Autosomal dominant Emery-Dreifuss muscular dystrophy caused by a mutation in the lamin A/C gene identified by exome sequencing: a case report

Kristy Iskandar1*, Sunartini1, Farida Niken Astari2, Rizki Amalia Gumilang3, Nissya Ilma4, Ni Putu Shartyanie4, Guritno Adistyawan5, Grace Tan6, Gunadi7 and Poh San Lai6

Abstract

Background: Emery-Dreifuss Muscular Dystrophy (EDMD) is an uncommon genetic disease among the group of muscular dystrophies. EDMD is clinically heterogeneous and resembles other muscular dystrophies. Mutation of the lamin A/C (LMNA) gene, which causes EDMD, also causes many other diseases. There is inter and intrafamilial variability in clinical presentations. Precise diagnosis can help in patient surveillance, especially before they present with cardiac problems. Hence, this paper shows how a molecular work-up by next-generation sequencing can help this group of disorders.

Case presentation: A 2-year-10-month-old Javanese boy presented to our clinic with weakness in lower limbs and difficulty climbing stairs. The clinical features of the boy were Gower’s sign, waddling gait and high CK level. His father presented with elbow contractures and heels, toe walking and weakness of limbs, pelvic, and peroneus muscles. Exome sequencing on this patient detected a pathogenic variant in the LMNA gene (NM_170707: c.C1357T: NP_733821: p.Arg453Trp) that has been reported to cause Autosomal Dominant Emery-Dreifuss muscular dystrophy. Further examination showed total atrioventricular block and atrial fibrillation in the father.

Conclusion: EDMD is a rare disabling muscular disease that poses a diagnostic challenge. Family history work-up and thorough neuromuscular physical examinations are needed. Early diagnosis is essential to recognize orthopaedic and cardiac complications, improving the clinical management and prognosis of the disease. Exome sequencing could successfully determine pathogenic variants to provide a conclusive diagnosis.

Keywords: Emery-Dreifuss muscular dystrophy, Exome sequencing, Laminopathies, LMNA, Case report
EDMD is the presence of contracture in the neck, elbow, and heels in the patient or their relatives [3]. Mutation of the Lamin A (LMNA) gene that encodes lamin A/C protein, which causes EDMD, also causes a wide range of other diseases [4]. Thus, the overlapping genotype and phenotype similarities with other muscular dystrophies present diagnostic challenges. A precise diagnosis of EDMD is vital because the disease is associated with life-threatening cardiac conditions. Patients have clinical variabilities in disease progression, life expectancies, and prognoses. Hence genetic counselling is essential for affected families once the disease has been diagnosed conclusively.

**Case presentation**

A 2 year-10-month-old male boy of Javanese descent presented to Universitas Gadjah Mada Academic Hospital with weakness of the lower limbs. The boy had an unremarkable birth history from nonconsanguineous parents (Fig. 1). There was no cognitive impairment, no seizure, visual or auditory impairment, and no bowel or bladder dysfunction. He walked at 12 months. Other developmental milestones were also unremarkable. He was vaccinated for age-appropriate immunizations according to the national immunization program guidelines.

The patient was conscious and afebrile on physical examination with no tachycardia or facial dysmorphic features. There was weakness in the proximal of the upper limbs and distal in the lower limbs. Facial weakness was not detected. No obvious calf pseudohypertrophy and no ankle joint contracture were observed (Fig. 2a). Follow-up at six years old, the patient presented wasting in the upper arm, Achilles contracture, and limitation of neck flexor because of neck contractures (Fig. 2b).
strength examination was 4/5 on the upper and 4/5 on the lower limbs, with no cervical weakness. Swaying movements were present on walking. No toe walking was observed. The sensitivity of all digits was intact. Tendon and cutaneous reflexes were normal. He could walk without support, and the Gower sign was positive. The cardiorespiratory examination was unremarkable. No medical treatment had been given.

Laboratory examinations showed an increased creatine kinase (CK) level of 2485 UI/L, increased LDH level at 1078 U/L, haemoglobin count of 11.6 g/dl, white blood cell count of 9200 cells/μL and normal transaminase level. ECG showed no abnormality of conduction with normal p waves. Echocardiography showed normal structure and function of the heart. Significantly, the patient had no cardiac symptoms at this point.

Investigation revealed that was no family history of members except for the father. History taking revealed the father presented with motoric disturbances and was diagnosed with acute flaccid paralysis at eight years old. He started toe walking and could not raise his hands against gravity since he was eight years of age, and there was no history of fever. At the time of the clinical presentation, he was easily exhausted and had difficulty climbing stairs. No shortness of breath and no swelling of the feet were found. On physical examination, there was no facial weakness. He could not bend his neck downwards nor sidewardly. He had profound contractures of the elbow and heels (Fig. 3). Muscle wasting and weakness were found in scapulohumeroperoneal regions, with no contractures of fingers. He had decreased physiological reflex and no pathological reflex. Lordosis and scoliosis were detected. He has swaying and tiptoeing in his walk. He could ride a motorcycle by himself and was capable of performing his normal occupation. The father had increased CK level at 518 UI/L, but other blood results were within normal limits. Based on the clinical features, we suspected this was a case of EDMD with a differential diagnosis of limb-girdle muscular dystrophy. No NCS-EMG and MRI findings were available of the patient and the father as they did not consent to these procedures.

Exome sequencing was carried out on Illumina Hiseq 4000 platform (Illumina, San Diego, CA) at a mean read depth of 100x. Genomic DNA libraries were prepared by Agilent SureSelect Human All Exon V5 Kit (Agilent Technologies, Santa Clara, CA) following the manufacturer’s protocol and sequenced through our laboratory at the National University of Singapore [4]; heterozygous variant involving a C to T transition in exon 7 of the LMNA gene (NM_170707: c.C1357T) was found (Fig. 4a). This variant leads to a missense mutation, Arg453Trp (R453W), that was previously reported to cause Autosomal Dominant EDMD. This variant was validated by Sanger sequencing in the patient. Targeted screening of this variant showed presence in the father, confirming this as a familial mutation (Fig. 4b). The variant was also classified as pathogenic based on the ACMG curation guidelines.

Knowing the EDMD phenotypes, we further examine the cardiac function of the father. Electrocardiography showed bradycardia with a heart rate of 40–50 bpm and total atrioventricular block with atrial fibrillation (Fig. 5). Echocardiography showed hypokinetic and dilatation of heart muscles, also thrombus suspicion in the left ventricle. Sinus node dysfunction was suspected; thus, atrioventricular block medication was administered. The cardiologist planned for urgent permanent pacemaker placement and further management of cardiomyopathy.

**Discussion and conclusion**

Although initially grouped together with the other X-linked muscular dystrophies, most notably the dystrophinopathies forms, EDMD has become accepted as a separate and distinctive type after a thorough clinical evaluation of patients. A triad of presentations characterizes the disease course. The first two characteristic features are the weakness of the proximal muscle in childhood which initially affects the lower extremities, along with elbow flexion contractures and shortening of the Achilles tendon, consequently generating toe walking. Adults with EDMD manifest a waddling gait, lardotic stance and absence of the deep tendon reflexes. The third characteristic consists of arrhythmias, ranging from junctional rhythm (atrial standstill) to atrial fibrillation and even sudden cardiac death [5].
The serum CK level among the affected family members is also increased, although not in the similar range as in DMD or BMD. Other critical differences compared to DMD/BMD are the absence of developmental delay or the calf pseudohypertrophy. In 1966, this disease entity was differentiated and is currently known as X-linked EDMD [6].

EDMD creates a diagnostic challenge due to its similarities in the clinical presentation and laboratory findings with other muscular dystrophies. However, early diagnosis is crucial to prevent early mortality and morbidity from cardiac complications and muscular contractures. It is also essential to provide genetic screening for family members of the patients to determine risk.

In neuromuscular disorder, a nerve conduction study with electromyography is essential to determine which structure is involved. As contracture or spasticity with weakness can be part of an upper motor neuron involvement, an MRI to rule out a central affection or an NCS-EMG with a myopathic pattern to support EDMD may be necessary to support their diagnosis [7]. Moreover, because the father had acute flaccid paralysis since he was eight years old, it is suggested that Charcot Marie Tooth (CMT) should be ruled out by NCS-EMG as some
Table 1  Phenotype presentations of EDMD that are reported to be associated with R453W

| Age (y.o) | Sex | Onset (Age) | Inheritance | Phenotype | Cardiac | Ref |
|-----------|-----|-------------|-------------|-----------|---------|-----|
| 8         | F   | 2y          | De Novo     | Ankle contracture | Sinus arrhythmia | Fan et al. [13] |
| 4         | M   | 2y          | De Novo     | Ankle contracture | Normal | Fan et al [13] |
| 14        | F   | 4y          | De Novo     | Ankle contracture, scoliosis | Sinus tachycardia | Fan et al [13] |
| 8         | M   | 2y          | De Novo     | Elbow & ankle contractures | Normal | Fan et al [13] |
| 54        | F   | N/A         | N/A         | Muscle weakness and contractures | Dilated cardiomyopathy, conduction disease | Bernasconi et al. [14] |
| 21        | F   | N/A         | N/A         | Muscle weakness and contractures | Dilated cardiomyopathy, conduction disease | Bernasconi et al. [14] |
| 4         | M   | 2y          | De Novo     | Proximal lower limb weakness, both sides of ankle contractures | Normal | Lin et al. [14] |
| 14        | F   | 4y          | De Novo     | Proximal and distal lower limb weakness, spine and both sides of ankle contractures | Tachycardia, ultrasonic cardiogram is normal | Lin et al. [15] |
| 3         | F   | 1y          | De Novo     | LGMD, proximal lower limb weakness, both sides of ankle contractures | Normal | Lin et al. [15] |
| 29        | M   | 4y          | De Novo     | Weakness in both legs, slow gait, ankle contracture, stiff neck, scoliosis | AV block I | Lee et al. [16] |
| 46        | M   | N/A         | AD          | Wasting and weakness of the proximal muscles, mild Achilles and elbow contractures, slight spine rigidity, lumbar hyperlordosis | AV block III, AFib, SVT, Hypokinesia of IVS and anterior wall of LV, EF 15%, pacemaker | Madej-Pilarczyk et al. [8] |
| 36        | M   | N/A         | AD          | Contracture, spine rigidity | SVEB, SVT, VEB, AV Block 1, ICD | Niebroj-Dobosz et al. [16] |
| 44        | M   | N/A         | AD          | Contracture, spine rigidity | AV Block 1,2,3, atrial standstill, nsVT, EF 36%, Pacemaker, ICD | Niebroj-Dobosz et al. [17] |
| 21        | F   | N/A         | AD          | Contracture, spine rigidity | SVEB, SVT, ICD | Niebroj-Dobosz et al. [17] |
| 34        | M   | 8y          | AD          | Slowly progressive humero-peroneal muscular weakness. Rigid spine, elbow and Achilles contractures | AV Block III, pacemaker at age 31; died at age 34 of heart failure; | Meinke et al. [18] |
| 37        | N/A | N/A         | N/A         | LGMD, contractures | Afib | Magagnotti et al. [18] |
| 24        | M   | N/A         | AD          | Mild proximal weakness. Neck and heel cord contractures | Echocardiogram shows mildly enlarged left atrium and ventricle, mild global hypokinesia and reduced systolic function, estimated LVEF 45% | Scharner et al. [19] |
| 36        | M   | N/A         | N/A         | EDMD phenotype | First degree heart block | Scharner et al. [19] |
| 32        | M   | N/A         | De Novo     | Limb-girdle, proximal, upper, distal lower muscle. Neck, elbow, ankle, knee contractures | Beta blockers at age 22, pacemaker at age 32 | Scharner et al. [19] |
| 19        | M   | 4y          | De Novo     | Limb-girdle, proximal, upper, distal lower muscle. Neck, elbow, ankle contractures | Normal | Scharner et al. [19] |
| 28        | F   | 6y          | AD          | Leg weakness (footdrop like gait). Elbow contracture | EMG-diffuse myopathic process; cardiac involvement | Scharner et al. [19] |
| 7         | M   | 3y          | De Novo     | LGMD, proximal lower extremity weakness, hip contractures | Normal | Scharner et al. [19] |
| 32        | N/A | 4y          | De Novo     | No loss of ambulation | N/A | Deconinck et al. [20] |
| 42        | N/A | 2y          | De Novo     | Loss of ambulation | N/A | Deconinck et al. [20] |
| 27        | N/A | 1y          | AD          | No loss of ambulation | N/A | Deconinck et al. [20] |
| 4         | F   | 2y          | AD          | Proximal limb muscle weakness, lordosis, calf hypertrophy | Normal | Park et al. [21] |
### Table 1 (continued)

| Age (y.o) | Sex  | Onset (Age)     | Inheritance | Phenotype                                      | Cardiac                                           | Ref                          |
|-----------|------|-----------------|-------------|------------------------------------------------|--------------------------------------------------|------------------------------|
| N/A       | F    | 10y             | AD          | Generalized muscle atrophy, spine rigidity, and spine, elbow, knee, ankle contractures | SVEB, SVT                                        | Niebroj-Dobosz et al. [22]   |
| 1 patient | N/A  | N/A             | N/A         | Proximal limb weakness without joint contracture, LGMD 1B | Cardiomyopathy with conduction defect in 34 yo patient | Astejada et al. [23]         |
| 5 patients| N/A  | N/A             | N/A, AD     | Joint contractures. 2 patients have rigid spine syndrome. 1 patient has humeroperoneal muscle involvement with Achilles and elbows contractures, and hind neck |                                                    | Astejada et al. [23]         |
| 47        | F    | N/A             | AD          | N/A                                            | Afb, ICD                                          | Golzi [24]                   |
| 49        | M    | 6y              | De novo     | Elbows and achilles contractures, rigid spine   | Afb with appropriately functioning VVIR, Pacemaker| Sanna et al. [25]           |
| 16        | NA   | N/A             | N/A         | Shoulder, hip, elbow, ankle, rigid spine contractures | None                                             | Vytopil, et al. [26]        |
| 10        | NA   | N/A             | AD          | Rigid spine                                    | None                                             | Vytopil, et al. [26]        |
| 46        | NA   | N/A             | N/A         | Rigid spine, axial and proximal myopathies     | Conduction defects, pacemaker                     | Vytopil, et al. [26]        |
| 15        | F    | 2y              | AD          | Proximal weakness. elbow, ankle contractures, mild neck stiff, rigid spine | Normal                                           | Colomer et al. [27]         |
| 12        | F    | 2y              | AD          | Proximal weakness. elbow, ankle contractures, slight neck stiff, rigid spine | Normal                                           | Colomer et al. [27]         |
| 46        | F    | 7y              | De novo     | Proximal weakness. elbow, ankle contractures, stiff neck rigid spine, wheelchair bound 44 years | AV Block 26 y, pacemaker 31 y                     | Colomer et al. [27]         |
| 38        | M    | Childhood       | AD          | Limb girdle, upper, proximal, distal, lower muscle weakness. elbow and neck contractures | Pacemaker                                        | Bower et al. [28]           |
| 33        | M    | N/A             | AD          | Muscle weakness, distal wasting, rigid spine, Achilles contractures and sometimes elbows | Arrhythmia                                       | Sewry, et al. [29]          |
| 35        | M    | N/A             | AD          | Muscle weakness, distal wasting, rigid spine, Achilles contractures and sometimes elbows | Arrhythmia                                       | Sewry, et al. [29]          |
| 10 months | M    | N/A             | AD          | Normal                                          | Arrhythmia, ventricular dysfunction              | Sewry, et al. [29]          |
| 17        | M    | N/A             | AD          | Ventricular dysfunction                        | Arrhythmia, ventricular dysfunction              | Sewry, et al. [29]          |
| 19        | NA   | 3y              | De Novo     | Both arms wasting, stiff neck, elbow, hip, Achilles contractures | Arrhythmia, ventricular dysfunction              | Bonne, et al. [30]          |
| 33        | N/A  | 8y              | De Novo     | Humeroperoneal wasting, elbow, hip, Achilles contractures, stiff neck, rigid spine, kyphosis | Pacemaker                                        | Bonne, et al. [30]          |
| 39        | M    | 4y              | AD          | Mild proximal wasting, elbow, hip, Achilles contractures, stiff neck, rigid spine, scoliosis | Arrhythmia, normal echocardiography              | Bonne, et al. [30]          |
| 40        | M    | 5y              | AD          | Proximal wasting, scapular winging, elbow, hip, Achilles contractures, stiff neck, rigid spine, scoliosis | Arrhythmia normal echocardiography              | Bonne, et al. [30]          |
| 9         | M    | 3y              | AD          | Scapuloperoneal wasting, elbow, Achilles contractures, stiff neck, rigid spine | Normal                                           | Bonne, et al. [30]          |
| 7         | F    | 4y              | AD          | Scapuloperoneal wasting, elbow, achilles contractures, stiff neck, rigid spine | Normal                                           | Bonne, et al. [30]          |
| 49        | M    | N/A             | De Novo     | Atypical EMD                                    | Pacemaker, Restrictive cardiomyopathy, died et causa cardiac arrest | Di Barletta et al. [31]     |
| 39        | M    | N/A             | X-linked    | X-EMD or Rigid Spine Syndrome                   | Pacemaker                                        | Di Barletta et al. [31]     |
| 42        | M    | N/A             | X-linked    | X-EMD or Rigid Spine Syndrome                   | Tachyarrhythmia and AV block                     | Di Barletta et al. [31]     |
| 21        | M    | N/A             | X-linked    | X-EMD                                           | None                                             | Di Barletta et al. [31]     |
of CMT’s variants were thought to be due to LMNA gene mutation. However, as we did not have data on NCS-EMG and MRI of the father of the case index, molecular analysis was performed to resolve the diagnosis for this case.

EDMD has three main genetic patterns: X-linked recessive, autosomal dominant, and autosomal recessive, with the X-linked EDMD arising from emerin gene chromosome mutation (Xq28) being the most common. Autosomal recessive inheritance is extremely rare [8]. The emerin protein is located in the inner nuclear membrane of body cells, predominantly in skeletal and cardiac muscles. Mutation in the emerin gene causes premature termination in mRNA translation, disrupting protein synthesis and eventually nuclear functioning [9]. The autosomal dominant and recessive patterns of EDMD are known to be caused by mutations of the Lamin A/C genes (LMNA) gene on 1q21.2-q21.3. This mutation contributes to the disorder of cardiac and skeletal muscles. Lamin A/C proteins configure the inner nuclear membrane, which plays a significant role in mechanically stabilizing the nuclear envelope and cell signalling. Lamin A/C gene has 12 exons that produce at least four types of RNA via alternate splicing, including lamins A, Aδ10, C and C2. Lamin A and C are intermediate filament proteins. Their defects in the nuclear cells’ mechanical integrity cause disruption in the regulation of tissue-selective transcription alterations and defects in cell proliferation.

From the genetic aspect, two hotspot mutations of LMNA have been reported: (1) Arg453Trp/R453W, consistently identified in EDMD, and (2) Arg482Trp/Gln/Leu(R482W/Q/L), consistently identified in patients presenting with partial lipodystrophy (FPLD). Mutations leading to striated muscle laminopathy (EDMD/LGMD1B/DCM-CD) are distributed all along the LMNA gene [10] (Fig. 4). As one of the most frequent mutations that are responsible for 16% of AD-EDMD cases, the exchange of arginine 453 by tryptophan (R453W) causes an abnormal nuclear phenotype [11, 12]. Therefore, this mutation is not uncommon. The R453W is a hot spot mutation previously associated with, and some phenotypes reported can be seen in Table 1.

AD-EDMD has been reported with a broader clinical spectrum and higher frequency of de novo mutations than the X-linked form. Later and mild involvement of contracture in LGMD1B, which were re-classified as EDMD2, can contribute to its delayed diagnosis [32].

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy in childhood. For discriminating EDMD from DMD patients, DMD children will have the following features: (a) delay in the acquisition of walking, which usually happens between 16 and 18 months; (b) early pseudohypertrophy of calves; (c) no elbow retractions; (d) CK values up to 100 times the maximum normal value; and (e) increased values of transaminases, which are never observed in patients with EDMD from either emerin or lamin A/C gene defects [33]. Moreover, the neurological examination of the father highlighted both muscular and cardiac characteristics making possible the suspicion of EDMD in our patient. In Indonesia, this is the second case of EDMD reported [14]. Moreover, our case is the first muscular dystrophy report from Indonesia using the whole-exome sequencing approach showing the utility of this approach together with clinical manifestation and usual diagnostic tests for establishing a diagnosis. However, it should be noted that many institutions worldwide do not have access to genetic testing. Although rare, there could be under-reporting of such cases due to a lack of precise molecular diagnosis because of clinical heterogeneity of this disease. This study highlights the importance of comprehensive genetic screening together with clinical features and usual diagnostic tests to further investigate suspicious cases that could resemble some form of DMD.

Most the EDMD cases are sporadic cases. Therefore, presenting the same symptoms in two family members is unusual. Early presentation of EDMD in a boy would be easily mistaken as DMD. EDMD can be inherited by an X-linked pattern, which further shows similarity with DMD. Furthermore, precise diagnosis is essential, as attested in this case, where severe cardiac involvement in the father could be detected and treated earlier.

We report a mutation in the LMNA gene underlying an autosomal dominant form of EDMD. EDMD phenotypes resemble the more common form of muscular dystrophy, i.e. dystrophinopathies (DMD/BMD), and may also be inherited in an x-linked inheritance pattern. EDMD should be considered when diagnosing a child with a clinical suspicion of DMD. Early diagnosis, intervention, targeted management, and counselling are crucial to increasing the health and life quality of EDMD patients.

Abbreviations
AD: Autosomal Dominant; AV: Atrio Ventricular; AVB: Atrio Ventricular Block; BMD: Becker Muscular Dystrophy; CK: Creatine Kinase; DCM-CD: Familial dilated cardiomyopathy with conduction systems disease; DMD: Duchenne Muscular Dystrophy; ECG: Electrocardiography; EDMD: Emery-Dreifuss Muscular Dystrophy; ICD: Implantable Cardioversion Defibrillator; LGMD: Limb-Girdle Muscular Dystrophy; LGMD1B: Limb-Girdle Muscular Dystrophy Type 1B; LMNA: Lamin A/C; N/A: Not available; PM: Pacemaker; VVIR: Ventricular pacing; ventricular sensing, inhibition response and rate-adaptive, used for ventricular pacemakers.

Acknowledgements
We are thankful to the patient and his family for their collaboration. We are also grateful to all staff and nurses caring for the patient.
Authors’ contributions
KI wrote, designed the study and edited the manuscript. S supervised and reviewed the manuscript. FNA and GA collected and analyzed the clinical data. RA wrote the manuscript, collected and analyzed the clinical data. NI, NPS, and G collected data, edited and revised the manuscript. GT performed and analyzed the genetic experiments. PSL designed the study, analyzed the genetic data, reviewed, edited and revised the manuscript. All the authors read and approved the final manuscript.

Funding
The NUS-UGM-Tahir Foundation grant supported this study. The funding body did not influence study design, data analysis, data interpretation, and manuscript writing.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Ethical Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital approved this study (KE/FK/1081/EC/2020). The authors attest that full and informed consent was obtained from the father as a patient and a parent.

Consent for publication
Written informed consent was obtained from the father as a patient and a parent for the publication of this case report, images, and all information contained in it.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Neurology Division, Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/UGM Academic Hospital, Jl. Kabupaten (Lingkar Utara), Yogyakarta 55291, Indonesia. 2 Department of Neurology, UGM Academic Hospital, Yogyakarta, Indonesia. 3 Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/ UGM Academic Hospital, Yogyakarta, Indonesia. 4 Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia. 5 Department of Physical Medicine and Rehabilitation, UGM Academic Hospital, Yogyakarta, Indonesia. 6 Division of Human Genetics, Department of Pediatrics Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. 7 Pediatric Surgery Division, Department of Surgery/Genetics Working Group/Translational Research Unit, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia.

Received: 2 September 2021   Accepted: 10 October 2022
Published online: 17 October 2022

References
1. The Portal of Rare Diseases and Orphan Drugs. http://www.orpha.net/consor/cgi-bin/OCExp.php?L=En&Expert=261. Accessed 29 June 2021.
2. Blone S, Maestrini E, Rivella S, Mancini M, Regis S, Romero G, et al. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. Nat Genet. 1994;4(4):323–7.
3. Emery AE. Emery-Dreifuss muscular dystrophy - a 40 year retrospective. Neuromuscul Disord. 2000;10(4–5):228–32. https://doi.org/10.1016/S0960-896X(00)00105-0 (PMID: 1083246).
4. Tomar S, Moomty V, Sethi R, Chai J, Low PS, Hong STK, et al. Mutational spectrum of dystrophinopathies in Singapore: Insights for genetic diagnosis and precision therapy. Am J Med Genet Part C Semin Med Genet. 2019;181(2):230–44.
5. Pillers DAM, Von Bergen NH. Emery–dreyfuss muscular dystrophy: A test case for precision medicine. Appl Clin Genet. 2016;9:27–32.
6. Emery AE, Dreifuss FE. Unusual type of benign x-linked muscular dystrophy. J Neurol Neurosurg Psychiatry. 1966;29(4):336–42.
7. Mercier E, Courisell S, Allsop J, Jungbluth H, Kinali M, Bonne G, Schwartz K, Bydder G, Dubowitz V, Muntoni F. Selective muscle involvement on magnetic resonance imaging in autosomal dominant Emery-Dreifuss muscular dystrophy. Neuropediatrics. 2002;33(1):10–4.
8. Madej-Pilarczyk A, Marchel M, Ochman K, Ciegelska J, Steckiewicz R. Low-symptomatic skeletal muscle disease in patients with a cardiac disease – Diagnostic approach in skeletal muscle laminopathies. Neurol Neonoch Pol. 2018;52(2):174–80.
9. Ostlund C, Worman H. Nuclear envelope proteins and neuromuscular diseases. Muscle Nerve. 2003;27(933–406).
10. Bonne G, Yao RB, Béroud C, Boriani G, Brown S, De Visser M, et al. 108th ENMC International Workshop, 3rd Workshop of the MYO-CLUSTER project: EUROMEN, 7th International Emery-Dreifuss Muscular Dystrophy (EDMD) Workshop, 13–15 September 2002, Naarden, The Netherlands. Neuromusc Disord. 2003;13(6):508–15.
11. Roblek M, Schuchner S, Huber V, Ollram K, Vlcek-Vesely S, Foisner R, et al. Monoclonal antibodies specific for disease-associated point-mutants: Lamin A/C r435w and r482w. PLoS One. 2010;5(5):e10604.
12. Håkeliem AM, Delbarre E, Gaustad KG, Buendia B, Collas P. Expression of the myodystrophic R435W mutation of lamin A in C2C12 myoblasts causes promoter-specific and global epigenetic defects. Exp Cell Res. 2008;314(8):1869–80.
13. Fan Y, Tan D, Song D, Zhang X, Chang X, Wang Z, et al. Clinical spectrum and genetic variations of LMNA-related muscular dystrophies in a large cohort of Chinese patients. J Med Genet. 2021;58(5):326–33.
14. Bernasconi P, Carboni N, Riggio C, Siciliano G, Polito L, Maggi L, et al. Elevated tgf b2 serum levels in emery-dreifuss muscular dystrophy: Implications for myocyte and tenocyte differentiation and fibrogenic processes. Nucleus. 2018;9(1):337–49.
15. Lin HT, Liu X, Zhang W, Liu J, Zuo YH, Xiao JX, et al. Muscle magnetic resonance imaging in patients with various clinical subtypes of LMNA-related muscular dystrophy. Chin Med J (Engl). 2018;131(12):1472–9.
16. Lee Y, Lee JH, Park HJ, Choi YC. Early-onset LMNA-associated muscular dystrophy with later involvement of contracture. J Clin Neurol. 2017;13(4):405–10.
17. Niebroj-Dobosz I, Sokolowska B, Madej-Pilarczyk A, Marchel M, Hausmanowa-Petruśewicz I. Dysfunctional laminAs as mediators of oxidative stress in emery-dreifuss muscular dystrophy. Folia Neuropathol. 2017;55(3):193–8.
18. Meinke P, Mattioli E, Haeque F, Antoku S, Cumbamaro M, Straatman KR, et al. Muscular dystrophy-associated sun1 and sun2 variants disrupt nuclear-cytoskeletal connections and myonuclear organization. PLoS Genet. 2014;10(9):e1004605.
19. Chaner J, Brown CA, Bower M, Iannaccone ST, Khati IA, Escolar D, et al. Novel LMNA mutations in patients with Emery-Dreifuss muscular dystrophy and functional characterization of four LMNA mutations. Hum Mutat. 2011;32(2):152–67.
20. Deconinck N, Dion E, Yaou RB, Fereiro A, Eymard B, Briñas L, et al. Differentiating Emery-Dreifuss muscular dystrophy and collagen VI-related myopathies using a specific CT scanner pattern. Neuromuscul Disord. 2010;20(8):517–23.
21. Park YE, Hayashi YK, Goto K, Komaki H, Hayashi Y, Inuzuka T, et al. Nuclear changes in skeletal muscle extend to satellite cells in autosomal dominant Emery-Dreifuss muscular dystrophy/limb-girdle muscular dystrophy 1B. Neuromusc Disord. 2009;19(11):29–36. https://doi.org/10.1016/j.nmd.2008.09.018.
22. Niebroj-Dobosz I, Marchel M, Madej A, Sokolowska B, Hausmanowa-Petruśewicz I. Circulating autoantibodies to troponin I in Emery-Dreifuss muscular dystrophy: Implications for myocyte and tenocyte differentiation and fibrogenic processes. J Neurol Neurosurg Psychiatry. 2007;78(10):1158–60.
25. Sanna T, Dello Russo A, Toniolo D, Vytopil M, Pelargonio G, De Martino G, et al. Cardiac features of Emery-Dreifuss muscular dystrophy caused by lamin A/C gene mutations. Eur Heart J. 2003;24(24):2227–36.
26. Vytopil M, Benedetti S, Ricci E, Galluzzi G, Dello Russo A, Merlini L, et al. Mutation analysis of the lamin A/C gene (LMNA) among patients with different cardiomyopathic phenotypes. J Med Genet. 2003;40(e132):1–5.
27. Colomer J, Iturriaga C, Bonne G, Schwartz K, Manilal S, Morris GE, et al. Autosomal dominant Emery-Dreifuss muscular dystrophy: A new family with late diagnosis. Neuromuscul Disord. 2002;12(1):19–25.
28. Bower M, Meriggioli MN, Zammit PS, Felice K, Ellis JA, Brown CA, et al. Novel and recurrent EMD mutations in patients with Emery-Dreifuss muscular dystrophy, identify exon 2 as a mutation hot spot. J Hum Genet. 2011;56(8):589–94. https://doi.org/10.1038/jhg.2011.65.
29. Sewry CA, Brown SC, Merceri E, Bonne G, Feng L, Camici G, et al. Skeletal muscle pathology in autosomal dominant Emery-Dreifuss muscular dystrophy with lamin A/C mutations. Neuropathol Appl Neurobiol. 2001;27(4):281–90.
30. Bonne G, Merceri E, Muchir A, Urtizberea A, Bécané HM, Recan D, et al. Clinical and molecular genetic spectrum of autosomal dominant Emery-Dreifuss muscular dystrophy due to mutations of the lamin A/C gene. Ann Neurol. 2000;48(2):170–80.
31. Di Barletta MR, Ricci E, Galluzzi G, Tonali P, Mora M, Morandi L, et al. Different mutations in the LMNA gene cause autosomal dominant autosomal recessive Emery-Dreifuss muscular dystrophy. Am J Hum Genet. 2000;66(4):1407–12.
32. Zhu Y, Zhang H, Sun Y, Li Y, Deng L, Wen X, et al. Serum Enzyme Profiles Differentiate Five Types of Muscular Dystrophy: Dis Markers. 2015;2015:543282.
33. Achmad C, Zada A, Affani M, Iqbal M, Martanto E, Purnomowati A, et al. A novel de novo mutation in lamin A/C gene in emery dreifuss muscular dystrophy patient with atrial paralysis. J Atr Fibrillation. 2017;9(6):1–4.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:
• fast, convenient online submission
• thorough peer review by experienced researchers in your field
• rapid publication on acceptance
• support for research data, including large and complex data types
• gold Open Access which fosters wider collaboration and increased citations
• maximum visibility for your research: over 100M website views per year

Learn more biomedcentral.com/submissions