Consent to publish

Written informed consent for publication of medical data and genetic data was obtained from all family members.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 is available in the Supplementary Files section.

Figures

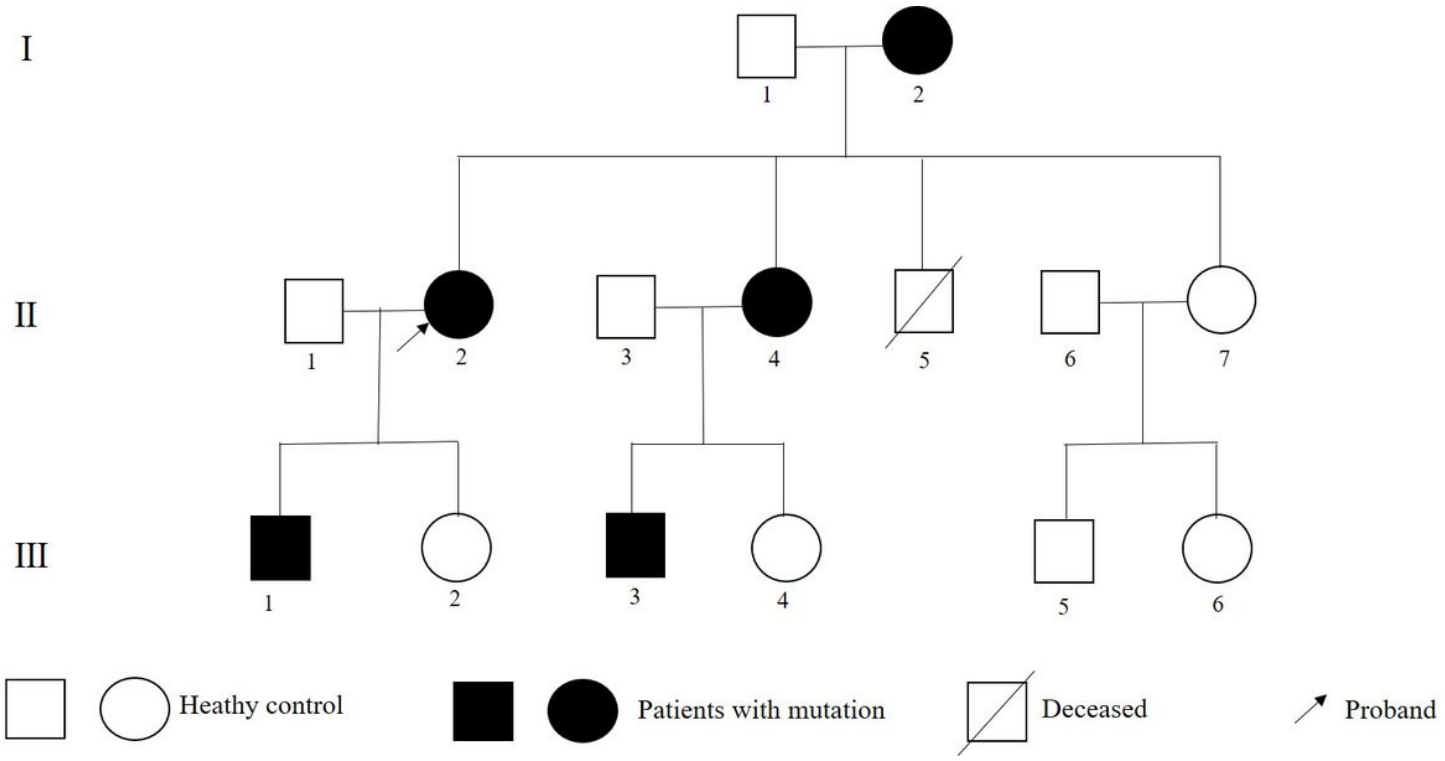

Figure 1

Pedigree structure of the family. Family members are identified by generations and numbers. Squares, male family members; circles, female members.

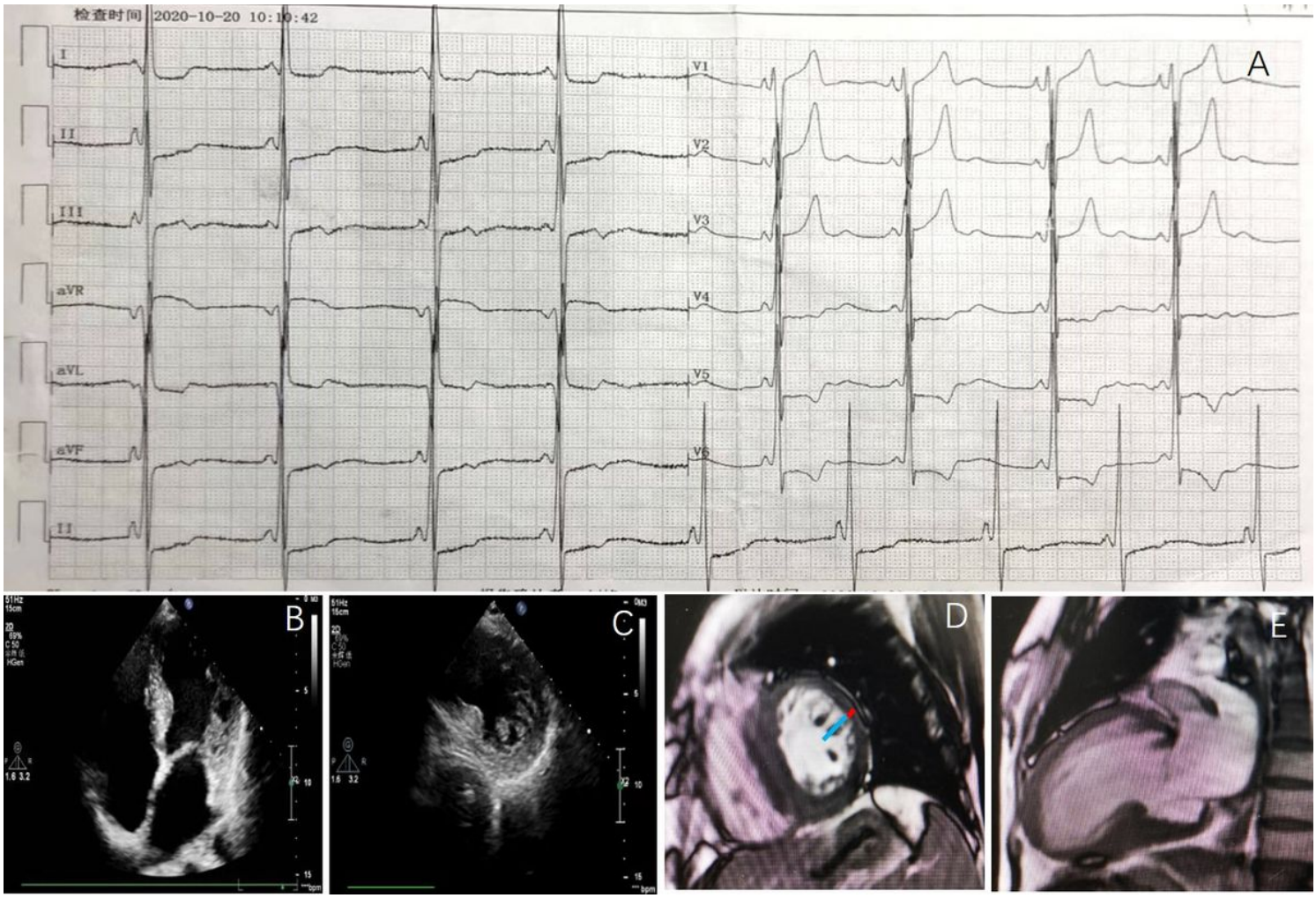

Figure 2

The electrocardiogram, transthoracic echocardiography, and cardiac magnetic resonance of the proband. A: The A 12-lead electrocardiogram showed sinus rhythm and LV hypertrophy. Nonspecific ST-T wave changes in the anterolateral leads and Q wave in the inferior leads. B: Echocardiographic apical 4-chamber view echocardiography showed basal segment of interventricular septum was thick.
C: Echocardiographic short axis view indicated prominent left ventricular apical trabeculations. D: Cardiac magnetic resonance image of short axis at the level of the apical segments showed abundant trabeculation overlying a very thin compacted myocardial layer in the lateral left ventricular wall. Blue bar: trabecular thickness; red bar: compacted wall thickness. E: Cardiac magnetic resonance image of long axis 2-chamber projection showed the layer of non-compact myocardium.

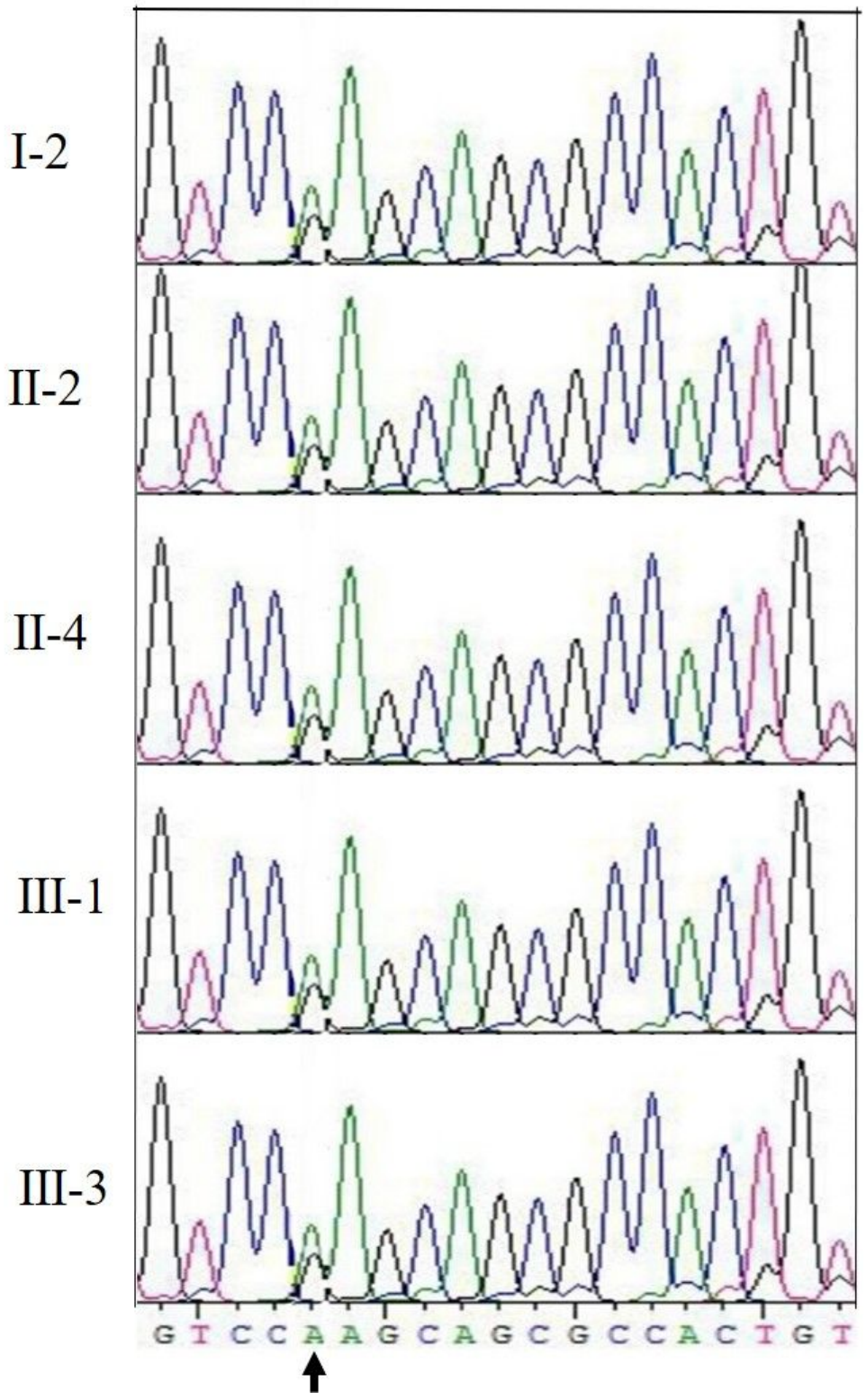

Figure 3

A disease-causing mutation of PRKAG2 in LVNC family, black arrow indicated missense variant c.905G A.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table.xlsx
- supplementarymaterial.docx