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Case Report

New Deletion in *LAMP2* Causing Familial Danon Disease. Effect of X-Chromosome Inactivation

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Abstract

Danon disease (DD), a rare X-linked genetic illness with a poor prognosis, is caused by a mutation in the lysosome-associated membrane protein 2 gene (*LAMP2*). Three main clinical features of this pathology are cardiomyopathy, skeletal myopathy, and mental retardation. Most Danon disease mutations create premature stop codons resulting in the decrease or absence of *LAMP2* protein.

The present case reports the frameshift variant c.190_191delAC in the *LAMP2* in the family with sudden cardiac death history and three members with cardiomyopathy. The presenting phenotype in a female proband with c.190_191delAC was isolated dilated cardiomyopathy in her thirties whereas in two males, DD presented as hypertrophic cardiomyopathy and mild skeletal myopathy since childhood. To examine the contribution of X-inactivation to cardiomyopathy onset we estimated the X-inactivation status in the heart tissue of the affected female. We observed the random pattern (66:34) with the proportion of cardiomyocytes expressing healthy *LAMP2* allele reduced to 34%. Deletion c.190_191delAC has led to a complete loss of function *LAMP2* due to a single copy of this gene in males. In a woman, cardiomyopathy developed because of both the *LAMP2* mutation and a decrease in the expression of a healthy allele in the heart.

Based on the strong association of truncating *LAMP2* mutations with DD and phenotypes in affected members, the variant c.190_191delAC was classified as pathogenic.

Keywords

cardiomyopathy, chromosome X inactivation, Danon disease, *LAMP2*, lysosome-associated membrane protein 2

INTRODUCTION

Danon disease (DD), a rare X-linked genetic illness with poor prognosis, was described in 1981 by Danon. Three main clinical features of the pathology are cardiomyopathy, skeletal myopathy, and mental retardation.[1] DD is caused by loss-of-function mutations in the *LAMP2* gene (Xq24) that encodes for lysosome-associated membrane protein-2, lower levels of which causes autophagy disrupted. The clinical presentation is more problematic in males who are hemizygous for *LAMP2*. Women are usually affected but tend to have a milder and more variable phenotype than males.[2]

The prevalence of DD is unknown but is considered to

be less than one case per million.[3,4] According to the study of 50 pediatric patients with HCM, two cases of Danon disease (4%) were found.[5] The estimated prevalence of 1%–6% in patients with unexplained left ventricular hypertrophy (LVH) was reported.[6] The high prevalence of DD (12%) was found in young female patients with non-ischemic heart failure.[7]

In this study, we present a detailed clinical report on familial cardiomyopathy resulting from mutation c.190_191delAC firstly identified in the *LAMP2* gene. We compare cardiac phenotypes between family members and show the development of early cardiac dysfunction and hypertrophic cardiomyopathy in males. We demonstrate a critical decrease of healthy *LAMP2* allele expression in the female carrier heart due to X chromosome inactivation.

MATERIALS AND METHODS

Ethics statement

Informed consent was obtained from all participants and clinical surveillance and genetic investigations were performed in accordance with the recommendations of the local ethics committee of the Belarusian State Medical University and the Scientific Board of the Institute of Genetics and Cytology of the National Academy of Sciences.

CASE REPORT

A 34-year-old female patient with previous history of Caesarean section was admitted to the Scientific and Practical Center of Cardiology (Belarus) with symptoms of congestive heart failure (HF). During the last trimester of the her third pregnancy, she suffered from swelling, shortness of breath and weakness. Dilatation of the heart chambers and systolic left ventricular (LV) dysfunction were established. Her electrocardiogram (ECG) showed sinus tachycardia and pre-excitation with a positive delta wave in the inferior leads and negative T waves in the anterior leads. Chest X-ray revealed massive cardiomegaly. Transthoracic 2D-Echo study revealed global hypokinesia, severe LV systolic dysfunction and an ejection fraction of 30%. Coronary angiography was normal. Diagnosis of peripartum cardiomyopathy was made and the patient received standard heart failure treatment.

During the next few months after delivery despite the medical therapy, the patient developed progressive heart failure with symptoms consisting of decreased exercise capacity, tiredness, dyspnoea, orthopnoea, oedema, and palpitations. After 14 months, she was readmitted to the emergency department with acute heart failure, atrial and ventricular tachyarrhythmias. The patient ultimately underwent heart transplantation 5 weeks later.

The electrocardiogram showed atrial flutter, atypical left bundle branch block (LBBB) with pseudo-infarction signs of Sodi-Pollares (abnormal QS in leads I, aVL, V5-V6) ***(Fig.***

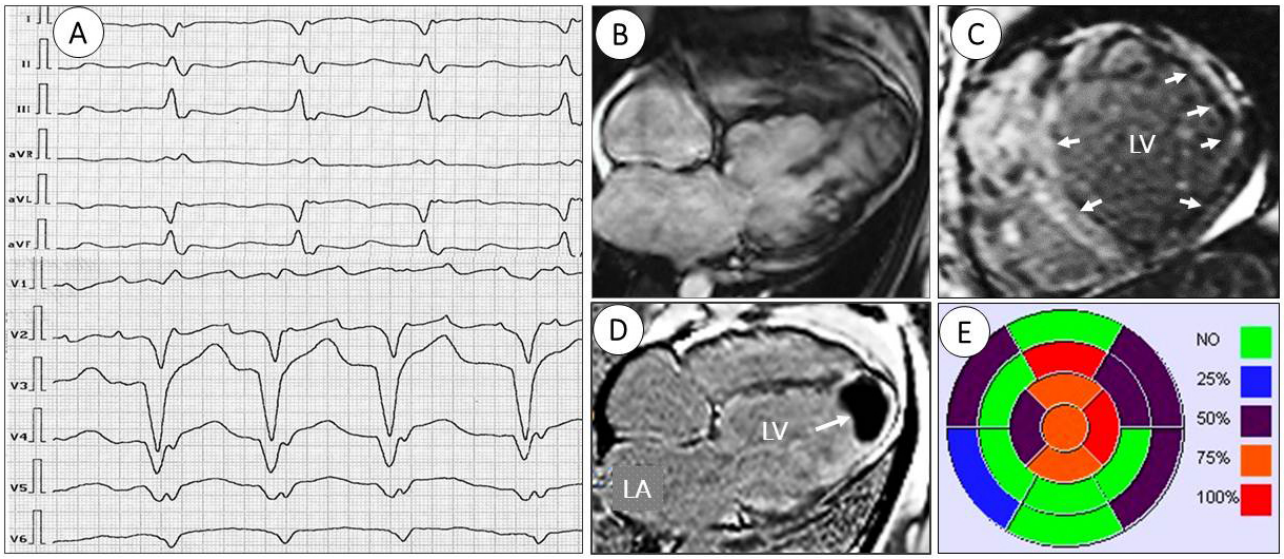

Figure 1. Cardiac anomalies identified in the proband. **A.** Electrocardiogram of the proband demonstrating atrial flutter, atypical left bundle branch block with pseudo-infarction signs of Sodi-Pollares (abnormal QS in leads I, aVL, V5-V6) and Cabrera sign (notch on the ascending S wave in lead V4 with a duration of 40 ms); **B.** Cardiac MRI plan the 4-chamber cine on the long axis image shows aneurysmal bulging of left ventricular apex with thrombus; **C.** T1-native mapping with signs of apical aneurysm and thrombus 34×27 mm; **D.** Late-gadolinium enhancement imaging on the short axis indicates presence of midwall myocardial contrast delay pattern with extensive linear fibrosis of left ventricular free wall, anterio-inferio-lateralis and septal myocardial scarring (arrowheads); **E.** Tissue LV characteristic: bull's eye map image demonstrates late gadolinium enhancement (short axis, 16 segments; grade 0-100%) a diffuse pattern of intramural and transmural fibrosis in the apex, anterior and anterolateral LV wall.

***1A)**. Cardiovascular magnetic resonance imaging revealed biventricular dilatation and systolic dysfunction (15% ejection fraction of both ventricles), apex aneurysm with thrombosis, multiple areas of late enhancement with extensive diffuse mid-myocardial pattern contrasting delay and transmural fibrosis in the anterior and anterolateral LV wall (calculated myocardial mass index 127 g/m^2). Expansive fibrotic changes in the dilated left ventricle are shown in* ***Figs 1B**-**E**.*

The neuromuscular examination revealed no specific abnormalities, especially no muscle weakness. Pertinent laboratory parameters included elevated lactate dehydrogenase (420 U/l; normal range, 120–250 U/l), elevated N-terminal pro b-type natriuretic peptide (16766 pg/ml; normal range, 0–450 pg/ml), elevated aspartate transferase (279 U/l; normal range, 13–35 U/l) and elevated γ-glutamyl transpeptidase (99 U/l; normal range, 7–45 U/l). All other serum parameters were normal as well as creatine phosphokinase. Genetic evaluation and cascade screening were proposed to the proband in that the family history construction showed a sudden cardiac death of her mother at the age of 30 years.

Molecular genetic analyses

DNA and RNA isolation

Genomic DNA from buccal cells was extracted by phenol/chloroform from all available family members and used for NGS and Sanger sequencing.

To measure X-chromosome inactivation status in the heart muscle, we isolated genomic DNA from the left ventricle sample of proband II-2 obtained from heart transplantation. DNA was extracted with Tri-Reagent according to the protocol of Sigma-Aldrich (USA). Total RNA from the control and patient's cardiac muscle was isolated using the Innu SPEED Tissue RNA Kit (Analytik Jena, Germany). RNA was reverse transcribed using ProtoScript II First Strand cDNA Synthesis Kit (New England Biolabs Inc.) and oligo-dT primers. RNA quality was analyzed by electrophoresis in 1% agarose gel and spectrophotometry.

DNA sequencing

We performed the NGS of the proband (II-2) using the TruSight Cardiomyopathy sequencing panel on the MiSeq System (Illumina Inc., USA). We estimated the quality control of raw NGS data with FASTQC, performed alignment using BWA against the reference genome NCBIbuild37 (UCSC hg19), generated the VCF with GATK4 HaplotypeCaller. Variants were annotated by ANNOVAR using dbSNP IDs, Exome Variant Server, The 1000 Genomes Browser, the Genome Aggregation Database, ClinVar and REVEL.

The Sanger sequencing was performed for variant confirmation and family genotyping. The exon 3 of *LAMP2* was amplified with designed primers (Supplemental Appendix 1) and FIREPol Master Mix (Solis BioDyne, Estonia), purified with ExS-Pure™ Enzymatic PCR purification kit (NimaGen B.V., The Netherlands) and directly sequenced using Big Dye Terminator v3.1 cycle sequencing kit and 3500 Genetic Analyzer (Applied Biosystems, USA).

XCI status measurement by the human androgen receptor (HUMARA) assay

XCI status was evaluated by the methylation of Hin6I sites in the androgen receptor gene (AR) in three independent experiments. This gene is reliably methylated when inactivated and correlated with X-chromosome inactivation. In brief, 2 mg DNA was digested with the methylation-sensitive endonuclease Hin6I in the final concentration 1U/nl (ThermoFisher, USA). Then the AR locus, containing (CAG)n repeat, was amplified both in digested and undigested DNA samples with primers, labeled with FAM (Primetech ALC, Belarus). The primer sequences and PCR-conditions were described previously.[8] PCR products were detected at 3500 Genetic Analyzer and visualized with the help of GeneMapper software (Applied Biosystems, USA). XCI status was estimated as the calculated ratio between peak areas of the AR alleles of digested and non-digested DNA. The same test was performed with the affected son's DNA obtained from buccal epithelium.

Quantitative real-time RT-PCR

To estimate the expression of healthy *LAMP2* allele in the proband II-2, we designed TaqMan assay specific for c.190_191delAC (NM_001122606.1) using Beacon Designer software (Bio-Rad Inc., USA) (Supplementary data, Table 1S). The MIF and B2M were selected as endogenous reference genes for comparative analysis of gene expression.[9,10] For relative quantification of *LAMP2* mRNA expression, we used RNA samples obtained from normal heart muscles of three females (40, 42, and 64 years old) as a control. Their tissue samples were taken during surgery for valve or septum correction. These women did not have dilated cardiomyopathy (DCM).

Statistical analysis

Relative quantification of *LAMP2* mRNA level between patient and controls was calculated by the ΔΔCt method.[11] Student's t-test determined the statistical significance to have a value of $p<0.05$, which was sufficiently significant.

The statistical analysis was performed to assess whether the heterozygotes with strongly inactivated healthy allele tended to have earlier cardiomyopathy manifestation than heterozygotes with weak inactivation of a healthy allele. Published data of the XCI ratio in females with *LAMP2* mutations were used to calculate Pearson correlation coefficients. The statistical significance was assessed through a confidence interval.

RESULTS

New truncating mutation c.190_191delAC identified in *LAMP2* gene

To detect the genetic reason for dilated cardiomyopathy in the proband, we performed NGS with the TruSight Cardiomyopathy sequencing panel, harboured 174 genes. A 2bp-deletion c.190_191delAC was identified in exon 3 of the *LAMP2* gene. It results in the frameshift, creating a premature stop codon at position 11 of the new reading frame, denoted p.Val64Asnfs*11. The total predicted length of truncated *LAMP2* protein is 74 amino-acid residues instead of 410. It means the protein lacks the transmembrane domain, cytosolic tail and most part of the luminal domain. Such rearrangement leads to loss of *LAMP2* function.

Family genotyping revealed that the proband's two sons have inherited c.190_191delAC variant. It results in the total absence of the native protein and early clinical phenotype in the boys. The family pedigree is shown in **Fig. 2**.

Males with c.190_191delAC show early cardiac phenotypes

ECG abnormalities as a high ECG voltage were observed in two sons with the mutation (III-2, III-3) at a very early age. One of them (III-3) didn't show any significant neuromus-

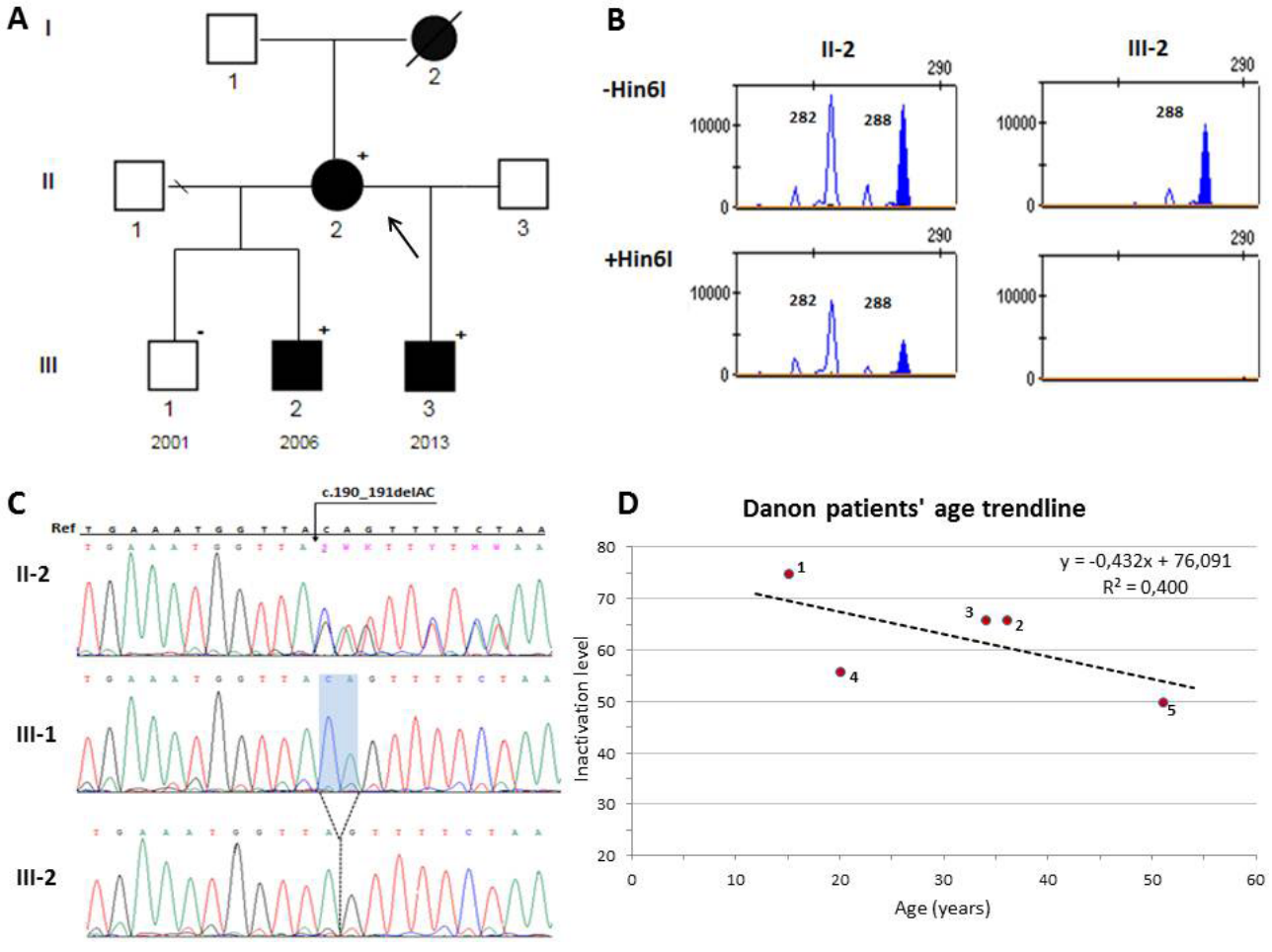

Figure 2. A. The family history reconstruction. The arrow denotes the proband. Symbols (+) and (-) indicate *LAMP2* mutation carriers and non-carriers, respectively. The absence of symbol denotes that no DNA was available for analysis. 2001, 2006, 2013 – years of birth; **B.** X-chromosome inactivation pattern in the proband (II-2; extracted from heart muscle) and affected son (III-2; extracted from buccal epithelium). Undigested (–Hin6I) and digested (+Hin6I) DNA samples are shown in the upper and lower plots respectively. The only 288-bp PCR fragment detected in the son (III-2) indicating the chromosome bearing c.190_191delAC. The absence of the corresponding peak area after Hin6I denoted that digestion of the active allele was sufficient; **C.** Mutation detection by DNA sequencing; **D.** Relationship between age of cardiomyopathy onset and inactivation level of a healthy allele in Danon patients. The single circles represent the data points, the line represents the quadratic trendline of the corresponding data set, and the numbers correspond to the cases in **Table 1.**

Table 1. Published data of XIC ratio in females with *LAMP2* mutations

No	Percentage of inactivated healthy allele	Age at cardiomyopathy diagnosis	Age at HT	Mutation	Method of XCI analysis	Reference
1	75 in heart 86 in WBCs	15 (HCM)	29	c.940delG, p.Ala314Glnfs*32	Flow cytometry	Majer et al.[12]
2	66 in skeletal muscle 60 in WBCs	36 (HCM)	52	294G>A, p.Try98*	HUMARA	Fanin et al.[13]
3	66 in left ventricle	34 (DCM)	37	c.190_191delAC, p.Val64Asnfs*11	HUMARA, RT-qPCR	This report
4	56 in left ventricle 61 in septum 38 in WBCs	20 (HCM)	23	c.453delT, p. Phe151fs	immune-histochemistry, HUMARA	Bottillo et al.[14]
5	50 in left ventricle	51 (DCM)	54	c.864+1G>A, p.Val248_Val288del	RT-qPCR	Sivitskaya et al.[15]
6	70 in WBCs	Asymptomatic at the age of 38	-	c.808dupG, p.Ala270Glyfs*3	HUMARA	Chen et al.[16]
7	57 in WBCs	25 (DCM)	28	c.445_449delGACCT, p.Asp149Phefs*2	HUMARA	Gurka et al.[7]
8	46 in WBCs	23 (DCM)	24	c.418delC, p.Leu139Phefs*8	HUMARA	Gurka et al.[7]
9	40 in WBCs	12 (HCD)	21	Deletion of exons 4-8 g.17916_29069del11154	HUMARA	Majer et al.[17]
10	30 in WBCs	11 (HCD)	-	Deletion of exons 4-9C g.19925_45401del25477	HUMARA	Majer et al.[17]
11	30 in WBCs 42 in buccal swabs 50 in urine 59 in hair follicles	Asymptomatic at the age of 41	-	Duplication of exons 4-5: g.15815_22218dup6404	HUMARA	Majer et al.[18]
12	20 in WBCs	16 (HCD)	27	c.718C>T, p.Gln240*	HUMARA	Gurka et al.[7]
13	18 in WBCs	Asymptomatic at the age of 60	-	c.277G>A, p.Gly93Arg	HUMARA	Xu et al.[19]

DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; HT: heart transplantation; HUMARA: human androgen receptor assay; WBCs: white blood cells.

cular involvement due to his young age. However, during the follow-up period, an elevated CK level was found (746 U/l; normal range, 24–124 U/l) and ambulatory HM study at 7 years of age demonstrated frequent premature ventricular contractions (PVCs) up to 6500 PVCs/24 h. He was symptomatic for palpitations and Echo confirmed the mild LV hypertrophy (LV septum thickness was 13 mm with absent LV outflow tract obstruction).

The older brother (III-2), who is mutation carrier as well, demonstrated an extreme high ECG voltage and pronounced left ventricular hypertrophy with deep negative T waves (**Supplementary data, Fig. 1S**). He had elevated levels of serum CK and liver ferments, mild proximal muscle weakness, learning disability and attention-deficit hyperactivity disorder. Abnormalities in laboratory parameters included serum alanine aminotransferase (93 U/l; normal range, 9–36 U/l), serum aspartate aminotransferase (115 U/l; normal range, 15–40 U/l), serum CK (945 U/l; normal range, 24–124 U/l), serum isoenzyme CK (56 U/l; normal range, 0–24 U/l), and serum γ-glutamyl transpeptidase (72 U/l; normal range, 7–45 U/l). The chest X-ray revealed mild cardiomegaly. Echo showed LV hypertrophy with speckles in the myocardium and good contractility (calculated indexed mass was 159 g/m^2, maximum septal thickness 17

mm). Cardiac MRI revealed asymmetric LV hypertrophy with papillary muscle and septum hypertrophy, fibrosis of the anterolateral papillary muscle and LV anterolateral segments of the apex with local increase in T1- native mapping **(Supplementary data, Fig. 1S)**. Their clinical data at different ages are presented in **Table 2.**

Except for the XCI process, other factors could affect the in vivo allelic expression of X-linked gene.[20] To evaluate *LAMP2* mRNA expression, we performed quantitative real-time RT-PCR (RT-qPCR) and obtained similar results. Comparing to controls, the expression level of healthy *LAMP2* allele was ~70% lower in the proband II-2 than in

Table 2. Evolution of clinical phenotypes in affected family members with c.190_191delAC

Parameter	Proband, female (II-2)		Child, male (III-2)		Child, male (III-3)	
Age, years	34	36	10	14	3	7
Cardiomyopathy	DCM	DCM	N	HCM	N	HCM
Left ventricular end-diastolic volume / BSA, ml/m^2	158	203	62	78	37	47
Intraventricular septal diameter diastole, mm	10	9	12	17	6	13
Left ventricular ejection fraction, %	30	15	70	74	71	73
Calculated myocardial mass index, g/m^2	111	127	93	159	56	92
Creatine kinase level, muscle soform	N	N	↑	↑	↑	↑
Arrhythmia	WPW, SVT	AF, PVCs, nsVT	N	PVCs (546/24h)	PVCs (354/24h)	PVCs (6457/24h)
Heart transplantation, age	-	36	-	-	-	-
Skeletal myopathy	N	N	N	+ (mild)	N	+ (mild)
Developmental delay	N	N	N	+ (mild)	N	N

↑: elevated; +: present; N: negative or normal; BSA: body surface area; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; AF: atrial flutter; nsVT: non-sustained ventricular tachycardia; SVT: supraventricular tachycardia; PVCs: premature ventricular contractions; WPW: Wolff-Parkinson-White syndrome

Decrease of healthy *LAMP2* allele expression in the heart leads to cardiac phenotype in a female

To assess the portion of cardiomyocytes expressing healthy *LAMP2* allele, we measured X-chromosome inactivation in heart muscle of proband II-2 **(Fig. 2)**. The plots indicate a quantitative measure of the fluorescent PCR products. The AR gene amplification of undigested genomic DNA identified the woman as heterozygote of CAG-repeat: 282 and 288 bp fragments in equal proportion. After Hin6I-digestion and following AR-amplification the peak areas were decreased according to the methylated status of the gene. As a result, we observed random X-inactivation at 66:34 ratio. It means that the proportion of cells expressing healthy *LAMP2* allele of the X-chromosome (282 bp) was reduced to 34%.

control subjects (0.31±0.04, p<0.05). It means, only one-third of *LAMP2* transcripts can be translated into the native protein. We did not observe the skewed XCI in proband II-2, but the obvious decrease of healthy allele expression in the heart led to severe cardiac phenotype.

We found 13 detailed reports of DD cases published until January 2021 where XCI status was measured **(Table 2)**. Of note, the XCI ratio was variable in different tissues: the X-inactivation in urine, hair follicles, buccal swabs and leucocytes did not correspond to that in affected tissues (heart, skeletal muscles). To assess the relation between XCI pattern and age of cardiomyopathy onset, we considered only cases where XCI was measured in skeletal or cardiac muscles (n=5). We had to exclude from analysis asymptomatic persons as well because it is possible that they will develop symptoms in the future. Despite these limitations, we have attempted to evaluate the relationship between the XCI and

age of cardiomyopathy onset and found a visible inverse linear correlation **(Fig. 2D)**. Women with strongly inactivated healthy X-chromosome had earlier *LAMP2*-cardiomyopathy manifestation compared with weak inactivation. Nevertheless, the Pearson correlation coefficient was statistically insignificant -0.63, CI 95% [-0.97:0.56].

DISCUSSION

We identified a new *LAMP2* variant in a family with a history of heart failure and described disease variability and outcomes in three affected members. The variant c.190_191delAC leads to severe morbidity for male and female carriers and can be classified as pathogenic according to the criteria reported by Richards et al.[21] In the presented case the affected woman (II-2) has only cardiac involvement manifested as phenocopy of dilated cardiomyopathy in her thirties. The search for a causal variant by NGS led to the identification of new *LAMP2* mutation and correction of the initial diagnosis for Danon disease. This pathology often stays unrecognized in women due to the absence of the specific signs. Because females have two X chromosomes, they have a milder and more variable phenotype than males. The onset of DD is in late adulthood and shows a slower progression. In the observed family, the presenting phenotype in the female proband was dilated cardiomyopathy in her thirties, whereas her two sons had hypertrophic cardiomyopathy since their childhood. As is expected, the clinical picture for the sons does not promise an optimistic scenario.

Like many other X-linked diseases, the severity of DD in females depends on XCI status in affected tissues. However, the data on the impact of XCI on Danon phenotype published until today is limited **(Table 2)**. We consider it is important to collect data about the DD onset and XCI status in women. This must have prognostic significance, especially in families where several female members carry *LAMP2* mutation. In the case published by Arad et al.[22], seven women with the pathogenic *LAMP2* variant have been reported in the same family. Six of them were asymptomatic at the age of 14–49 years at the moment of publication, while one woman died from congestive heart failure at 44 years. This variability can be explained by the different degrees of the mutant X chromosome inactivation: more in asymptomatic members and less in a deceased woman. Moreover, DD cannot be excluded in young asymptomatic females in their future life. Disease development prognosis is required for such families.

We have attempted to evaluate the relationship between the XCI in muscle and cardiomyopathy onset as the main life-threatening symptom. The limited data did not allow us to demonstrate the reliable linear correlation. But these results reveal the need for further investigation of tissue-specific XCI and clinical outcomes in female DD patients.

Unfortunately, the XCI status in blood cells as the most available tissue is not appropriate for DD prognosis. The XCI pattern is specific to tissue or organ compartments where clinical features are observed – heart, skeletal muscle and brain. Since the heart tissue is often unavailable for investigation, the severity of cardiac phenotypes in women with *LAMP2* mutations remain difficult to predict.

In conclusion, the 2bp-deletion c.190_191delAC in *LAMP2* was identified in the family with sudden cardiac death history and three members with cardiomyopathy. Based on the strong association of truncating *LAMP2* mutations with Danon disease and clinical phenotypes observed in carriers, c.190_191delAC can be classified as pathogenic. In males it led to completely lost of function *LAMP2* due to a single copy of this gene. In a woman, cardiomyopathy developed because of both the *LAMP2* mutation and a decrease in the expression of a healthy allele in the heart.

Appendix A. Supplementary data

Table 1S. Specification of LAMP2 primer and probe sequences

Primer name	Binding site position	Sequence (5'-3')	product length, bp
Primers used for Sanger sequencing of exon 3 (refer to NM_007995.1)			
LAMP2 (3F)	19116-19135	GGGGTCAGTGGGAGGGTTAT	490
LAMP2 (3R)	18646-18665	CACAGCAAACCAGGCAAAGG	
TaqMan assay for exon 3 of *LAMP2* (refer to NM_001122606.1)			
F(LAMP2_ex3)	284-303	ATTCAGAAAATGCCACTTGC	146
R(LAMP2_ex3)	411-430	TCTGATCATCCCCACAAATG	
Probe (LAMP2_ex3)	359-385	FAM-CTTATAAAACTGTAACCATTTCAGACC-BHQ1	

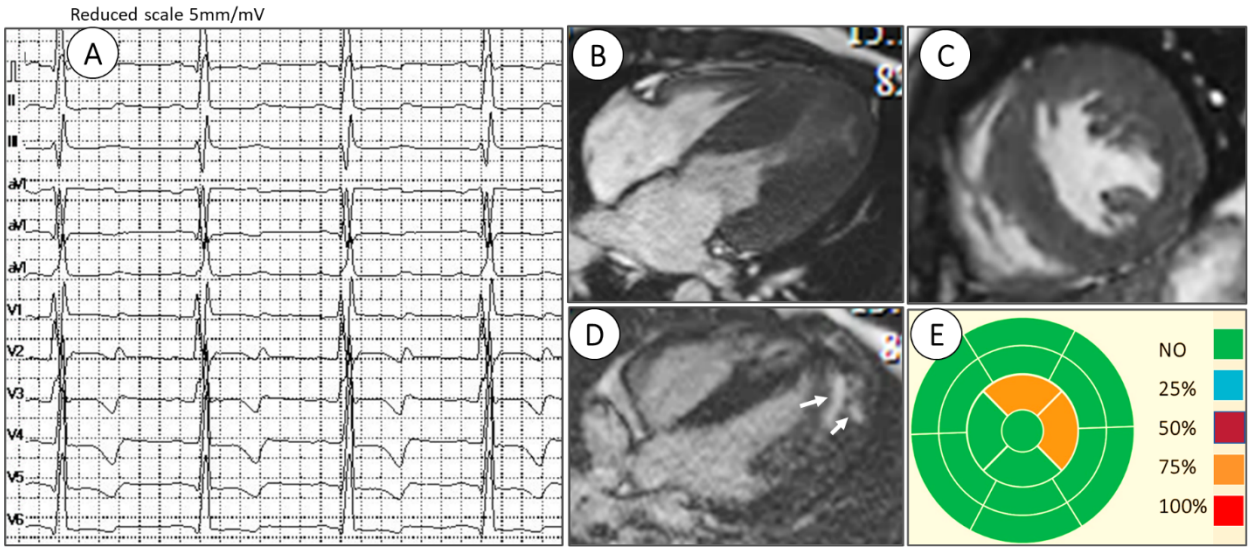

Figure 1S. Cardiac abnormalities in carrier (III-2) *LAMP2* mutation: **(A)** Patient's ECG is registered at age 14, showing normal sinus rhythm, LV hypertrophy and prominent T wave inversion in leads I, V3-V6; **(B)** Cardiac MRI plan the 4-chamber cine on the long axis image shows LV hypertrophy (maximum septal thickness 17 mm); **(C)** Cardiac short-axis orientation with two-chamber view image of LV hypertrophy; **(D)** Late-gadolinium enhancement imaging on the long axis indicates presence of midwall myocardial contrast delay pattern with fibrosis of the anterolateral papillary muscle and anterolateral segments of the LV apex (arrowheads); **(E)** Tissue LV characteristic: bull's eye map image demonstrates late gadolinium enhancement (short axis; grade 0-100%).

Author contributions

L.S. and T.V. - study design, manuscript preparation; T.V. - clinical investigations, L.S. and A.L. - NGS data and mutation analysis; N.D., O.D., and N.Z. - data interpretation and manuscript editing.

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Competing Interests

The authors have declared that no competing interests exist.

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Новая делеция в *LAMP2*, связанная с семейным случаем болезни Данона. Эффект инактивации Х-хромосомы

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Резюме

Болезнь Данона (БД) - редкое Х-сцепленное заболевание с плохим прогнозом. Развитие болезни связано с мутациями в гене лизосома-ассоциированного мембранного протеина 2 (*LAMP2*). Тремя основными клиническими признаками этой патологии являются кардиомиопатия, скелетная миопатия и умственная отсталость. Большинство мутаций, связанных с болезнью Данона, образуют преждевременные стоп-кодоны, что приводит к снижению количества или полному отсутствию белка *LAMP2*.

В статье описан вариант сдвига рамки считывания c.190_191delAC в *LAMP2*, выявленный в семье с внезапной сердечной смертью в анамнезе и кардиомиопатией у трёх её членов. У женщины-пробанда вариант c.190_191delAC вызвал развитие изолированной дилатационной кардиомиопатии в возрасте 30 лет, тогда как у двух членов семьи мужского пола БД проявилась гипертрофической кардиомиопатией и лёгкой скелетной миопатией в детском возрасте.

Чтобы изучить роль инактивации Х-хромосомы в развитии кардиомиопатии, мы оценили статус Х-инактивации в сердечной ткани пробанда. Мы наблюдали случайный паттерн (66:34) с уменьшением доли кардиомиоцитов, экспрессирующих нормальный аллель *LAMP2*, до 34%.

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Делеция c.190_191delAC привела к полной потере функции *LAMP2* у мужчин из-за единственной копии этого гена. У женщины кардиомиопатия явилась результатом как самой мутации в *LAMP2*, так и снижением экспрессии нормальной копии гена в сердце. На основании явной ассоциации мутаций, приводящих к образованию усеченного белка *LAMP2*, с БД и специфичных фенотипов у трёх членов семьи, вариант c.190_191delAC был классифицирован как патогенный.

Ключевые слова

кардиомиопатия, инактивация X-хромосомы, болезнь Данона, LAMP2, лизосома-ассоциированный мембранный белок 2