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

Larysa Sivitskaya¹, Tatiyana Vaikhanskaya², Nina Danilenko³, Aleh Liaudanski³, Oleg Davydenko³, Nikolai Zhelev⁴,⁵

¹ Genomed Health Care Centre, Diagnostic Department, Warsaw, Poland
² Republican Scientific and Practical Center of Cardiology, Minsk, Belarus
³ Institute of Genetics and Cytology, National Academy of Sciences, Minsk, Belarus
⁴ University of Dundee, Dundee, United Kingdom
⁵ Medical University of Plovdiv, Plovdiv, Bulgaria

Corresponding author: Larysa Sivitskaya, Genomed Health Care Centre, Diagnostic Department, Warsaw, Poland; Email: lsivitskaya@yahoo.com; Tél.: +375-293-88-52-59

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

In this study, we present a detailed clinical report on familial cardiomyopathy resulting from mutation c.190_191delAC firstly identified in the \textit{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 \textit{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 Cesarean 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. 1).
Cardiovascular magnetic resonance imaging revealed biventricular dilatation and systolic dysfunction (15% ejec-
tion fraction of both ventricles), apex aneurysm with throm-
bosis, multiple areas of late enhancement with extensive
diffuse mid-myocardial pattern contrasting delay and trans-
mural fibrosis in the anterior and anterolateral LV wall (cal-
culated myocardial mass index 127 g/m2). Expansive fibrotic
changes in the dilated left ventricle are shown in Figs 1B-E.

The neuromuscular examination revealed no specific ab-
normalities, especially no muscle weakness. Pertinent labo-
atory 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; nor-
mal range, 13–35 U/l) and elevated γ-glutamyl transpep-
tidase (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
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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-
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 аalanine 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/m², maximum septal thickness 17

| 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.
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. 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 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.

| Parameter | Proband, female (II-2) | Child, male (III-2) | Child, male (III-3) |
|-----------|------------------------|---------------------|---------------------|
| Age, years | 34                     | 36                  | 10                  |
| Cardiomyopathy | DCM | DCM | N | HCM |
| Left ventricular end-diastolic volume / BSA, ml/m² | 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/m² | 111    | 127    | 93      | 159   | 56    | 92    |
| Creatine kinase level, muscle soform | N      | N      | ↑       | ↑     | ↑     | ↑     |
| Arrhythmia | WPW, SVT | AE, 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%.
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 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 | CACAGCAAAACCAGGCAAAGG | |
| **TaqMan assay for exon 3 of LAMP2** (refer to NM_001122606.1) | | | |
| F(LAMP2_ex3) | 284-303 | ATTCAGAAAATGCCACTTGC | |
| R(LAMP2_ex3) | 411-430 | TCTGATCATCCCCACAAATG | 146 |
| Probe (LAMP2_ex3) | 359-385 | FAM-CTTATAAAACTGTAACCATTTCAGACC-BHQ1 | |
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 X-хромосомы

Лариса Сивицкая1, Татьяна Вайханская2, Нина Даниленко3, Олег Левданский3, Олег Давыденко3, Николай Желев4,5

1 Медицинский центр „Геномед”, Диагностическое отделение, Варшава, Польша
2 Республиканский научно-практический центр „Кардиология”, Минск, Беларусь
3 Институт генетики и цитологии НАН, Минск, Беларусь
4 Университет Данди, Данди, Великобритания
5 Медицинский университет – Пловдив, Пловдив, Болгария

Адрес для корреспонденции: Лариса Сивицкая, Медицинский центр „Геномед”, Диагностическое отделение, Варшава, Польша; Email: lsivitskaya@yahoo.com; Тел.: +375-293-88-52-59

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Резюме

Болезнь Данона (БД) - редкое X-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 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 гипертрофическая кардиомиопатия и лёгкой скелетной миопатией в детском возрасте.

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