

# A Novel Mutation Of The *EMD* Gene In A Family With Cardiac Conduction Abnormalities And A High Incidence Of Sudden Cardiac Death

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**Background:** Emery-Dreifuss muscular dystrophy, caused by mutations in genes such as emerin (*EMD*) or lamin A/C (*LMNA*), is a disorder affecting the joints, muscles, and heart, with a wide spectrum of patient phenotypes including muscle wasting and cardiac conduction defects.

**Methods and results:** Here we report a multi-generation family from the Hunan Province of China. Affected family members displayed an uncommon clinical presentation of serious cardiac conduction abnormalities at an early age and a high incidence of sudden cardiac death along with mild skeletal muscular atrophy and joint contracture. Clinical analysis of affected members provided evidence of X-linked recessive inheritance. Consequently, using Sanger sequencing of X chromosome exomes, we identified a novel duplication mutation (c.405dup/p.Asp136X) in the *EMD* gene as the cause for the disease in this family. This variant is a novel mutation that has not been previously reported in Pubmed, Clinvar or other cases reported in the Human Gene Mutation Database.

**Conclusion:** Our finding expands the mutation spectrum of Emery-Dreifuss muscular dystrophy and provides a rationale for *EMD* mutation testing in cases of X-linked inherited cardiac conduction disease and sudden cardiac death, even in those lacking pathognomonic neuromuscular features.

**Keywords:** Emery-Dreifuss muscular dystrophy, emerin, sudden cardiac death, cardiac conduction abnormalities, mutation

## Introduction

Emery-Dreifuss muscular dystrophy (EDMD) is a rare inherited disease characterized clinically by humero-peroneal muscle atrophy and weakness, multi-joint contractures, spine rigidity and cardiac insufficiency with conduction defects.<sup>1-3</sup> EDMD is caused by mutations in different genes with approximately 50% of cases linked to mutations in *EMD* (*STA*), *LMNA*, *FHL1*, *SYNE1*, *SYNE2*, *LUMA* and *SUN1*.<sup>4</sup>

EDMD1, one common type of EDMD, has an X-linked recessive pattern of inheritance and is caused by mutations in the *EMD* gene (OMIM 310300) on chromosome Xq28.<sup>5</sup> The *EMD* gene contains five introns and six exons that span 2.2 kb of genomic DNA. *EMD* encodes a protein known as emerin, which belongs to the family of type II integral membrane proteins anchored to the inner nuclear membrane via hydrophobic tails, with the remainder of the molecule projecting into the nucleoplasm.<sup>6</sup> Emerin is involved in a number of biological processes, including direct and indirect regulation of transcription factor activity and localization,

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intra- and intercellular signaling, nucleo-cytoskeletal mechanotransduction, nuclear structure,<sup>7</sup> chromatin condensation, as well as epigenetic modifications.<sup>8,9</sup> Since most of the mutations in *EMD* are premature termination point or frame-shift mutations, they typically result in absence or decreased production of full-length emerin.

In EDMD1, the first symptoms of the disease are usually seen in the first decade of life and manifest as ankle and elbow contractures and spine rigidity. These symptoms precede muscle atrophy and weakness, which are typically visible in the second to third decades of life.<sup>10</sup> Symptoms involving the skeletal muscles usually arise before cardiac disease, which initially includes sinus bradycardia, supra-ventricular tachyarrhythmia and paroxysmal atrial fibrillation.<sup>10</sup> Atrial standstill and heart insufficiency emerge later in the fourth or fifth decades of life. The phenotypic variability in disease presentation among patients makes diagnosis relatively difficult, with physicians often relying on gene sequencing and duplication analysis. However, this type of diagnostic approach obviously necessitates the responsible mutation having already been identified.

In this study, we identified a Chinese family with EDMD1 associated with a novel duplication mutation (c.405dup/p. Asp136X) in the *EMD* gene. The affected family members displayed an uncommon clinical presentation of serious cardiac conduction abnormalities at an early age and a high incidence of sudden cardiac death (SCD) along with mild skeletal muscular atrophy and joint contracture. Our finding expands the mutation spectrum of *EMD* and provides a rationale for *EMD* mutation testing in cases of X-linked inherited cardiac conduction disease (CCD) and SCD, even in those lacking pathognomonic neuromuscular features.

## Materials And Methods

### Subjects

The proband, a 28-year-old man, was admitted to our clinical due to slight dyspnea. Electrocardiogram (ECG) showed sinus bradycardia and occasional sinus cardiac arrest. Upon further inquiry, the proband revealed that there were several cases of SCD in his family. Due to the family disease history of the proband, we decided to investigate his family carefully. Extensive genealogical records provided by the proband were utilized for pedigree construction. A questionnaire on health history was completed, medical records were collected, and electrocardiographic

screening was performed for each individual. The available medical records for all deceased individuals were also reviewed.

The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University in China. Written informed consent was obtained from all study participants or their legal representatives or guardians.

### Clinical Evaluation

All subjects of the family underwent serial physical examinations, 24 hr ambulatory electrocardiogram, transthoracic echocardiography (TTE), electromyography muscle (EMG), magnetic resonance spectroscopy (MRI) and blood sampling for creatine kinase (CK) measurements.

### Genetic Analysis

Genomic DNA was extracted from a peripheral venous blood sample of each subject using the QiAamp<sup>®</sup> DNA Blood Mini Kit (Qiagen Corp., USA). To complete the X chromosome exome sequencing (X-exome sequencing), genomic DNA (3mg) was sheared to produce 180bp fragments. Illumina adapters were added using SureSelect XT kit reagents (Agilent Technologies, Santa Clara, CA). The adapter-ligated DNA underwent hybridization with the X-exome targeted biotinylated RNA baits (SureSelect X chromosome demo kit, Agilent Technologies) for 24 hrs at 65°C. Hybridized DNA X-exome targets were captured using streptavidin-coated magnetic beads. The X-exome targets of interest were eluted and barcoded/indexed after a series of washes to remove the non-targeted, unbound genome fragments. The sample was indexed and sequenced to obtain approximately 50 average coverage using 2×100-base pair paired end reads (HiSeq2000, Illumina, San Diego, CA). SOAP aligner (soap2.21) and SOAP snp (v.1.03)<sup>11</sup> were used for single nucleotide polymorphism (SNP) calling, whereas BWA (Burrows-Wheeler Aligner) and GATK (Genome-Analysis-Tool-Kit)<sup>11</sup> were used for indel detection. The reads were aligned to the UCSC reference genome (Hg19) and variants were called with a probabilistic variant detection. All variants present in dbSNP137 (MAF > 0.01), the 1000 Genome variants database, HapMap exomes and an in-house database containing the WES data from 1000 normal individuals were then filtered out. The data interpretation rules were according to the guidelines of American College of Medical Genetics and Genomics (ACMG).<sup>12</sup>

Sanger sequencing was performed as follows: PCR primer sequences were designed through Ensembl (<http://asia.ensembl.org/index.html>). Mutation analysis of genes

by direct sequencing was performed on the PCR products. The sequencing results were then analyzed using Chromas 2.33 and compared with the sequences in the NCBI GenBank database.

## Immunoblotting Of Lymphocytes

Peripheral blood samples were collected from all participants and lymphocytes were separated using lymphocyte separation medium (MP, USA). The cells were washed twice with phosphate-buffered saline (PBS) solution and lysed with RIPA lysis buffer (Beyotime, China) containing a proteinase inhibitor (Beyotime, China). Protein concentrations were measured using the Pierce BCA Protein Assay Kit (Thermo-Fisher Scientific, USA) and samples were stored at  $-80^{\circ}\text{C}$  until use. Total protein aliquots were loaded onto a 10% sodium dodecyl sulfate polyacrylamide gel for electrophoresis and were then transferred onto PVDF membranes. The membranes were blocked for in Tris-buffered saline with Tween-20 (TBS-T) containing 5% non-fat milk. Membranes were then incubated overnight at  $4^{\circ}\text{C}$  with a 1:500 dilution of the anti-emerin antibody (ab54996, Abcam, USA) followed by the horse radish peroxidase-conjugated goat anti-rabbit IgG secondary antibody (1:6000 dilution, BioTeke, China) and detection using the Enhanced Chemiluminescence Substrate Kit (Thermo-Fisher, USA).

## Immunofluorescence Of Mucosa Exfoliating Cells

For all subjects, specimens of mucosa exfoliating cells from the cheek oral mucosa were used for immunofluorescence analysis. In brief, the inner surface of the cheek was first cleaned with a piece of gauze wetted with PBS and then gently scraped with a plastic spatula measuring  $1.5 \times 4\text{cm}$ . The collected cells were smeared on to a polylysine coated glass slide and left to dry. After fixation with cold methanol for 10 mins at room temperature and rinsing in PBS, the samples were incubated with an anti-emerin antibody (ab54996) (Abcam, USA, dilution 1:50) in Tris-HCl-phosphate buffered saline (TBS) containing 1% bovine serum albumin (Abcam, USA) overnight at  $4^{\circ}\text{C}$ . The samples were then incubated with Alexa Fluor<sup>®</sup> 448 goat anti-mouse antibody (Life Technologies Corp. USA) for 1 hr in the dark at room temperature. After the samples were counterstained with Hoechst 33,258 to visualize nuclei (Sigma Corp. USA), a Nikon E600 fluorescent microscope was used for visualization photo acquisition.

## Results

### Clinical Evaluation Of Proband

A 28-year-old man came to our clinical complaining slight dyspnea. ECG and 24 hr ambulatory electrocardiogram of the man revealed sinus bradycardia, atrial escape rhythm and occasional sinus cardiac arrest (Figure 1A and B). Echocardiography displayed mild left ventricle dilation but normal systolic function (ejection fraction: 68%, left ventricular end diastolic diameter: 50 mm). He denied the use of alcohol, tobacco or drugs. The patient (proband) had a normal birth and developed without any obvious signs or symptoms of neuromuscular disease (Figure 1E). No obvious muscular atrophy was detected through visual inspection. However, serum creatine phosphokinase (CK) levels were high (CK = 1234.8 U/L; normal: 24–195 U/L). The electromyography (EMG) evaluation displayed chronic myogenic damage (Figure 1C), and muscular MRI showed mild fatty infiltration in the skeletal muscle (Figure 1D).

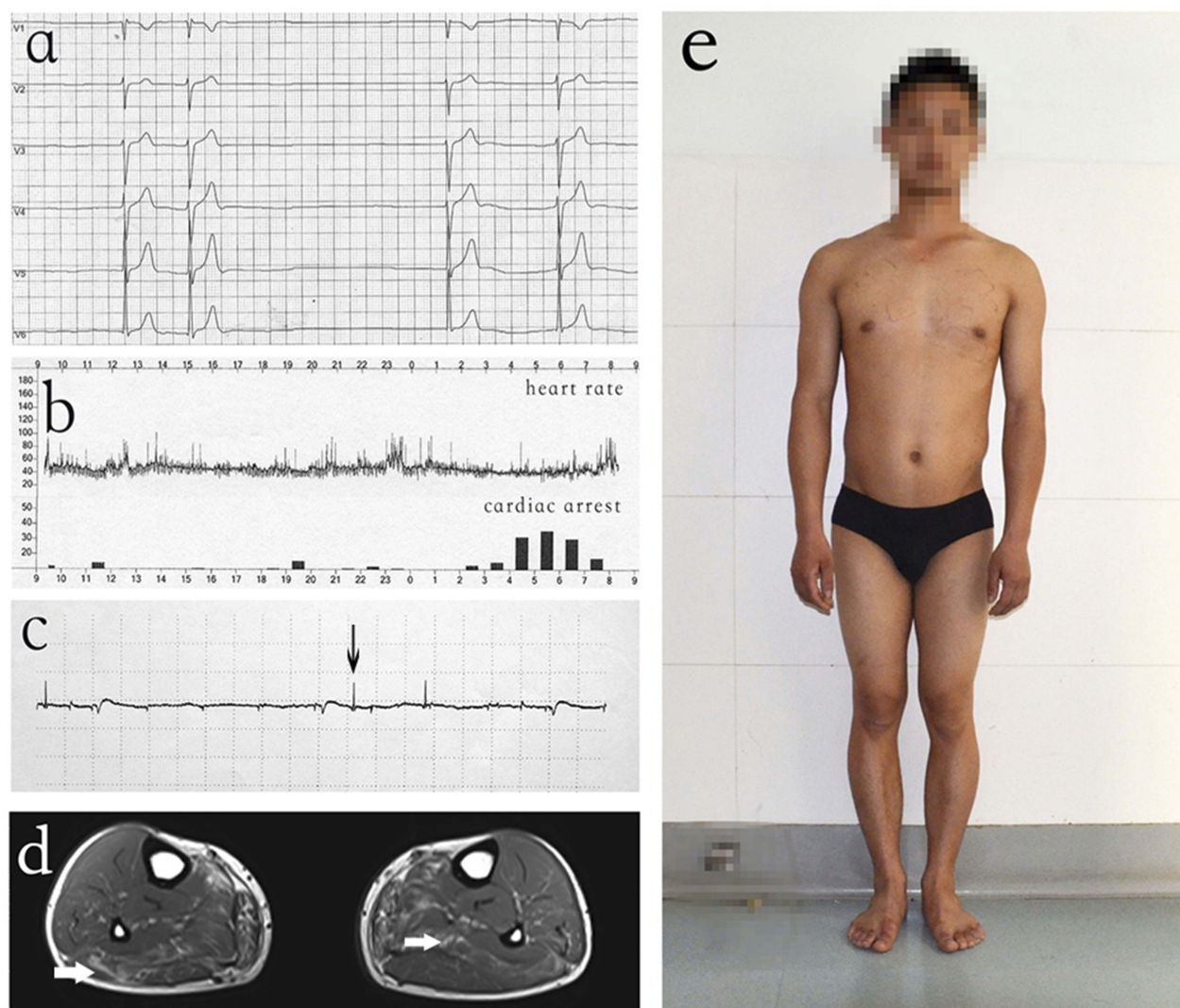
### Cardiac Conduction Abnormalities Were Observed In Multiple Members Of The Proband Family In X-Linked Recessive Manner

The patient (proband) also mentioned that some of his family members died suddenly. We then decided to determine whether any other members of the family also display similar phenotypes. This pedigree, from the Hunan Province of China, consisted of 77 family members (38 males and 39 females) across six generations (Figure 2). In this family, ECG analysis showed serious cardiac conduction abnormalities in family members III-5, IV-4, IV-29, V3 and V4 (proband). In addition, III-3, III-7, III-8, IV-30 died from SCD. Other members had no obvious cardiac complications. The main clinical features of the other affected members were similar to those of the proband (Table 1). None of the female heterozygous carriers (ranging between 2–82 years of age) had skeletal muscular dystrophy, joint contracture or serious cardiac complications in our study. Clinical analysis of the pedigree provided evidence of X-linked recessive inheritance (Figure 2).

### A Novel Duplication Mutation (c.405dup/p.Asp136X) Was Identified In The Patients

Since the pedigree (Figure 2) provided evidence of X-linked recessive inheritance, X-exome sequencing was performed





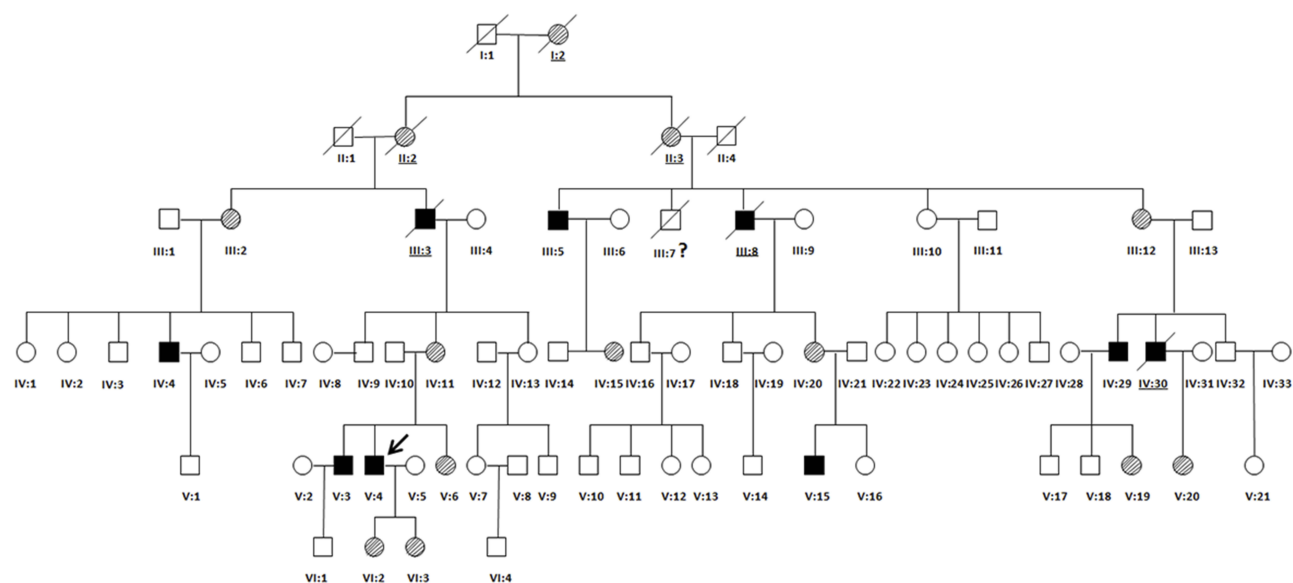
**Figure 1** Clinical characteristics of proband (V-4). **(A)** ECG showed sinus bradycardia and occasional sinus cardiac arrest. **(B)** 24 hr ambulatory electrocardiogram showed the changes in heart rate and sinus cardiac arrest in a day. **(C)** EMG displayed spontaneous electromyographic activity in limb muscles. **(D)** Muscular MRI showed mild fatty infiltration in the skeletal muscle. **(E)** The patient (proband) developed without any obvious symptoms of neuromuscular disease.

for the proband. Approximately 7,653 exons on the X chromosome were captured and sequenced. The average base coverage depth of the X chromosome exome sequencing was 98.32 and 93.79% of genomic regions covered more than 20 times. According to the ACMG guidelines, we identified that the *EMD* mutation c.405dup in exon5 was a possible candidate mutation. Mutation screening for the candidate mutation was performed on all living individuals in the pedigree by PCR-Sanger sequencing. This variant was also identified by Sanger sequencing (Figure 3). The novel duplication mutation (c.405dup/p.Asp136X) resulted in a premature termination at position 136. This variant was a novel mutation and has not yet been reported in Pubmed, Clinvar or in any other previous cases of HGMD.

## The Mutation Leads To Absent Of EDMD Proteins

Immunoblotting of peripheral blood lymphocytes revealed that emerlin protein expression was present in the heterozygous individuals. The expression of emerlin in hemizygous individuals was completely absent (Figure 4A).

The immunofluorescence results of mucosa exfoliating cells demonstrated an absence of emerlin expression in nuclei of all hemizygous members, while about 50% of nuclei of heterozygous female carriers of the *EMD* mutation were positive for emerlin staining (Figure 4B), indicating that emerlin expression from the wild type allele occurs only when that allele is not inactivated by random X chromosome inactivation.



**Figure 2** Family Pedigree. All individuals in the pedigree are identified by their Roman numerals below the symbol. Arabic numerals denote each individual in a generation. Squares represent males, and circles represent females. The proband (V-4) is designated with an arrow. Open symbols are unaffected individuals, filled symbols are hemizygous individuals, symbols with backslashes are heterozygous individuals, and symbols with diagonal lines indicate deceased subjects. Underlined numerals are obligate carriers who did not undergo molecular analysis. Numeral with a question mark (?) is an individual with an uncertain genetic status.

## Discussion

In this current study discovered a novel duplication mutation in the *EMD* gene that led to the development of EDMD1 in a multi-generation Chinese family. The family consists of 77 members, of which all of the hemizygous members suffered from cardiac conduction disorder (Figure 2). This study is particularly novel since previous studies were limited in the amount of data from large families displaying similar cardiac phenotypes that we report here. Mutations in *EMD* are very rare, with an estimated incidence of 0.13/100,000.<sup>13</sup> To date, approximately 150 different *EMD* mutations have been reported.<sup>10</sup> In our study, we identified a duplication mutation (c.405dup/p.Asp136X) of *EMD* which is a novel variant that has not yet been reported in HMGD cases, Clinvar or Pubmed. We also revealed that patients with this mutation no longer express emerlin protein, including any of the potential small isoforms (Figure 4). Ultimately, our study expands the genetic spectrum of the EDMD1 disease presentation and provides an additional genetic marker for diagnostic measures.

Thus far, the correlations between gene mutations and phenotypes have not been fully characterized. In EDMD1, symptoms involving the skeletal muscles usually arise before cardiac disease.<sup>10</sup> However, the patients in our study were characterized by early serious cardiac

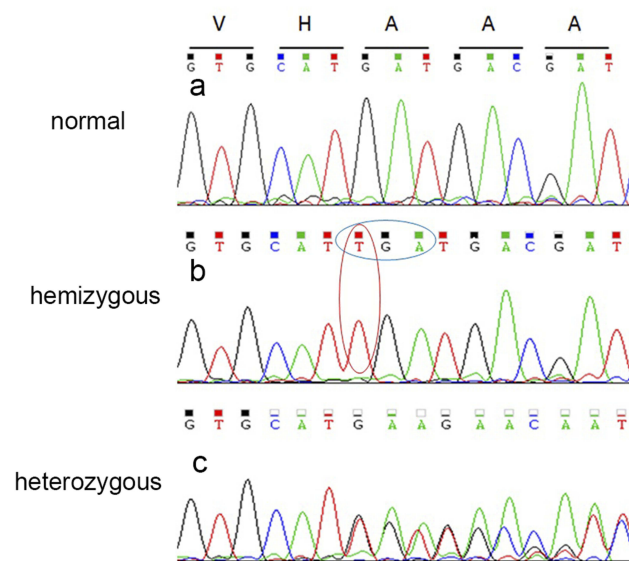
conduction abnormalities accompanied by mild skeletal muscular dystrophy and joint contracture. To date, fewer than five *EMD* mutations have been reported in patients with predominant cardiac diseases and mild skeletal muscle disorders.<sup>14–16</sup> These cases, together with our findings, may reveal that environmental or genetic modifications, such as functionally overlapping proteins, may contribute to the observed clinical variability caused by *EMD* mutations. Furthermore, female carriers of an *EMD* mutation have no muscular symptoms, but some may be at risk of cardiac arrhythmias and sudden death. Sakata K et al reported that approximately 20% of the female carriers in their study developed overt cardiac disease necessitating pacemaker implantation and pharmacotherapy.<sup>14</sup> However, none of the female carriers in our study (range, 2–82 years of age) had serious cardiac complications.

In this pedigree, SCD occurred in 4 of 10 patients (40%). Of the other 6 surviving patients, 5 developed serious cardiac conduction abnormalities, and a pacemaker eventually needed to be implanted in a 35-year-old patient (IV:29). SCD is a serious cardiac complication and is an important cause of mortality in the EDMD population.<sup>17,18</sup> Although the youngest patient did not have signs of cardiac conduction abnormality, paroxysmal bradyarrhythmia was observed in the ECG measurements. There is a general consensus regarding the efficacy of the implantable cardioverter-defibrillator (ICD) in primary prevention of

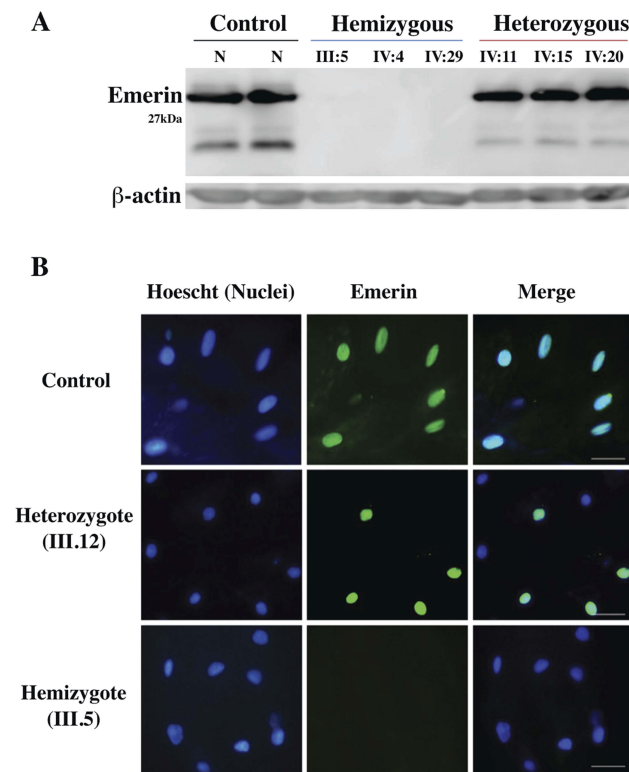
Table 1 Clinical Features Of The Proband And 9 Affected Family Members

Case	Sex	Age (Year)	Muscle InvolveMent	Echocardiogram				Holter Recording	EMG	CK (U/ L)	MRI
				LAD (mm)	LVEDD (mm)	RAD (mm)	LVEF (%)				
III-3	M	SCD at 35	(-)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
III-5	M	61	Mild	80	68	46	67	SB, AVJEB, MPVB, RBBB	Chronic myogenic damage	508	Mild muscular atrophy in vastus medialis and deltoideus triangularis, mild Achilles tendon calcification
III-7	M	SCD at 30	(-)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
III-8	M	SCD at 42	(-)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
IV-4	M	45	(-)	46	56	60	69	Af, III°AVB, AVJEB	Chronic myogenic damage	491	Mild muscular atrophy at deltoideus triangularis
IV-29	M	40	(-)	32	48	46	71	DDR-PM at 32 year	Chronic myogenic damage and activity damage in muscular	1067	N/A
IV-30	M	SCD at 28	(-)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
v-3	M	32	(-)	41	48	40	63	III°AVB, AVJEB	Activity myogenic damage	1174	Normal
V-4	M	28	(-)	32	50	56	68	SB, AER, SA	Activity myogenic damage	1235	Normal
V-15	M	7	(-)	22	38	28	76	Paroxysmal SB	Normal	351	Normal

**Abbreviations:** SCD, sudden cardiac death; LAD, left atrial diameter; LVEDD, left ventricular end diastolic diameter; RAD, right atrial diameter; LVEF, left ventricular ejection fraction; EMG, electromyography; CK, creatine phosphokinase, (normal: 24–195 U/L); SB, sinus bradycardia; AVJEB, junctional escape rhythm; MPVB, multifocal ventricular premature beat; RBBB, right bundle branch block; Af, atrial fibrillation; AVB, atrioventricular block; AER, atrial escape rhythm; SA, sinus arrest; (-), absence; N/A, not available.



**Figure 3** Sequencing results of EMD mutation. (A) Image a shows results for a normal individual. Sanger sequencing demonstrated a duplication mutation (c.405dup) in exon 5 of EMD in the hemizygous individual (B) and the overlapping peaks in the heterozygous individual (C).



**Figure 4** Immunoblot and immunohistochemistry results revealed that EMD hemizygous individuals do not express emerlin protein. (A) Immunoblotting of emerlin protein (29 kDa) expression from total protein extracts of lymphocytes from the hemizygotes (III:5, IV:4, IV:29), heterozygotes (IV:11, IV:15, IV:20) and a normal control, with use of the emerlin monoclonal antibody. No emerlin protein bands were detected in the hemizygous patients. (B) Left panels, nucleus (Hoechst) staining (blue); middle panels, emerlin staining (green); right panels, merged emerlin and nucleus staining. Patients include a normal male control, heterozygote female (III:12) and a male hemizygote (III:5). Scale bar represents 50  $\mu$ m.

SCD in EDMD patients with reduced ejection fraction values<sup>19</sup> or with ventricular arrhythmias.<sup>20</sup> However, reports thus far may have been biased by cases of autosomal dominant disease.<sup>21–23</sup> In patients with Emery–Dreifuss and limb-girdle type 1B muscular dystrophies associated with *LMNA* mutations, sudden death is responsible for 30% of all deaths.<sup>23</sup> However, the incidence rate of SCD in EDMD1 is unknown because of the scarcity cases.<sup>18,24–26</sup> Therefore, the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death<sup>20</sup> considered that management of the rare X-linked recessive Emery–Dreifuss muscular dystrophy associated with mutations in the emerlin gene is complicated by a lack of clinical data; in the absence of gene-specific information, it seems reasonable to adopt the management strategy used in the dominant form of Emery–Dreifuss.

SCD is a leading cause of mortality, with an annual incidence of one death per 1000 person-years, affecting all ages.<sup>27</sup> However, no obvious extra-cardiac causes may be identified by post-mortem examination in some cases of SCD. Therefore, the identification of genetic factors that predispose these patients to SCD is important because this enables genetic testing that may contribute to diagnosis and risk stratification.<sup>28</sup> Currently, most studies have focused on genes that encode ion channels (*SCN5A*, *HCN4*, *KCNJ2*),<sup>29,30</sup> structural proteins (*LMNA*, *DES*, *JUP*), cardiac transcription factors (*NKX2-5*, *TBX5*), gap junctions (*Cx40*) and energy metabolism regulators (*PRKAG2*),<sup>28,31,32–34</sup> but few studies have selected *EMD* as a positional candidate gene for sequencing. Our findings provide a rationale for *EMD* mutation testing in cases of X-linked inherited CCD or SCD, even if pathognomonic neuromuscular features may not be obvious. Once an *EMD* mutation is identified, genetic testing should be offered to at-risk men and women. The mechanism by which the emerlin mutation causes sudden death is unclear. The presumed mechanism could be emerlin regulation of megakaryoblastic leukaemia 1 (MKL1)–serum response factor (SRF) activity.<sup>7</sup> MKL1 (also known as MAL or MRTF-A) is a mechano-sensitive transcription factor with important roles in the cardiovascular system.<sup>7</sup>

In conclusion, we identified a novel duplication mutation (c.405dup/p.Asp136X) in the *EMD* gene in a multi-generation Chinese family with EDMD1. The pedigree displayed an uncommon clinical presentation of serious cardiac conduction abnormalities at an early age and a



high incidence of SCD. This discovery expands the mutation spectrum of *EMD* and indicates the importance of *EMD* in SCD. Moreover, our study provides a rationale for *EMD* mutation testing in cases of X-linked inherited CCD or SCD, even if there is a lack of other obvious pathologic markers. However, the correlations between the gene mutation type and phenotype or observed clinical variability need further research.

## Statement Of Ethics

The patient (proband) provided written informed consent for the case details to be published. The study protocol has been approved by the research institute's committee on human research.

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## Disclosure

The authors report no conflicts of interest in this work.

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