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Whole exome sequence reveals genetic profiles of primary cardiomyopathy and genotype-phenotype association in Chinese population

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Abstract

Background Primary cardiomyopathies are major causes of heart failure, placing a substantial burden on both individuals and society. Revealing its genetic profiles can lead to a better understanding of the mechanism and is critical for disease prevention and treatment.

Method Primary cardiomyopathy patients were enrolled and whole exome sequence was conducted to analyze their genetic profiles. Retrospective clinical information extraction and analysis of sequence data were implemented.

Results A total of 77 primary cardiomyopathy patients were enrolled, comprising 65 patients with dilated cardiomyopathy (DCM) and 12 with hypertrophic cardiomyopathy (HCM). Among the DCM patients, 13 variants classified as pathogenic (P) or likely pathogenic (LP) were identified in 12 patients (18.46%), predominantly in genes associated with the nuclear envelope and sarcomere. Among HCM patients, 6 P/LP variants were discovered in 6 (50%) patients. Taking variants of uncertain significance (VUS) into consideration, an analysis of the association between the number of variants carried by patients and their clinical characteristics revealed that DCM patients with more than one variant had a higher proportion of hyperuricemia.

Conclusions We map a comprehensive profile of primary cardiomyopathy in Chinese population and, for the first time, identify a possible association between hyperuricemia and the number of genetic variants carried by DCM patients.

Keywords Whole exome sequence, Dilated cardiomyopathy, Hypertrophic cardiomyopathy, Genetic profile, Genotype-phenotype association

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Introduction

Heart failure (HF) is a rapidly growing public health issue, affecting over 37.7 million individuals worldwide [1]. Cardiomyopathies are a diverse group of heart muscle diseases characterized by abnormal hypertrophy or dilation of the ventricles due to mechanical or electrical dysfunction, impairing the heart's ability to pump blood and leading to HF symptoms. Primary cardiomyopathies, such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) are significant contributors of HF, accounting for 20%~30% HF cases [1]. Despite advances in drug treatments, the clinical prognosis of HF remains poor, with mechanical assist devices and heart transplantation being the only options for patients with end-stage HF [2–4]. Understanding the underlying mechanisms of these diseases is crucial for improving treatment outcomes and advancing gene therapy research.

Primary cardiomyopathy is widely thought to have a genetic basis [5]. With the decreasing time and economic cost with whole exome sequencing (WES) technology, more and more genetic loci have been found to be associated with cardiomyopathy [6]. DCM is defined by the presence of left ventricular dilatation and contractile dysfunction. Variants in more than 60 genes, including those encoding sarcomere, desmosome, cytoskeleton, nuclear lamina, mitochondria, and calcium-handling proteins, are implicated in 35% of DCM cases [7]. HCM is a primary myocardial disorder characterized by left ventricular hypertrophy that occurs in the absence of identifiable processes that could account for such remodeling. A genetic cause can be identified in 40–50% of HCM patients tested for common sarcomere-related genes, including *MYBPC3*, *MYH7*, *TNNI3*, *TNNT2*, *TPM1*, *ACTC1*, *MYL2*, and *MYL3* [8]. The two most common genes, *MYBPC3* and *MYH7*, accounting for 70–80% of all genotype positive HCM patients [4]. Genetic testing is continually uncovering novel genetic variants associated with cardiomyopathies [9–11]. However, most existing data are derived from European and American populations, and more than half of primary cardiomyopathy cases still lack identified genetic causes. Thus, it is essential to conduct and summarize more WES data on Chinese patients with primary cardiomyopathy.

WES can be utilized to reveal the genetic profiles of the population and to identify significant variants. On this basis, genotype-phenotype association analysis was conducted to further elucidate the clinical significance of these variants. Research has shown that the number of pathogenic variants an individual carries has a definite impact on clinical symptoms: the more variants carried, the worse the clinical prognosis and cardiac structural parameters [12]. Uric acid as a metabolic product has garnered significant attention from researchers. Observational studies [13] and Mendelian randomization studies [14, 15] have demonstrated a causal relationship between uric acid levels and adverse cardiovascular events. Building upon this foundation, our study explores the relationship between the number of genetic variants and uric acid levels.

In our study, WES was performed in 77 patients with sporadic primary cardiomyopathy. Clinical information was extracted from electronic medical records. Further analysis between genetic data and clinical characteristics revealed an association between the number of variants carried by patients and hyperuricemia, both of which are potential risk factors for adverse outcomes in DCM.

Materials and methods

Subjects and clinical evaluation

We enrolled 77 patients with sporadic cardiomyopathy in the Second Xiangya Hospital of Central South University (Changsha, China) from 2019 to 2022, including 65 DCM patients and 12 HCM patients. Diagnoses were based on the consensus of three clinical physicians, considering detailed medical records, echocardiography, and cardiac MRI findings. DCM is diagnosed by identification of left ventricular or biventricular systolic dysfunction (LVEF < 50%) and dilatation (defined as left ventricular end-diastolic volumes or diameters > 2SD from normal values corrected for body surface area and age) that can't be explained by uncontrolled hypertension, valvular heart disease, congenital heart disease, or ischemic heart disease [16]. HCM was considered present when the left ventricular wall thickness, in any segment, was ≥ 13 mm in adults or when the wall thickness Z score was > 2.5 in children/adolescents, without other clinical syndromes (e.g., aortic stenosis, uncontrolled hypertension) capable of causing the observed hypertrophy [17]. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. Written informed consent was obtained from all patients.

Whole exome sequencing

Genomic DNA was extracted from peripheral blood using the DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA, USA). DNA concentration was measured by Qubit® DNA Assay Kit in Qubit® 2.0 Flurometer (Life Technologies, CA, USA). A total of 1 μg of genomic DNA was used to prepare DNA sample. Sequencing libraries were generated using Agilent SureSelect Human All Exon V6 kit (Agilent Technologies, CA, USA) following manufacturer's recommendations. The clustering of the samples was performed on a cBot Cluster Generation System using Hiseq PE Cluster Kit (Illumina), and the DNA libraries

were sequenced on Illumina Hiseq platform to generate 150 bp paired-end reads.

Bioinformatics analysis

The raw data from the Illumina Hiseq platform was converted to short reads (FASTQ format) containing sequence and quality information. Quality control was performed by discarding paired reads if > 10 nucleotides were aligned to adapters, if > 10% of bases were uncertain, or if > 50% of bases had a Phred quality score < 5. The valid sequencing data were mapped to the reference human genome (UCSC hg19) using Burrows-Wheeler Aligner (BWA) software, and variant calling was performed using Verita Trekker. SNPs and InDels were annotated using Enliven and ANNOVAR, incorporating databases including dbSNP,1000 Genomes, ExAC, gnomAD, HGMD and HGVS. Variants were further characterized by aligning against databases such as Consensus CDS, RefSeq, Ensembl, and UCSC to determine amino acid alterations.

Variants classification

Minor allele frequency (MAF) for each variant was determined based on data from ethnically matched 1000 Genomes, Exome Aggregation Consortium, and Genome Aggregation Database (gnomAD). Variants with MAF ≥ 0.001 were excluded from further analysis. Only single nucleotide variants (SNVs) occurring in exons or canonical splice sites were analyzed, with synonymous SNVs discarded.

Variant function was assessed using PolyPhen-2, SIFT, Mutation Taster, and CADD. Only variants deemed non-benign by all four software were retained. A cardiomyopathy panel from Blueprint Genetics, including 217 genes (Table S4) related to cardiomyopathies (HCM, DCM, RCM, LVNC, ARVC, and severe syndromes with cardiomyopathic phenotypes), was used to further classify genes for ACMG assessment [18]. Ultimately, variants classified by ACMG as pathogenic (P), likely pathogenic (LP), or of uncertain significance (VUS) were retained.

Sanger sequencing

Retained variants were validated by Sanger sequencing. Primer pairs were designed using Integrated DNA Technologies (IDT) and SnapGene software (ver 6.0.2). The primer sequences are available in Table S3. Sequencing of the PCR products was conducted by Tsingke Biological Technology (Beijing, China).

Clinical data extraction

The clinical data were extracted and compared by two cardiovascular specialists. If there was a discrepancy, a third one would review the data. The clinical data, including examination and test results as well as medical history, were extracted from EHRs after patient recruitment concluded in 2022. We focused on obtaining clinical data from the initial examination and test results recorded during the first admission for treatment. This approach was chosen to better represent the patients' baseline status before any therapeutic interventions, thereby minimizing the confounding effects of subsequent treatments on genotype-phenotype association analyses.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 8 and SPSS 24. Patient characteristics were presented as means ± SD for normally distributed continuous data; medians (IQR) were used otherwise. Categorical data were presented as numbers (percentages). Continuous variables were compared using the Student's t-test, Kruskal-Wallis test, or one-way ANOVA, depending on distribution. A two-tailed Chi-square test (or Fisher's exact test when any subgroup contained ≤ 5 observations) was used for categorical variables. Logistic regression analysis was used in the exploration of the relationship between the number of variant and uric acid level to account for confounding factors, including NYHA classification, age, BMI, serum creatinine and smoking history. A P-value < 0.05 was considered statistically significant.

Results

Demographic and clinical features of patients

A total of 77 patients diagnosed with primary cardiomyopathy were included in this study, consisting of 65 patients with DCM and 12 with HCM. Among all patients, 22 (28.57%) were females and average age of onset of cardiomyopathy was 31.06 ± 16.37 years. A history of smoking was present in 24 patients (31.17%). Significant differences were observed between DCM and HCM patients in LVEDD, LVEF, and LVD, except for RVD, which is an expected difference between these two disease groups ($P < 0.001$). 52 patients (67.53%) had NTpro-BNP levels above 1000 pg/ml, and 49 patients (63.64%) had hyperuricemic levels. The differences between DCM and HCM were not statistically significant in these parameters (Table 1).

Variant filtering and Gene Classification

After rigorous quality control, variants were filtered based on their effect, frequency, and in-silico algorithm predictions. These filtered variants were intersected with panel genes and subsequently assessed using ACMG guidelines, followed by Sanger sequencing. Among the 65 DCM and 12 HCM patients, 110 variants were discovered in 63 patients. These variants were further classified into 19 P/LP variants in 18 patients (23.37%), 60 VUS in 45 patients, and 31 B/LB variants in 22 patients, indicating that the etiology of at least 23.37% of patients in our cohort could be partly explained by genetic causes. The

Table 1 Baseline characteristics in CM patients

Baseline characteristics	All (*n* = 77)	DCM(*n* = 65)	HCM(*n* = 12)	*P*-Value [c]
Age at onset (years)[a]	31.06 ± 16.37	30.42 ± 17.07	34.58 ± 11.87	0.42
Female sex, n(%)[b]	22(28.57%)	19(29.23%)	3(25.00%)	0.76
NYHA class III/ IV, n(%)	57(74.03%)	53(81.54%)	4(33.33%)	0.0015
Smoking history, n(%)	24(31.17%)	21(32.31%)	3(25.00%)	0.74
LVEDD, mm [a]	61.37 ± 13.90	64.92 ± 12.84	46.09 ± 9.84	< 0.0001
LVEF, n (%) [a]	35.68 ± 16.38	29.21 ± 10.40	59.18 ± 16.41	< 0.0001
RVD, mm [a]	34.23 ± 6.49	34.52 ± 6.63	32.64 ± 5.68	0.38
IVSD, mm [a]	10.55 ± 4.78	8.75 ± 2.03	19.2 ± 4.75	< 0.0001
NTpro-BNP > 1000 pg/ml, n(%)	52(67.53%)	45(67.16%)	7(58.33%)	0.45
Hyperuricemia [c]	49(63.64%)	39(58.21%)	6(50.00%)	0.51
Atrial fibrillation, n (%)	6(7.79%)	6(9.23%)	0(0.00%)	0.33
Left Bundle branch block, n (%)	17(22.08%)	15(23.08%)	2(16.70%)	0.62
History of radiofrequency ablation, n (%)	3(3.89%)	2(3.08%)	1(8.33%)	0.40
History of ICD, n (%)	9(11.69%)	8(12.31%)	1(8.33%)	0.69
History of heart transplantation, n (%)	8(10.39%)	7(10.77%)	1(8.33%)	0.80

[a] Values are given as means ± SD

[b] Calculated between DCM patients and HCM patients using either unpaired t test for quantitative data, or Chi-square test or Fisher exact test for qualitative data, P value equals to or less than 0.05 is regarded as statistically significant

[c] Defined as a level of fasting blood uric acid higher than 420 μmol/L in men and 360 μmol/L in women

flowchart for variant filtering and classification is shown in Fig. 1.

Variants analysis in DCM patients

Among 65 DCM patients, 13 variants classified as P/LP in 12(18.46%) patients were discovered. The majority of these variants were found in genes associated with the nuclear envelope and sarcomere (5 in *LMNA* and the other 8 variants in *TNNT2*, *TTN*, *MYH7*, *FBN1*, *DTNA*, *BRAF*, *TPM1* and *GATA6*). Except for 3 frameshift variants found in *TTN*, *LMNA* and *GATA6*, the remaining variants are missense variants. Of these 13 rare variants, 7 (53.85%) have been reported in the Clinvar database. Taking VUS into consideration, 65 variants were identified in 46 DCM patients, of which 28 (43.08%) were novel variants not previously reported in ClinVar. Among these, 24 variants were related to sarcomere and nuclear envelope genes (11 in *TTN*, 6 in *LMNA*, 4 in *TNNT2* and other three in *MYH6* and *MYH7*). Variants in DCM classified as B/LB according to the ACMG 2015 guidelines were excluded from further analysis. (Fig. 2, Table S1).

Traditionally, cardiomyopathies are considered monogenic diseases. However, increasing evidence suggests that multiple variants may have cumulative effects on penetrance and disease severity [19–21]. In our DCM cohort, 14 (21.54%) patients had multiple variants, 32 (49.23%) had a single variant, and 19 (29.23%) had no variant.

Variants analysis in HCM patients

Among 12 HCM patients, 6 P/LP variants were identified in 6 patients (50%), with 3 were in *MYH7* and 3 were in *MYBPC3*. Including VUS variants, 14 variants were discovered in 11 patients, and 3(25%) *TTN* variants were found in 3 patients (Fig. 3). In terms of varinats function, only two variants in MYBPC3 were frameshift variants, the remaining were missense variants. There is only one patient having two variants. Seven variants in HCM classified as B/LB were excluded from further analysis as well. (Table S1).

Association analysis of the number of variants and clinical symptoms in DCM patients

To explore the potential impact of variants on clinical symptoms, DCM patients were divided into three groups based on the number of variants classified as P/LP and VUS: DCM with multiple variants, DCM with one variant, and DCM without a variant. The New York Heart Association (NYHA) class and blood uric acid levels were statistically significant in subgroup analysis. DCM patients with multiple variants had the worst NYHA class, all classified as NYHA class III/IV. There was a significant association between blood uric acid levels and the number of variants: For the group with multiple variants, 92.86% of DCM patients had hyperuricemia. When compared to the group without variants, the OR is 10.111 (95% CI: 95% CI: 1.177–86.848, $p = 0.014$). For the group with a single variant, 56.52% of patients had hyperuricemia. Compared to the group without variants, the OR is 17.875 (95% CI: 1.925-165.992, $p = 0.004$). After applying the Bonferroni correction for multiple testing, the differences between both the multiple variant and single variant groups compared to the no variant group remained statistically significant. (Table 2). To accounting for potential confounding factor influencing the relationship between the number of variants and uric acid levels,

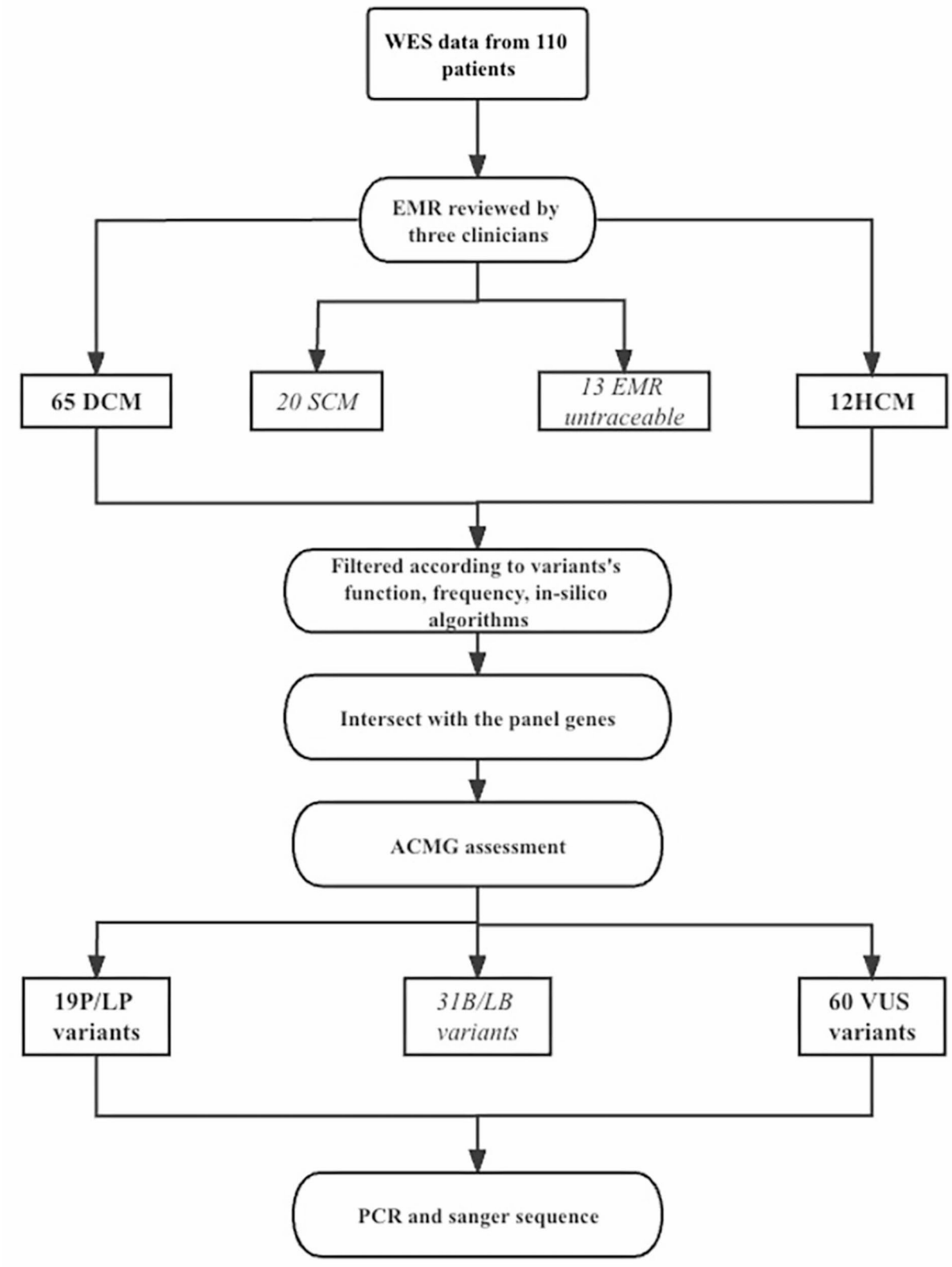

Fig. 1 (See legend on next page.)

(See figure on previous page.)

Fig. 1 Flow chart of variant filtering and classification

WES data from 110 patients were analyzed using electronic medical records and diagnostic criteria, including medical history, physical examination, lab tests, and imaging data. Among them, 65 patients were diagnosed with DCM, 12 with HCM, and 20 with SCM due to hypertension and coronary artery disease; the latter were excluded from further analysis. Variants underwent quality control and were filtered based on effect, frequency, and in-silico predictions, then assessed using ACMG guidelines. This resulted in 19 pathogenic/likely pathogenic variants, 60 variants of unknown significance, and 30 benign/likely benign variants, the latter of which were excluded from further analysis

we performed a multivariate binary logistic regression analysis. The results showed that even after adjusting for NYHA classification, age, BMI, serum creatinine and smoking history, the number of variants still had a significant impact on uric acid levels ($P = 0.015$).

We also categorized the patients into two groups based on the presence of the P/LP variant: the P/LP group ($N = 12$) and the control group ($N = 53$). No significant differences were observed between the groups, except that IVSD was significantly lower in the P/LP group. However, due to the small sample size of the P/LP group ($N = 12$), the statistical power of this finding is limited. However, upon integrating the data from Table 2 and accounting for VUS, significant differences in uric acid levels and cardiac function emerged between the groups. This implies potential clinical significance of VUS in relation to these symptoms, with the possibility that some pathological variants may be concealed among these VUS variants. (Table S2).

Discussion

We reviewed the clinical data and performed WES on 77 Chinese patients with primary cardiomyopathy, including 65 DCM patients and 12 HCM patients. After rigorous quality control, variants were filtered according to their effect, frequency, and in-silico algorithm predictions, then intersected with panel genes, followed by ACMG assessment and Sanger sequencing. A total of 19 P/LP variants were identified in 18 patients, indicating that 23.37% of our cardiomyopathy patients could be well-explained by genetic variants. Among patients with DCM, *TTN*, *LMNA*, *TNNT2*, *MYPN*, *DSC2* and *MYBPC3* were the most commonly mutated genes, accounting for 49.23% of the total variants. In HCM patients, 6 P/LP variants were identified in 6 patients (50%), with 3 were in MYH7 and 3 were in MYBPC3. In the genotype-phenotype analysis, we found that patients carrying multiple variants had worse NYHA grades and a higher proportion of hyperuricemia. However, these results were not found in the subgroup carrying only P/LP variants.

Each cardiomyopathy has a characteristic genetic profile. HCM were largely understood as genetic disease of sarcomere genes [22], with a prevalence estimated at 1 in 500 individuals [23]. In contrast, more than 250 genes spanning 10 gene ontologies have been implicated in DCM, reflecting its complex and diverse genetic architecture [24, 25], with an estimated prevalence of 1 in 250 individuals [5]. This aligns with the larger number of DCM patients in our cohort and the more complex genetic profile of DCM.

The number of variants one carrying was associated with clinical symptoms. This result is consistent with the findings of Jizheng Wang, who divided 529 unrelated HCM patients into three groups based on the dosage of rare variants. Patients with multiple rare variants were younger at diagnosis, had greater maximum left ventricular wall thickness, and larger left atria. The presence of multiple rare variants was a risk factor for malignant outcomes in HCM [12]. Similarly, in our study, the presence of multiple variants was associated with worse NYHA class in DCM. However, this effect was not observed when we considered only P/LP variants. Lei Xiao also found that the phenotype of DCM patients with deleterious variants was similar to that of patients without deleterious variants [26]. This suggested that VUS also play an important role in the pathogenesis of DCM and need to be actively explored [27]. Importantly, VUS may be reclassified over time. Our team previously reported a TNNI3K variant in arrhythmogenic right ventricular cardiomyopathy by constructing TNNI3K plasmids. The effects of the TNNI3K variant (c.1538T > C) were investigated by real-time polymerase chain reaction and western blot, which added PS3 evidence and reclassified the variant from VUS to LP [28]. Still there is a study in which 8% of HCM patients who initially received a VUS result had their variant reclassified as LP upon re-examination [29].

Our study also found that the number of variants carried by patients was associated with hyperuricemia. The proportion of hyperuricemia was 92.86% in patients with multiple variants, 56.52% in patients with one variant, and 42.11% in patients without any variants. The relationship between blood uric acid levels and chronic heart disease has been previously investigated and aligns with our findings. As early as 1997, F. Leyva found that blood uric acid levels were strongly correlated with inflammatory markers in patients with chronic heart failure, consisting with a role for increased xanthine oxidase activity in the inflammatory response in patients with chronic heart failure [30]. Several retrospective studies have shown that uric acid levels in patients with idiopathic cardiomyopathy [13], peripartum cardiomyopathy [31], dilated heart disease [32] and pediatric dilated cardiomyopathy [33]

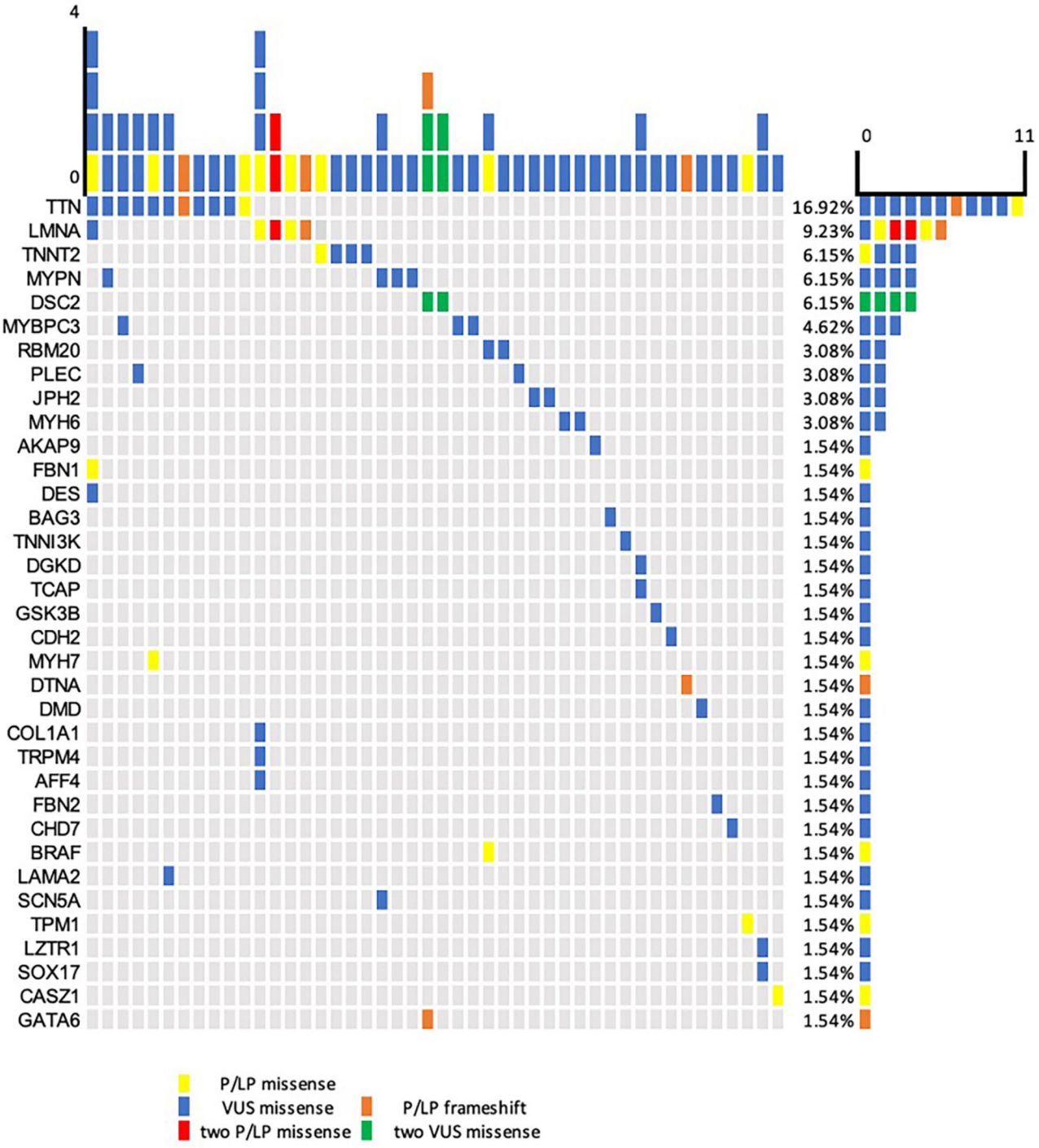

Fig. 2 65 variants distribution in 46 DCM patients
Among 65 DCM patients, 65 variants in 46 DCM patients were discovered and 28 (43.08%) were novel. 24 out of 65 variants were sarcomere and nuclear envelop related genes (11 in *TTN*, 6 in *LMNA*, 4 in *TNNT2* and other three in *MYH6* and *MYH7*)

were associated with adverse outcomes and ultrasound indicators. A study involving 122 patients with dilated heart disease even suggested that uric acid levels were better predictors of prognosis than NT-proBNP [34]. Similarly, in our study, it was the uric acid level rather than NT-proBNP that was associated with the number of variants carried by the patients. Some prospective studies [35–37] and mendelian randomization studies also confirmed the association between uric acid level and risk of different types of cardiac events [14, 15, 38]. Some mendelian randomization studies confirmed the causal relationship between uric acid level and cardiac outcomes

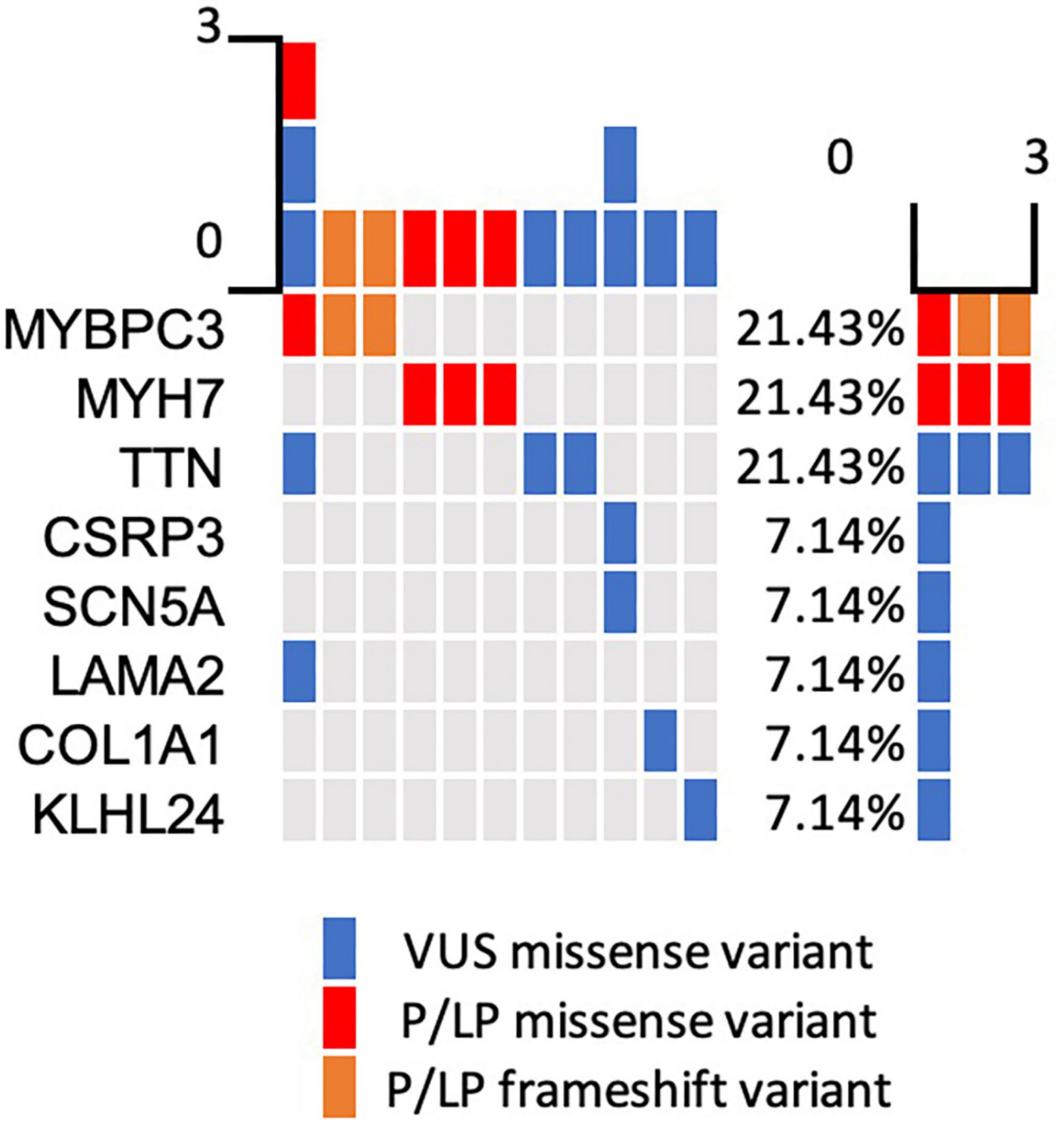

Fig. 3 14 variants distribution in 11 HCM patients
14 variants were discovered in 11 patients, and 3(25%) *TTN* variants were found in 3 patients. As for the variants function, only two variants in *MYBPC3* were frameshift variants, remaining were all missense variants

[39, 40]. For the first time, our study suggested an association between uric acid levels and the number of variants in cardiomyopathy-related genes. We hypothesize that there may be some links between cardiomyopathy-related genes and uric acid-regulating genes. For example, nuclear myosin regulates gene transcription, which is modulated through phosphorylation of the myosin regulatory light chain. This is also present in the nuclei of cardiomyocytes, and its binding sequence has been identified in the promoter of the xanthine oxidase gene, an important enzyme for uric acid production. Additionally, there may be some confounding factors that need to be further explored, and the exact mechanisms should be

Table 2 Association analysis of the number of variants and clinical symptoms in DCM patients

Characteristics	> 1 variants($n=14$)	1 variant($n=32$)	0 variant ($n=19$)	*P*-Value [c]
Age at onset (years)[a]	23.80 ± 7.79	30.74 ± 18.64	33.42 ± 16.10	0.33
Female sex, n (%)[b]	3(21.43%)	11(34.38%)	4(21.05%)	0.50
NYHA class III/IV, n(%)	14(100%)	23(71.88%)	17(89.47%)	0.04
Smoking history, n(%)	3(21.43%)	9(28.13%)	8(42.11%)	0.40
LVEDD, mm [a]	66.92 ± 11.86	62.86 ± 12.63	68.84 ± 11.07	0.22
LVEF, n(%)[a]	27.08 ± 7.43	29.86 ± 10.85	30.26 ± 11.39	0.68
RVD, mm [a]	34.92 ± 6.27	32.74 ± 6.53	35.58 ± 6.05	0.29
IVSD, mm [a]	8.73 ± 1.56	9.14 ± 1.62	8.25 ± 2.72	0.43
NTpro-BNP > 1000pg/mlL, n(%)	12(85.71%)	22(68.75%)	13(68.42%)	0.45
Hyperuricemia [c]	13(92.86%)	18(56.52%)	8(42.11%)	0.01
Atrial fibrillation, n (%)	2(14.29%)	3(9.38%)	1(5.26%)	0.74
Left Bundle branch block, n (%)	2(14.29%)	4(12.50%)	4(21.05%)	0.82
History of radiofrequency ablation, n (%)	0(0.00%)	2(6.25%)	0(0.00%)	0.71
History of ICD, n (%)	2(14.29%)	3(9.38%)	3(15.79%)	0.80
History of heart transplantation, n (%)	3(21.43%)	2(6.25%)	1(5.26%)	0.28

[a]Values are given as means ± SD

[b] Calculated between subgroups using either one-way ANOVA test for quantitative data, or Chi-square test or Fisher exact test for qualitative data, P value equals to or less than 0.05 is regarded as statistically significant

[c] Defined as a level of fasting blood uric acid higher than 420 μmol/L in men and 360 μmol/L in women

investigated in larger cohorts with more detailed clinical information.

Genetic testing is recommended for patients with DCM and HCM in clinical practice, as up to 50% of relatives may carry a pathogenic variant, enabling early intervention and improving clinical outcomes. Gene therapy for cardiomyopathy is an emerging field, with efforts using adeno-associated virus (AAV) vectors to correct myocyte function in various cardiomyopathies, such as Duchenne muscular dystrophy, mitochondrial cardiomyopathy, Barth syndrome, Brugada syndrome, and heart failure in animal models [41–44]. Additionally, small RNA therapeutics, like antisense oligonucleotides, can modulate gene expression [45, 46]. However, these strategies have so far been limited to animal models, and significant progress is needed before gene therapy can be implemented in clinical settings.

Although our study provides valuable insights into the genetic spectrum and clinical characteristics of primary cardiomyopathy in Chinese population, it has some limitations. First, due to economic constraints, the sample size in our study is relatively small. As a result, phenotypic analysis includes not only P/LP variants but also VUS. Given the limited population-based WES data currently available in China, particularly in central and southern regions, our study offers valuable insights into the genetic profile of cardiomyopathy. Future studies with larger sample sizes and a focus solely on P/LP variants are needed for more robust genotype-phenotype association analyses. Second, more detailed follow-up data can provide a better understanding of the association with clinical outcomes. Collecting clinical features from electronic medical records may miss important outcomes, such as heart transplantation, ICD implantation, heart and renal failure, due to delayed follow-up. Additionally, gathering detailed information on factors such as medication history (particularly diuretics) and dietary habits could help better adjust for confounding effects. Lastly, we used a cardiomyopathy gene panel to identify variants and describe the genetic landscape of cardiomyopathy in the Chinese population. It is important to acknowledge that this approach is limited to detecting novel variants within known genes and does not facilitate the discovery of new genes.

Conclusions

We map a comprehensive profile of primary cardiomyopathy in Chinese population and, for the first time, identify a possible association between hyperuricemia and the number of genetic variants carried by DCM patients.

Abbreviations

HF	Heart failure
DCM	Dilated cardiomyopathy
HCM	Hypertrophic cardiomyopathy
WES	Whole exome sequence
P	Pathogenic
LP	Likely pathogenic
VUS	Variant of uncertain significance
SCM	Secondary cardiomyopathy
ARVC	Arrhythmogenic right ventricular cardiomyopathy
RCM	Restrictive cardiomyopathy
MAF	Minor allele frequency
ANOVA	Analysis of variance
RVD	Right ventricular internal dimension
LVEDD	Left ventricular end-diastolic dimension
LVEF	Left ventricular ejection fraction
IVSD	Inter-ventricular septal thickness

ACMG	American College of Medical Genetics
NYHA	New York Heart Association
AAV	Adeno-associated virus
EHR	Electronic health record

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12864-025-11323-4.

Supplementary Material 1

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Author contributions

L.X., Y.F.Y, and R.L.L., conception and design; R.L.L., K.G, L.W and Y.Y performed clinical data extraction; R.L.L, Y.Y., L.W. and K.G. contributed to blood specimen collection and DNA extraction; R.L.L. and K.G. analysis and interpretation; R.L.L., Y.F.Y and L.X. wrote the paper.

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Data availability

Our sequencing data have been submitted to the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/?term=SUB13493983) and are now publicly available. The data can also be accessed in Table S1, which contains the same information as that uploaded to ClinVar. Requests for clinical information should be directed to the corresponding author, accompanied by a valid reason.

Declarations

Ethics approval and consent to participate

This study was implemented in accordance with the principle of the Declaration of Helsinki and approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. Written informed consents were obtained from all the patients.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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