SUPPLEMENTAL MATERIAL

Supplemental Table 1: Patients excluded from analysis

Reason for exclusion	# of patients	% of total
Mutation other than deletion	65	32.2
Deletion > 12 exons	7	3.5
Insufficient cardiac information [a]	97	48.0
Possible DMD [b]	5	2.5
Suspected Viral Myocarditis	2	1.0
No cardiac dystrophin expression [c]	18	8.9
Other [d]	8	4.0
Total	**202**	**100**

a. Information on the patient age at the time of cardiac evaluation was missing, or, for published case reports, a qualitative description without specific echocardiography measurements was provided.

b. These patients were diagnosed as BMD but were either wheelchair dependent in their early teens, or younger than 12 years of age, had no family history of the disease, had out-of-frame deletion mutations, and a severe skeletal muscle involvement.

c. Among these patients, 17 had mutations affecting non-coding regions some of which were not deletions [1-7]. Only one patient in this category has a deletion mutation affecting the coding region. These patients represent 8 independent families.

d. These patients had deletions of 12 or less exons within the rod domain affecting exons 12 to 44. Because of their heterogeneity and low number they could not be included in the current analysis.

References:

1. Ferlini A, Galie N, Merlini L, Sewry C, Branzi A, Muntoni F. A novel Alu-like element rearranged in the dystrophin gene causes a splicing mutation in a family with X-linked dilated cardiomyopathy. *Am J Hum Genet.* 1998;63(2):436-446.
2. Bies RD, Maeda M, Roberds SL, Holder E, Bohlmeyer T, Young JB, Campbell KP. A 5' dystrophin duplication mutation causes membrane deficiency of alpha-dystroglycan in a family with X-linked cardiomyopathy. *J Mol Cell Cardiol.* 1997;29(12):3175-3188.
3. Saotome M, Yoshitomi Y, Kojima S, Kuramochi M. Dilated cardiomyopathy of Becker-type muscular dystrophy with exon 4 deletion--a case report. *Angiology.* 2001;52(5):343-347.
4. Yoshida K, Ikeda S, Nakamura A, Kagoshima M, Takeda S, Shoji S, Yanagisawa N. Molecular analysis of the Duchenne muscular dystrophy gene in patients with Becker muscular dystrophy presenting with dilated cardiomyopathy. *Muscle Nerve.* 1993;16(11):1161-1166.
5. Muntoni F, Wilson L, Marrosu G, Marrosu MG, Cianchetti C, Mestroni L, Ganau A, Dubowitz V, Sewry C. A mutation in the dystrophin gene selectively affecting dystrophin expression in the heart. *J Clin Invest.* 1995;96(2):693-699.
6. Muntoni F, Cau M, Ganau A, Congiu R, Arvedi G, Mateddu A, Marrosu MG, Cianchetti C, Realdi G, Cao A, Melis MA. Brief report: deletion of the dystrophin muscle-promoter region associated with X-linked dilated cardiomyopathy. *N Engl J Med.* 1993;329(13):921-925.
7. Milasin J, Muntoni F, Severini GM, Bartoloni L, Vatta M, Krajinovic M, Mateddu A, Angelini C, Camerini F, Falaschi A, Mestroni L, Giacca M. A point mutation in the 5' splice site of the dystrophin gene first intron responsible for X-linked dilated cardiomyopathy. *Hum Mol Genet.* 1996;5(1):73-79.

Supplemental Table 2: Affected patients.

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
3	2-7	XLDCM, BMD	[1] (Patient 1)	Age at consultation: 33 years. Mild myopathy with preferential cardiac involvement beginning from the second decade of life. CK= 800 U/L. Biopsy showed increased central nucleation, fiber splitting and fiber size variation, carnitine deficiency. Slightly fainter dystrophin staining intensity than normal controls. Western blot: reduced dystrophin size. Brother of #251. Negative family history.	Severe congestive cardiomyopathy. EF= 25%.	28	1
251	2-7	XLDCM, BMD	[1] (Patient 2)	Age at consultation: 28 years. Mild myopathy with preferential cardiac involvement beginning from the second decade of life. CK= 2000 U/L. Biopsy showed mild myopathy, increased numbers of central nuclei and fiber splitting, fiber size variation. Slightly fainter dystrophin staining intensity than normal controls. Western blot: reduced dystrophin size. Brother of #3. Negative family history.	Severe congestive cardiomyopathy. EF= 45%.	28	1
SL1032	3	BMD	UDP	Onset of skeletal muscle symptoms: 2 years. Age at diagnosis: 5.5 years. Toe walking. Wheelchair dependent: 30 years. Vignos Scale (34 years): upper = 3 / lower = 9.	EF = 35%. Palpitations. Peripheral edema. Clinically significant arrhythmia. Heart transplant at 34 years.	23	1
MJ03	3	BMD	MDAc	Age at diagnosis: 8 years. Calf hypertrophy. CK = 18,000 U/L. Ambulant at age 14. Negative family history.	Cardiac data at 13 years of age: EF = 50%. Cardiac data at 16 years of age: SF = 28.39%, LV diastolic septal thickness: 0.80cm, LVIDd = 55.3mm (1.02 z-score), LV diastolic wall thickness: 0.80cm. No global LV dysfunction, overall LV systolic wall motion is low-normal. Cardiac data at 18 years of age: LVID = 1.2sd, EPSS = 14mm, SF = 23%, EF = 45%.	13	1

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
SL187	3-7	BMD	UDP	Onset of skeletal muscle symptoms: 1 year. Elevated CK. Vignos Scale (24 years): upper = 1 / lower = 3. Positive family history.	DCM diagnosis. EF = 25%, SF = 8%. Heart transplant at 22 years.	22	1
MJ18	3-7	BMD	MDAc	Age at consultation and diagnosis: 25 years. Diffuse muscle stiffness, cramping, weakness. CK = 1200~2000 U/L. Biopsy showed mild muscle fiber atrophy with mild focal chronic inflammation.	Normal ECG. All valves normal, LV global systolic dysfunction and hypokinesis, EF = 35%.	29	1
SL59	3-7	BMD	MDAc	Onset of skeletal muscle symptoms: 3 years. Diagnosis: 10years. Wheelchair dependent: 25.5 years. Negative family history.	EF <20%; SF = 22%.	41	1
SL1077	3-11	BMD	UDP	Symptom of weakness. Wheelchair dependent: 17 years. Negative family history.	EF = 17%, SF = 8%.	19	1
20	5	XLDCM	[2] (Patient DCM 10)	Age at consultation: 12 years. Presented to the emergency room with dyspnoea, diaphoresis and vomiting for one week. Neurological exam showed no skeletal myopathy or abnormalities. CK = 270 U/L. Negative family history.	DCM diagnosis. LVEDd = 58mm (Z score 5.2), SF = 16%, EF = 30%. Moderate mitral regurgitation.	12	1
157	5-9	BMD, XLDCM	[3] (Patient 4)	Onset of skeletal muscle symptoms: 17 years. Age at consultation: 33 years. Wheelchair dependent.	Severe DCM, polymorphic PVCs. Symptoms of heart failure.	33	1
140	6-13	XLDCM, BMD	[4]	Age at consultation: 14 years. Neurological exam: mild generalized muscle weakness, slight muscular atrophy with a limb-girdle distribution. CK =5-15ukat/l (normal <3.3ukat/l). Normal EMG. Biopsy showed mild myopathy. Negative family history.	Congestive heart failure symptoms. Cardiomegaly by chest X-ray. ECG: tachycardia, left atrial and ventricular hypertrophy, and strain. LVEDd = 82 mm, SF = 11%, considerable left atrial dilatation. No coronary artery abnormalities per angiography. Patient died 1 month later. *Cardiac biopsy:* non-specific changes with interstitial fibrosis compatible with DCM.	14	1

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
250	45	BMD	[5] (Patient 2)	Age at consultation: 31 years. Mild progressive limb-girdle weakness, calf pseudohypertrophy, elevated CK. Biopsy showed discontinuous dystrophin staining.	LVEDd = 58mm, LVEDs = 47mm, EF = 47%, LV posterior wall = 10mm, Interventricular septum = 12mm. *Cardiac Biopsy:* No interstitial fibrosis. Dystrophin staining: discontinuous (partial or intermittent surface membrane staining).	31	2
145	45	BMD	[6] (Patient 6)	Age at consultation: 26 years. Major impairment of motor function. Wheelchair dependent. FVC = 42%.	ECG showed tall R wave in V1, lateral Q and T abnormal. QTc: 441ms. QT/PQ = 8.6. LVEDd = 66mm. SF = 13%.	26	2
193	45-47	BMD	[7] (Patient 1)	CK=265 U/L. Negative family history.	Onset of congestive heart failure symptoms. EF = 25%. *Cardiac Biopsy:* dystrophin staining showed reduced with rod domain antibody, irregular with amino- and carboxyl-terminal antibodies.	22	2
253	45-47	BMD	[8]	Age at consultation: 37 years. Muscle weakness present.	LVEDd = 58mm, EF = 42%.	37	2
110	45-47	BMD	[9] (Patient 20)	Age at consultation: 20 years. Clinical Severity: Mild. Dystrophin staining showed small number of negative fibers. Western blot: reduced amount (40%) and size (360 kDa). Positive family history.	Normal ECG. Normal Holter ECG. Normal LA volume. LV EDV = 64 mL/m^2. EF = 53%. LV wall motion: normal. RV EDV = 57 mL/m^2. RVEF = 70%. Normal RV wall motion.	20	2
189	45-47	BMD	[10] (Patient B27)	Age at consultation: 35 years. Cramps, myalgia, myoglobinuria, calf hypertrophy. CK = 378 U/L. Western blot: Normal dystrophin amount but reduced size (380 kDa).	ECG showed LBBB. Holter ECG showed polymorphic ventricular arrhythmias (Lown grade 3). LVEDV = 85 mL/m^2. EF = 39%. LV wall motion: anterior septum akinesia.	35	2
141	45-47	BMD	[6] (Patient 1)	Age at consultation: 17 years. Minor impairment of motor function. FVC = 96%.	ECG showed incomplete RBBB, QTc: 399ms. QT/PQ = 10.7. LVEDd = 51mm. SF = 24%.	17	2
148	45-47	BMD	[6] (Patient 12)	Age at consultation: 22 years. Minor impairment of motor function. FVC = 98%.	Normal ECG. QTc: 391ms. QT/PQ = 11.80. LVEDd = 55mm. SF = 29%.	22	2
149	45-47	BMD	[6] (Patient 14)	Age at consultation: 26 years. Minor impairment of motor function. FVC = 98%.	Normal ECG. QTc: 402ms. QT/PQ = 18.00. LVEDd = 55mm. SF = 16%.	26	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
138	45-47	BMD, XLDCM	[11]	Onset of skeletal muscle symptoms: 19 years. Wheelchair dependent at 34 years. Positive family history.	Cardiomegaly by chest X ray. ECG showed complete AV block, varying heart rate between 30–36 beats/minute. EF = 30%. Doppler showed mild-to-moderate mitral regurgitation. Family: Brother diagnosed with BMD and DCM.	49	2
SL1325	45-47	BMD	MDAc	Onset of skeletal muscle symptoms: 13 years. Diagnosed: 16 years. Symptoms: weakness, myalgias, cramping. Vignos Scale (28 years): upper = 1 / lower = 1.	Echo (18 years): abnormal, low EF. Echo (24 years): EF= 20%	18	2
SL1127	45-47	BMD	MDAc	Onset of skeletal muscle symptoms: 11 years. Diagnosed: 22 years. Symptoms: weakness, myalgias, cramping. Vignos Scale (29 years): upper = 1 / lower = 1.	EF = 30%	29	2
197	45-47	BMD, XLDCM	[7] (Patient 5)	CK=104-837U/L. Negative family history.	Onset of congestive heart failure symptoms. EF = 30%. *Cardiac Biopsy:* dystrophin staining showed reduced with rod domain antibody, irregular with amino- and carboxyl-terminal antibodies.	38	2
192	45-47	BMD, XLDCM	[12]	Age at consultation: 32 years. CK = 2780U/L. Neurological examination: normal except for slight calf hypertrophy. Biopsy showed fiber size variation with scattered atrophic fibers and fiber hypertrophy, internalized nuclei, some necrotic fibers and fiber splitting, moderate increase of connective tissue. Western Blot: slight reduction in dystrophin size. Positive family history.	DCM diagnosis. ECG showed LBBB. Marked dilation of LV. LVEDd = 44mm, LVEDV = 201ml, EF = 17%, moderate regurgitation, thrombus in the apical region of the LV chamber. *Cardiac Biopsy:* hypertrophic myocytes with huge and bizarre nuclei, focal interstitial fibrosis, mild endocardial fibrous thickening. Heart transplantation at age 31.	29	2
MJ02	45-47	BMD	MDAc	EMG at 7 years was normal but calf hypertrophy present. Onset of skeletal muscle symptoms: 22 years. Diagnosed at 32 years. Calf hypertrophy, progressive weakness and heaviness when climbing stairs. CK=1200U/L. Positive family history.	EF = 30%. Family: Grandfather died of DCM.	34	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
MJ20	45-47	BMD	MDAc	Onset of skeletal muscle symptoms: 10years. Diagnosed at 11years. Symptom of weakness. CK = 1245 U/L. Started cane use at age 19 and wheelchair at 23. Partially ambulatory. Biopsy showed marked variability in muscle fiber size, 10-120 μm. Positive family history.	Cardiac data at 19 years of age: DCM diagnosis. Cardiac medications started. Cardiac data at 35 years of age: EF = 55%.	19	2
AH05	45-47	BMD	MDAc	Onset of skeletal muscle symptoms: 5 years. Could not keep up with peers in terms of running. Diagnosis: 18 years. Difficulty climbing stairs and getting up from the floor, calf hypertrophy. CK = 2516 U/L. Biopsy showed fiber size variation (10-125 micrometers in diameter), marked connective tissue proliferation. Wheelchair dependent by 42 years. Negative family history.	Normal ECG. EF = 51%. SF = 32%.	39	2
228	45-47	BMD	[13]	Unavailable.	EF = 42%, LVEDd = 58mm. Diagnosis of DCM based on WHO criteria. Negative for cardiac insufficiency based on European Society of Cardiology criteria.	37	2
198	45-48	XLDCM	[7] (Patient 6)	CK = 501U/L. Negative family history.	Onset of cardiac symptoms. EF = 18%. DCM diagnosis. *Cardiac Biopsy:* reduced dystrophin immunoreactivity with antibodies to the rod domain and irregular staining with antibodies to the amino- and carboxyl-terminal regions.	39	2
210	45-48	XLDCM	[14] (Patient 2)	Age at consultation: 33 years. No skeletal muscle symptoms. CK = 754U/L. Positive family history.	DCM diagnosis pre-dating cardiac data below. Cardiac data at 33 years of age: ECG showed LBBB. Interventricular septal thickness = 8mm; Posterior wall thickness = 8mm; LVEDd = 67mm; LVEDs = 52mm; SF = 22%.	33	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
212	45-48	XLDCM	[14] (Patient 4)	Age at consultation: 57 years. No skeletal muscle symptoms. CK = 438U/L. Positive family history.	DCM diagnosis pre-dating cardiac data below. Cardiac data at 57 years of age: ECG showed RBBB. Interventricular septal thickness = 9mm; Posterior wall thickness = 9mm; LVEDd = 65mm; LVEDs = 58mm; SF = 11%.	57	2
201	45-48	BMD	[15]	Onset of skeletal muscle symptoms: 3 years. Age at consultation: 33 years.	SF = 11%; LVEDd = 82; Interventricular septal thickness = 18mm; Posterior wall thickness: 18.	33	2
252	45-48	BMD	[8]	Age at consultation: 54 years.	LVEDd = 67mm, EF = 30%, met DCM criteria of WHO. Symptoms: dyspnoea, thoracic pain.	54	2
109	45-48	BMD	[9] (Patient 13)	Age at consultation: 15 years. Clinical Severity: mild. Biopsy showed few dystrophin negative fibers. Western blot: reduced dystrophin expression (40%) and size (370 kDa). Negative family history.	ECG showed incomplete RBBB. Normal Holter ECG. LA volume = 40 mL/m^2. LV EDV = 69 mL/m^2. EF = 51%. RVEDV = 84 mL/m^2. RVEF = 63%. RV wall motion apical hypokinesia.	15	2
112	45-48	BMD	[9] (Patient 25)	Age at consultation: 30 years. Clinical Severity: Moderate. Biopsy showed small number of dystrophin negative fibers. Western Blot: reduced amount (40%) and size (370 kDa). Positive family history.	ECG showed incomplete RBBB. Holter ECG showed isolated monomorphic PVCs (Lown grade 1). LA volume = 29 mL/m^2. LV EDV = 78 mL/m^2. EF = 48%. LV wall motion: diffuse hypokinesia. RV EDV = 64 mL/m^2. RVEF = 39%.	30	2
105	45-48	BMD	[9] (Patient 30)	Age at consultation: 36 years. Clinical Severity: Mild. Western Blot: normal amount but reduced size (380 kDa). Positive family history.	Symptomatic. ECG showed LBBB. Holter ECG showed polymorphic ventricular arrhythmias (Lown grade 3). Positive infra-Hisian block (His-ventricular interval 80ms). Pacemaker implanted. LA volume = 45 mL/m^2. LV EDV = 85 mL/m^2. EF = 39%. LV wall motion: anterior septal akinesia. RV EDV = 69 mL/m^2. RVEF = 65%. RV wall motion: septal akinesia.	36	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
182	45-48	BMD	[10] (Patient A14)	Age at consultation: 20 years. Cramps, myalgia, myoglobinuria, calf hypertrophy. CK = 28 U/L. Western blot: reduced dystrophin amount (40%) and reduced size (370 kDa).	ECG showed incomplete RBBB. Normal Holter ECG. LVEDV = 69 mL/m^2. EF = 51%.	20	2
227	45-48	BMD	[13]	Unavailable.	EF = 30%, LVEDd = 67mm. Diagnosed DCM based on WHO criteria. Diagnosed cardiac insufficiency based on European Society of Cardiology criteria.	54	2
195	45-48	BMD, XLDCM	[7] (Patient 3)	CK=2203U/L. Negative family history.	Onset of congestive heart failure symptoms. EF = 20%. *Cardiac Biopsy:* dystrophin staining reduced with rod domain antibody, irregular with amino- and carboxyl-terminal antibodies.	29	2
144	45-48	BMD	[6] (Patient 5)	Age at consultation: 25 years. Major impairment of motor function but ambulant. FVC = 77%.	Normal ECG. QTc: 404ms. QT/PQ = 8.8. LVEDd = 47mm. SF = 27%.	25	2
SL49	45-48	BMD	UDP	Onset of skeletal muscle symptoms: 6.5 years. Diagnosed at 17 years. Myalgia, cramping. Vignos Scale (52 years): upper = 1 / lower = 2. Positive family history.	Cardiac data at 47 years of age: SF = 28%. Cardiac data at 52 years of age: EF = 50%.	47	2
SL578	45-48	BMD	UDP	Onset of skeletal muscle symptoms: 29 years. Diagnosis: 35years. Symptom of weakness. Wheelchair dependent at 53 years. Vignos Scale (60 years): upper = 5 / lower = 8.	EF = 47%.	56	2
161	45-48	BMD, XLDCM	[16] (Patient 1)	Onset of skeletal muscle symptoms: 60 years. Difficulties in tilling the soil with a hoe and climbing hills and stairs. Age at consultation: 73 years. Neurological exam: moderate proximal muscular atrophy and weakness, waddling gait, mild calf hypertrophy, positive Gower's sign. Walks independently. Computed tomography scan: low-density areas in the proximal muscles, especially in the thighs. CK = 681U/L. Positive family history.	Diagnosis of congestive heart failure caused by DCM. Symptoms of paroxysmal chest discomfort and dyspnoea. Chest roentgenogram showed cardiomegaly and pulmonary congestion (cardiothoracic ratio = 61%). ECG showed prominent R wave in V1. EF = 27%, SF = 13.5%, positive LV hypokinesis, LVEDd = 66mm, LVEDs = 57mm.	70	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
164	45-48	BMD, XLDCM	[16] (Patient 4)	Onset of skeletal muscle symptoms: early 30's. Awkward gait. Started use of cane in his early 40's. Wheelchair dependent in his late 40s. Age at consultation: 53 years. Marked proximal muscular atrophy and weakness, no obvious hypertrophy in the calves. CK = 217U/L. Negative family history.	DCM diagnosis. Chest roentgenogram showed cardiomegaly, bilateral pleural effusion and pulmonary congestion. ECG showed prominent Q wave in I, aVL, V5-6. LV hypokinesis, LVEDd = 64mm, LVEDs = 60mm. EF = 16%, SF = 6.3%.	53	2
SL699	45-48	BMD	UDP	Onset of skeletal muscle symptoms: 10 years. Diagnosis: 22 years. Symptom of weakness. Wheelchair dependent at 48 years. Vignos Scale (48 years): upper = 2 / lower = 9.	EF = 50%.	47	2
SL8	45-48	BMD	UDP	Onset of skeletal muscle symptoms: 2 years. Diagnosis: 23 years. Weakness, hypertrophy, myalgia/cramping, myoglobinuria, cognitive dysfunction. Vignos Scale (40 years): upper = 1 / lower = 5. Negative family history.	EF = 29%.	27	2
SL42	45-49	BMD	UDP	Onset of skeletal muscle symptoms: 6 years. Diagnosis: 7 years. Symptom of weakness. Wheelchair dependent at 23 years of age. Vignos Scale (32 years): upper = 2 / lower = 9. Negative family history.	EF = 25%, SF = 14%.	32	2
224	45-49	XLDCM, BMD	[17]	Age at consultation: 23 years. No trouble in walking. Normal muscle mass except for pseudohypertrophy of calf and quadriceps muscles; normal muscle strength. Biopsy showed internal nuclei, mild variability in the fiber size with hypotrophic and hypertrophic fibers, rare splitting fibers in an otherwise well preserved muscle. Dystrophin staining: normal with rod domain antibodies, faint with N-terminal antibody, almost normal with few areas of discontinuity with C-terminal antibody. CK = 520U/L. Condition unchanged at 26 years of age. Brother of #225.	DCM diagnosis. Symptom of palpitations. Echocardiogram showed enlarged left ventricle. *Cardiac biopsy* on RV: mosaic pattern of negative and positive dystrophin cardiomyocytes. Faint staining with amino- and carboxyl-terminal antibodies.	19	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
225	45-49	XLDCM, BMD	[17]	Age: 6 years. Calf hypertrophy and elevated CK, no signs of muscle involvement. Brother of #224.	DCM diagnosis at 23 years. Symptoms of dyspnea even with mild physical activity. EF = 28%, LVEDd = 72 mm. Died of DCM at 29 years.	23	2
215	45-49	BMD	[9] (Patient 16)	Age at consultation: 16 years. Clinical Severity: mild. FVC = 109%. Western blot: reduced dystrophin expression (50%) and size (390 kDa). Negative family history.	ECG showed incomplete RBBB. Holter ECG showed isolated monomorphic PVCs documented >30/hr (Lown grade 1). LA volume normal. LV EDV= 65 mL/m^2. EF = 50%. RV EDV = 45 mL/m^2. RVEF = 51%.	16	2
MJ14	45-49	BMD	MDAc	Motor and cognitive delay. Classified as retarded at 33 years of age. Onset of skeletal muscle symptoms: 33 years. Frequent falling. Very mild muscle involvement. CK = 1700 U/L. Dystrophin staining shows correct localization at membrane in all fibers. Western Blot: reduced levels and size. Positive family history.	EF = 22%, dilated LV, no mitral regurgitation. Cardiac data at 37 years of age: Congestive heart failure. Chest X ray showed cardiomegaly.	36	2
SL48	45-49	BMD	UDP	Onset of skeletal muscle symptoms: 6.5 years. Diagnosis: 6 years. Calf hypertrophy, myalgia, cramping. Vignos Scale (31 years): upper = 1 / lower = 2.	EF = 40%.	28	2
147	46-49	BMD	[6] (Patient 11)	Age at consultation: 26 years. Minor impairment of motor function. FVC = 80%.	ECG showed LV hypertrophy. QTc: 430ms. QT/PQ = 10.00. LVEDd = 51mm. SF = 27%.	26	2
137	47	BMD, XLDCM	[18] (Patient 4)	Onset of skeletal muscle symptoms: 2 years. Awkward gait, could not run as fast as his peers. Diagnosed with limb-girdle muscular dystrophy (incorrectly) and DCM at age 23 years. Age at consultation: 34 years. Clinical status: marked proximal muscular atrophy and weakness, decreased deep tendon reflexes, and waddling gait.	Cardiac data at 23 years of age: DCM diagnosis. Cardiac data at 30 years of age: Occasional nocturnal orthopnea, exertional dyspnea, and hemoptysis due to left-sided heart failure.	23	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
69	47	BMD, XLDCM	[18] (Patient 3); [19] (Patient 1)	Onset of skeletal muscle symptoms: 9 years. Positive family history.	DCM diagnosis. ECG showed infarct pattern of LV posterolateral wall. Family: Affected uncle died of congestive heart failure at age 47 years.	25	2
97	47-48	BMD	[20] (Patient 16)	Onset of skeletal muscle symptoms: 15years. Biopsy showed positive dystrophic change in skeletal muscle. Negative family history.	Cardiac failure diagnosis. Death in same year.	51	2
104	48	BMD	[9] (Patient 19)	Age at consultation: 20 years. Clinical Severity: Mild. CK= 2700 U/L. Western blot: normal dystrophin expression but reduced size (370 kDa). Positive family history.	Normal ECG. Holter ECG showed isolated monomorphic PVCs (Lown grade 1). Normal LA volume. LV EDV = 65 mL/m^2. EF = 53%. RV EDV normal. RVEF normal.	20	2
152	48	BMD	[6] (Patient 19)	Age at consultation: 16 years. Minor impairment of motor function. FVC = 82%.	ECG showed RBBB, left ventricular hypertrophy, lateral Q wave. QTc: 403ms. QT/PQ = 9.30. LVEDd = 52mm. SF = 29%.	16	2
194	48	XLDCM	[7] (Patient 2)	CK = 63U/L. Negative family history.	Onset of congestive heart failure symptoms and DCM diagnosis. EF = 14%. *Cardiac Biopsy:* reduced dystrophin immunoreactivity with an antibody to the rod domain, and irregular staining with antibodies to the amino- and carboxyl-terminal domains.	24	2
190	48-49	BMD	[10] (Patient B28)	Age at consultation: 48 years. Cramps, myalgia, myoglobinuria, calf hypertrophy. CK = 4700 U/L. Western blot: reduced dystrophin amount (50%) and reduced size (390 kDa).	ECG showed LBBB. Holter ECG showed Lown grade 4b. LVEDV = 229 mL/m^2. EF = 34%. LV wall motion: diffuse hypokinesia.	48	2
71	48-49	XLDCM	[21] (Patient 1)	Age at consultation: 24 years. Dyspnea with mild physical activity, no cramps or myalgia associated with exercise. Neurological exam: no weakness or muscle wasting or hypertrophy. CK = 540 -867 U/L. Biopsy showed variable intensity of immunoreactivity among fibers, overall fainter than control. Positive family history.	DCM diagnosis. ECG showed Q waves in the inferior and posterior leads, incomplete RBBB. Holter ECG showed sustained ventricular arrhythmias monitoring. LVEDd = 73 mm, EF = 27%. Angiography showed no coronary artery disease. *Cardiac biopsy:* no active myocarditis.	24	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
226	48-49	BMD, XLDCM	[22] (Patient 2)	Age at consultation: 29 years. Elevated CK. Biopsy showed mild variability of fiber size and moderate interstitial fibrosis; dystrophin staining normal with carboxyl-terminal antibodies. Positive family history.	Cardiac data at 29 years of age: Cardiac symptoms of dyspnea. NYHA II. Marked LV dilation; LVEDV = 176 mL/m^2, EF = 26%. The patient was treated with high doses of captopril. Cardiac data at 30 years of age: Severe LV dilation; LVEDV = 166 mL/m^2, EF = 28%. *Cardiac Biopsy:* Positive but faint dystrophin immunofluorescence in all cardiomyocytes. Diffuse but faint over-expression of utrophin.	29	2
153	48-49	BMD, XLDCM	[23]	Onset of skeletal muscle symptoms: 32 years. Biopsy showed increased variability of muscle fiber diameter, rounded and abnormally shaped fibers, internalized myonuclei, slightly proliferated endomysial connective and fat tissue. Dystrophin staining patchy and irregular; reduced size by Western blot (380 kDa). Sarcoglycans and dystroglycan normally expressed. Utrophin detected in some muscle fibers.	Cardiac data at 26 years of age: DCM diagnosis. Cardiac data at 27 years of age: Cardiac transplant for end stage DCM.	26	2
AH11	48-49	BMD	MDAc	Onset of skeletal muscle symptoms: 30 years. Age at consultation: 42 years. Muscle pain and weakness. No calf hypertrophy. Normal reflexes. Related to #MJ13. Positive family history.	DCM diagnosis. EF = 15%. Family: Brother had heart attack at age of 47 years.	42	2
MJ13	48-49	BMD	MDAc	Onset of skeletal muscle symptoms and diagnosis: 25 years. Chest pain, muscle weakness, fatigue climbing upstairs, calf hypertrophy. CK = 658 U/L. Related to # AH11. Positive family history.	Severe chest pain, without vital sign and rhythm changes. Negative stress test. EF = 54%. LV free wall thickness: 0.9cm.	37	2
199	45-51	BMD, XLDCM	[7] (Patient 7)	CK=1442U/L. Positive family history.	Onset of congestive heart failure symptoms. ECG: Q waves in V4-6. EF = 35%. *Cardiac Biopsy:* dystrophin staining reduced with rod domain antibody, irregular with amino- and carboxyl-terminal antibodies.	43	3

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
63	45-53	BMD	[20] (Patient 8)	Onset of skeletal muscle symptoms: 15years. Skeletal muscle fibrosis. Positive family history.	Heart failure diagnosed.	36	3
209	45-55	XLDCM	[24]	Age at consultation: 36 years. Normal neurological exam. CK = 1,347U/L.	DCM diagnosis. LV dilatation (LVEDd = 72mm), diffuse hypokinesis of the left ventricular wall motion, reduced cardiac output, EF = 16%. Chest roentgenogram showed slight cardiomegaly, bilateral pleural effusion, and pulmonary congestion. ECG showed sinus tachycardia, poor R-wave progression in leads V,-V3 and flat T wave in leads I, aVL, V5 and V6. *Cardiac biopsy:* myocyte degeneration, irregularly shaped nuclei and interstitial fibrosis.	36	3
248	45-55	BMD	[25] (Patient 3)	Onset of skeletal muscle symptoms: 59 years. Mild limb muscle weakness. Age of BMD diagnosis: 69 years. Moderate proximal muscular atrophy, weakness, waddling gait, no calf pseudo hypertrophy. Clinical severity: moderate. Age at consultation: 76 years. Neurological examination: walking requires effort, muscular atrophy had slightly progressed. Clinical severity: moderate. CK = 669 IU/L. Negative family history.	First cardiac consultation at 69 years of age: ECG showed prominent R waves in V1. No LV hypokinesis. EF = 60%, SF = 32.1%, LVEDd = 56mm. Second cardiac consultation at 76 years of age: ECG showed prominent R waves in V1, slight LV hypokinesis. EF = 56%, SF = 28.9%, LVEDd = 44mm.	76	3
MJ06	45-55	BMD	MDAc	Diagnosis: 58 years. Positive family history.	Cardiac data at 63 years of age: EF = 15-20%, severe mitral regurgitation. Cardiac data at 64 years of age: ECG showed ventricular tachycardia, widened QRS complex with duration about 128msec and frequent PVCs. LV and LA enlargement.	63	3

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
196	48-51	XLDCM	[7] (Patient 4)	CK = 442-515U/L. Negative family history.	Onset of cardiac symptoms. Congestive heart failure diagnosed. EF = 30%. *Cardiac Biopsy:* reduced dystrophin immunoreactivity with an antibody to the rod domain, and irregular staining with antibodies to the amino- and carboxyl-terminal domains.	30	3
203	48-51	XLDCM	[26]	Age at consultation: 65 years. Investigated following incidental finding of elevated CK in his 5-year-old grandson. Normal muscle strength, no trophic changes. Normal CK. Normal EMG. Biopsy was normal apart from occasional small fibers and some internal nuclei. Dystrophin immunostaining: normal in distribution, slightly reduced in amount. Western blot: reduced size of dystrophin. Alpha-sarcoglycan, beta-sarcoglycan, gamma-sarcoglycan, spectrin and merosin showed normal distribution.	Cardiac data at 60 years of age: DCM diagnosis. Severe LV dilation with reduced EF and mitral and aortic regurgitation. Coronary arteriography showed very mild atherosclerosis without significant obstructive lesions. Died suddenly of cardiac arrest at age 68. Family: “Cardiomyopathy” caused the death of his mother and two brothers in their sixth decade.	60	3
211	48-52	XLDCM	[14] (Patient 3)	Age at consultation: 43 years. No skeletal muscle symptoms. CK = 96U/L. Positive family history.	DCM diagnosis pre-dating cardiac data below. Cardiac data at 43 years of age: ECG showed LBBB. Interventricular septal thickness = 9mm; Posterior wall thickness = 9mm; LVEDd = 72mm; LVEDs = 69mm; SF = 4%.	43	3
200	48-53	XLDCM	[7] (Patient 8)	CK below 200U/L. Negative family history.	Onset of cardiac symptoms. Congestive heart failure diagnosed. EF = 30%. *Cardiac Biopsy:* reduced dystrophin immunoreactivity with an antibody to the rod domain, and irregular staining with antibodies to the amino- and carboxyl-terminal domains.	50	3

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
208	49-51	XLDCM	[21] (Patient 2)	Age at consultation: 52 years. No muscle atrophy or pseudohypertrophy, normal muscle strength. CK= 84 U/L.	Cardiac data at 50 years of age: Onset of congestive heart failure symptoms. Cardiac data at 52 years of age: Dyspnoeic at rest, systolic murmur present. ECG showed negative T waves in leads V5-V6. Dilated LV (LVEDd = 70mm), EF = 20%, dilated RV and both atria. Moderate mitral and tricuspidal valve regurgitation. *Cardiac biopsy:* significant fibrosis, separating individual cardiomyocytes in some areas, gross variability of fiber size mainly due to hypertrophic cardiomyocytes; strong and continuous dystrophin staining with antibodies to amino-terminus, mid rod domain, and carboxyl-terminus. Slight reduction in amount by Western blot.	50	3
MJ01	51-52	BMD	MDAc	Onset of skeletal muscle symptoms: birth. Diagnosis: 5 years. Clinical findings: scoliosis since the teenage years, limited mobility at 29 years. Wheelchair dependent at 40 years of age.	Cardiac data at 33 years of age: Congestive heart failure. Pacemaker implanted. Cardiac data at 35 years of age: Severe LV dilation with global LV dysfunction, EF = 34%.	33	3

* Age refers to the youngest age in years at which the patient fulfills our criteria for classification as affected with cardiomyopathy.

Abbreviations:
AV: atrioventricular; **BMD:** Becker muscular dystrophy; **CK:** creatine kinase; **DCM:** dilated cardiomyopathy; **Dx:** diagnosis; **ECG:** electrocardiogram; **EDV:** end diastole volume; **EF:** ejection fraction (left ventricular unless otherwise specified); **EPSS:** E-point septal separation; **FVC:** forced vital capacity; **LA:** left atrium; **LBBB:** left branch bundle block; **LV:** left ventricle; **LVEDd:** left ventricular end-diastolic diameter; **LVEDs:** left ventricular end systolic diameter; **MDAc:** muscular dystrophy clinics of Nationwide Children's Hospital and The Ohio State University Medical Center; **NSI:** no specific information; **PVC:** premature ventricular contraction; **RA:** right atrium;

RBBB: right branch bundle block; **RV:** right ventricle; **SF:** shortening fraction; **UDP:** United Dystrophinopathy Project; **WHO:** World Health Organization.

Normal values for measured parameters:
CK: 200 U/L (unless otherwise stated); **EF:** above or equal to 55%; **EPSS:** below 5 mm; **FVC:** 80%-120% predicted; **Intraventricular Septal Thickness:** below 12mm; **LVEDd:** below 58 mm, 2 z scores, or 2 SD; **Posterior Wall Thickness:** below 12mm; **QTc:** below 440ms; **SF:** above or equal to 32%; **Vignos Scale:** described in *JAMA* (1963), 184:89-96.

Published Sources:

1. Gold R, Kress W, Meurers B, Meng G, Reichmann H, Muller CR: Becker muscular dystrophy: detection of unusual disease courses by combined approach to dystrophin analysis. *Muscle Nerve* 1992, 15:214-218.

2. Feng J, Yan J, Buzin CH, Towbin JA, Sommer SS: Mutations in the dystrophin gene are associated with sporadic dilated cardiomyopathy. *Mol Genet Metab* 2002, 77:119-126.

3. Novakovic I, Bojic D, Todorovic S, Apostolski S, Lukovic L, Stefanovic D, Milasin J: Proximal dystrophin gene deletions and protein alterations in becker muscular dystrophy. *Ann N Y Acad Sci* 2005, 1048:406-410.

4. Oldfors A, Eriksson BO, Kyllerman M, Martinsson T, Wahlstrom J: Dilated cardiomyopathy and the dystrophin gene: an illustrated review. *Br Heart J* 1994, 72:344-348.

5. Maeda M, Nakao S, Miyazato H, Setoguchi M, Arima S, Higuchi I, Osame M, Taira A, Nomoto K, Toda H, et al.: Cardiac dystrophin abnormalities in Becker muscular dystrophy assessed by endomyocardial biopsy. *Am Heart J* 1995, 129:702-707.

6. Steare SE, Dubowitz V, Benatar A: Subclinical cardiomyopathy in Becker muscular dystrophy. *Br Heart J* 1992, 68:304-308.

7. Arbustini E, Diegoli M, Morbini P, Dal Bello B, Banchieri N, Pilotto A, Magani F, Grasso M, Narula J, Gavazzi A, et al.: Prevalence and characteristics of dystrophin defects in adult male patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2000, 35:1760-1768.

8. Martins E, Silva-Cardoso J, Silveira F, Nadais G, Goncalves FR: Left ventricular function in adults with muscular dystrophies: genotype-phenotype correlations. *Rev Port Cardiol* 2005, 24:23-35.

9. Melacini P, Fanin M, Danieli GA, Fasoli G, Villanova C, Angelini C, Vitiello L, Miorelli M, Buja GF, Mostacciuolo ML, et al.: Cardiac involvement in Becker muscular dystrophy. *J Am Coll Cardiol* 1993, 22:1927-1934.

10. Melacini P, Fanin M, Danieli GA, Villanova C, Martinello F, Miorin M, Freda MP, Miorelli M, Mostacciuolo ML, Fasoli G, et al.: Myocardial involvement is very frequent among patients affected with subclinical Becker's muscular dystrophy. *Circulation* 1996, 94:3168-3175.

11. Akdemir R, Ozhan H, Gunduz H, Yazici M, Erbilen E, Uyan C, Imirzalioglu N: Complete atrioventricular block in Becker muscular dystrophy. *N Z Med J* 2004, 117:U895.

12. Piccolo G, Azan G, Tonin P, Arbustini E, Gavazzi A, Banfi P, Mora M, Morandi L, Tedeschi S: Dilated cardiomyopathy requiring cardiac transplantation as initial manifestation of Xp21 Becker type muscular dystrophy. *Neuromuscul Disord* 1994, 4:143-146.

13. Sousa RC, Silva P, Pais F, Fortuna A, Relvas S, Simoes L, Miranda O, Gama V: [Dilated cardiomyopathy in a patient with Becker's muscular dystrophy. A clinical case report]. *Rev Port Cardiol* 1993, 12:563-570, 511.

14. Shimizu M, Ino H, Yasuda T, Fujino N, Uchiyama K, Mabuchi T, Konno T, Kaneda T, Fujita T, Masuta E, et al.: Gene mutations in adult Japanese patients with dilated cardiomyopathy. *Circ J* 2005, 69:150-153.

15. Finsterer J, Stollberger C, Blazek G, Kunafer M, Prager E: Cardiac involvement over 10 years in myotonic and Becker muscular dystrophy and mitochondrial disorder. *Int J Cardiol* 2007, 119:176-184.

16. Yazaki M, Yoshida K, Nakamura A, Koyama J, Nanba T, Ohori N, Ikeda S: Clinical characteristics of aged Becker muscular dystrophy patients with onset after 30 years. *Eur Neurol* 1999, 42:145-149.

17. Politano L, Passamano L, Petretta VR, Nigro V, Papparella S, Nigro G, Santangelo L, M.G.Esposito, Come LI, Nigro G: Familial Dilated Cardiomyopathy Associated with the Typical Dystrophin BMD Mutation: Report on Two Additional Cases. *Acta Myol* 1999:3329-3336.

18. Yoshida K, Ikeda S, Nakamura A, Kagoshima M, Takeda S, Shoji S, Yanagisawa N: Molecular analysis of the Duchenne muscular dystrophy gene in patients with Becker muscular dystrophy presenting with dilated cardiomyopathy. *Muscle Nerve* 1993, 16:1161-1166.

19. Yazawa M, Ikeda S, Owa M, Haruta S, Yanagisawa N, Tanaka E, Watanabe M: A family of Becker's progressive muscular dystrophy with severe cardiomyopathy. *Eur Neurol* 1987, 27:13-19.

20. Saito M, Kawai H, Akaike M, Adachi K, Nishida Y, Saito S: Cardiac dysfunction with Becker muscular dystrophy. *Am Heart J* 1996, 132:642-647.

21. Muntoni F, Di Lenarda A, Porcu M, Sinagra G, Mateddu A, Marrosu G, Ferlini A, Cau M, Milasin J, Melis MA, et al.: Dystrophin gene abnormalities in two patients with idiopathic dilated cardiomyopathy. *Heart* 1997, 78:608-612.

22. Fanin M, Melacini P, Angelini C, Danieli GA: Could utrophin rescue the myocardium of patients with dystrophin gene mutations? *J Mol Cell Cardiol* 1999, 31:1501-1508.

23. Finsterer J, Bittner RE, Grimm M: Cardiac involvement in Becker's muscular dystrophy, necessitating heart transplantation, 6 years before apparent skeletal muscle involvement. *Neuromuscul Disord* 1999, 9:598-600.

24. Tasaki N, Yoshida K, Haruta SI, Kouno H, Ichinose H, Fujimoto Y, Urasawa N, Kawakami T, Taniguchi M, Kurushima S, et al.: X-linked dilated cardiomyopathy with a large hot-spot deletion in the dystrophin gene. *Intern Med* 2001, 40:1215-1221.

25. Nakamura A, Yoshida K, Fukushima K, Ueda H, Urasawa N, Koyama J, Yazaki Y, Yazaki M, Sakai T, Haruta S, et al.: Follow-up of three patients with a large in-frame deletion of exons 45-55 in the Duchenne muscular dystrophy (DMD) gene. *J Clin Neurosci* 2008, 15:757-763.

26. Palmucci L, Mongini T, Chiado-Piat L, Doriguzzi C, Fubini A: Dystrophinopathy expressing as either cardiomyopathy or Becker dystrophy in the same family. *Neurology* 2000, 54:529-530.

Supplemental Table 3: Non-affected patients.

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
216	3-4	BMD	[1] (Patient 22)	Age at consultation: 24 years. Clinical Severity: severe. Myoglobinuria. FVC = 92%. Positive family history.	ECG showed incomplete RBBB. Holter ECG showed isolated monomorphic PVCs (Lown grade 1). Normal LA volume. LV EDV = 50 mL/m^2. EF = 67%. Normal LV wall motion. Normal RV EDV. Normal RVEF.	24	1
218	3-4	BMD	[1] (Patient 29)	Age at consultation: 35 years. Clinical Severity: Severe. FVC = 75% (mild restrictive respiratory insufficiency). Positive family history.	Normal ECG. Holter ECG showed isolated monomorphic PVCs (Lown grade 1). Normal LA volume. LV EDV = 62 mL/ m^2. EF = 61%. Normal LV wall motion. Normal RV EDV. Normal RVEF. Normal RV motion.	35	1
AH15	3-4	BMD	MDAc	Ambulatory at 9 years of age.	EF = 55%, SF = 34%, EPSS = 5mm.	9	1
SL459	3-7	BMD	UDP	Vignos Scale (22 years): upper = 1 / lower = 2.	EF = 55%	25	1
99	3-9	BMD	[1] (Patient 1)	Age at consultation: 6 years. Clinical Severity: Mild. Skeletal muscle symptoms are present. CK = 1770 U/L. Western blot: reduced dystrophin expression (60%) and size (370 kDa). Negative family history.	Normal ECG. Normal LA volume. LV EDV = 37 mL/ m^2. EF = 60%. Normal LV wall motion. RV EDV=41 mL/ m^2. RVEF = 68%. Normal RV wall motion.	6	1
AH14	5	BMD	MDAc	Onset of skeletal muscle symptoms: 7 years. Age at consultation: 13 years. Clinical Severity: Mild. Skeletal muscle symptoms are present. Elevated CK. Biopsy: dystrophic changes; Dys2 staining positive but Dys 1 and Dys 3 severely reduced; Utrophin is upregulated. Western Blot: severely reduced dystrophin.	EF = 58%, SF = 31%, EPSS = 5mm, no mitral valve regurgitation, no sign of LV dilation.	13	1

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
AH02	5	BMD	MDAc	Onset of skeletal muscle symptoms: 10 years. Frequent falling, difficulty climbing stairs, calf hypertrophy, positive Gower's sign. CK = 7651 U/L. Negative family history.	LVEDd = 0.5sd, EF = 60%, SF = 40%.	14	1
SL188	45	BMD	UDP	Onset of skeletal muscle symptoms: 3 years. Diagnosis: 6 years. Weakness, calf hypertrophy and Gower's sign. Vignos Scale (14 years): upper = 1 / lower = 2.	EF = 63%, SF = 35%.	15	2
213	45-47	BMD	[1] (Patient 2)	Age at consultation: 6 years. Clinical Severity: Mild. CK = 5000 U/L. FVC = 56% (moderate restrictive respiratory insufficiency).	Normal ECG. Normal LA volume. LV EDV = 67 mL/ m^2. EF = 64%. Normal LV wall motion. RV EDV = 46 mL/ m^2. RVEF = 57%. Normal RV motion.	6	2
217	45-47	BMD	[1] (Patient 24)	Age at consultation: 28 years. Clinical Severity: Moderate.	ECG showed T wave changes. Normal Holter ECG. Normal LA volume. LV EDV = 69 mL/ m^2. EF = 55%. Normal LV wall motion. RV EDV = 66 mL/ m^2. RVEF = 64%.	28	2
106	45-47	BMD	[1] (Patient 28)	Age at consultation: 33 years. Clinical Severity: Moderate. Biopsy showed small number of dystrophin negative fibers. Western Blot: reduced amount (50%) and size (380 kDa). Positive family history.	Normal ECG. Holter ECG showed isolated monomorphic PVCs (Lown grade 1). LA volume = 29 mL/ m^2. LV EDV = 44 mL/ m^2. EF = 55%. Normal LV wall motion. RV EDV = 52 mL/ m^2. RVEF = 52%.	33	2
KJ03	45-47	BMD	MDAc	Onset of skeletal muscle symptoms: childhood. Diagnosis: 37 years. Age at consultation: 47 years. Patient is ambulant with wide-based gait with exaggerated lordosis and some waddle.	Echocardiography and stress test negative for cardiac dilation.	45	2
SL382	45-47	BMD	UDP	Onset of skeletal muscle symptoms: 1.5 years. Diagnosis: 9 years. Toe walking, myalgia, cramping. Vignos Scale (19 years): upper = 1 / lower = 1. Negative family history.	EF=57%, SF= 32%.	19	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
SL879	45-47	BMD	UDP	Vignos Scale (10 years): upper = 1 / lower = 1.	SF = 36.1%	10	2
MJ04	45-47	BMD	MDAc	Diagnosis: 10 years. Elevated CK. Onset of skeletal muscle symptoms: 12 years. Muscle fatigue, weakness, calf hypertrophy.	Echocardiography normal.	17	2
MJ09	45-47	BMD	MDAc	Diagnosis: age 4 years. Biopsy showed muscle fiber size variation and necrosis. Elevated CK. Negative family history.	EF = 60%, SF = 42.5%.	24	2
AH07	45-47	BMD	MDAc	Onset of skeletal muscle symptoms: 5 years. Muscle fatigue, calf hypertrophy, and hip pain. CK=18137 U/L. Biopsy showed no inflammation, mild fatty replacement and mild fibrosis. Staining for dystrophin, sarcoglycans, beta-dystroglycan and laminin showed strong undisrupted sarcolemmal staining. Western Blot: several dystrophin bands of reduced size. Positive family history.	LVEDd = 0.9 sd, EPSS = 2mm, SF = 40%, EF = 60%.	9	2
AH03	45-47	BMD	MDAc	Onset of skeletal muscle symptoms: 6 years. CK = 5650 U/L. Mild calf hypertrophy, mild lordosis, kyphosis, scoliosis, toe walking, positive Gower's sign, weakness, chronic pulmonary disease, developmental motor delay. Positive family history.	EF = 55%, SF = 33%.	10	2
AH10	45-48	BMD	MDAc	Diagnosis: 10 months of age. Onset of skeletal muscle symptoms: 8 years. Calf hypertrophy, muscle cramps. CK = 5 210 U/L. Positive family history.	EF = 58%, SF = 32.23%.	15	2
SL50	45-48	BMD	UDP	Onset of skeletal muscle symptoms: 6 years. Diagnosis: 6 years. Symptoms: weakness, myalgias, cramping. Negative family history. Vignos Scale (18 years): upper = 1/ lower = 1.	EF = 55%	18	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
214	45-48	BMD	[1] (Patient 4)	Age at consultation: 10 years. Clinical Severity: Mild. Myoglobinuria. CK = 7300 U/L. FVC = 69% (mild restrictive respiratory insufficiency). Positive family history.	ECG showed R/S>1. Normal Holter ECG. Normal LA volume. LV EDV = 50 mL/ m^2. EF = 62%. Normal LV wall motion. RV EDV = 74 mL/ m^2. RVEF = 43%. Normal RV motion.	10	2
181	45-48	BMD	[2] (Patient A13)	Age at consultation: 20 years. Cramps, myalgia, myoglobinuria, calf hypertrophy. CK = 1774 U/L. Western blot: normal dystrophin amount but reduced size (360 kDa).	ECG showed left anterior fascicular block. Normal Holter ECG. LV EDV = 72 mL/ m^2. EF = 63%.	20	2
207	45-48	BMD	[3]	Onset of skeletal muscle symptoms: 15 years. Cramps. Age at consultation: 41 years. CK = 406 U/L. No muscle weakness or fatigability. Muscle hypertrophy of glutei and calf muscles. Negative family history.	ECG showed flat T waves. Slight motility reduction of the LV posterior wall and increased LV EDV. Normal LV end-diastolic pressure, EF = 58%.	41	2
MJ26	45-48	BMD	MDAc	Shoulder girdle weakness and difficulty running since early childhood. Neurological exam at 18 years: CK = 2500-3300 U/L. Biopsy: fiber size variation, atrophic fibers, mild to moderate increase of internal nuclei. Western Blot: reduced dystrophin amount.	LVEDd = 0.5sd, SF = 37%, EF = 58%, no mitral regurgitation.	29	2
219	45-49	BMD	[1] (Patient 31)	Age at consultation: 50 years. Clinical Severity: Severe. FVC = 26% (severe restrictive respiratory insufficiency). Positive family history.	ECG showed incomplete LBBB. Holter ECG showed Lown grade 4b. Normal LA volume. LV EDV = 74 mL/ m^2. EF = 55%. Normal LV wall motion. Normal RV EDV. Normal RVEF. Normal RV motion.	50	2
103	48	BMD	[1] (Patient 10)	Age at consultation: 13 years. Clinical Severity: Mild. Skeletal muscle symptoms are present. CK = 3910 U/L. Western blot: reduced dystrophin expression (80%) and size (390 kDa). Positive family history.	ECG showed T wave changes and R/S>1. Normal Holter ECG. Normal LA volume. LV EDV = 49 mL/ m^2. EF = 58%. RV EDV = 55 mL/ m^2. RVEF = 56%.	13	2

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
184	48	BMD	[2] (Patient A17)	Age at consultation: 24 years. Cramps, myalgia, myoglobinuria, calf hypertrophy. CK = 18 U/L. Western blot: reduced dystrophin amount (60%) and reduced size (395 kDa).	ECG showed R/S>1. Normal Holter ECG. LV EDV = 88 mL/ m^2. EF = 56%.	24	2
114	48	BMD	[4] (Patients 1 & 2)	Onset of skeletal muscle symptoms: 3 years. Patients are twins. Symptoms: cramps and myalgia during routine activity. Negative Gower's sign. EMG showed myopathic features. CK = 2655 U/L. Age at consultation: 9 years. Biopsy showed slight variability in fiber staining for dystrophin. Western blot: slightly decreased size. Negative family history.	Normal ECG. Normal echocardiography.	3	2
108	48-49	BMD	[1] (Patient 12)	Age at consultation: 14 years. Clinical Severity: Mild. Skeletal muscle symptoms are present. FVC = 105%. Biopsy showed many dystrophin negative fibers. Western blot: reduced dystrophin expression (50%) and size (390 kDa). Positive family history.	ECG showed incomplete RBBB. Holter ECG showed Lown grade 1. Normal LA volume. LV EDV = 77 mL/ m^2. EF = 65%. Normal LV wall motion. RV EDV =110 mL/ m^2. RVEF = 56%. RV wall motion showed septal akinesia.	14	2
180	48-49	BMD	[2] (Patient A11)	Age at consultation: 18 years. CK = 6427 U/L. Cramps, myalgia, myoglobinuria, calf hypertrophy. Western blot: reduced amount (50%) and size (390 kDa).	ECG showed incomplete RBBB. Holter ECG showed isolated monomorphic PVCs (Lown grade 1). LV EDV = 86 mL/ m^2. EF = 58%. Normal LV wall motion.	18	2
100	45-51	BMD	[1] (Patient 5)	Age at consultation: 10 years. Clinical Severity: Mild. Skeletal muscle symptoms are present. CK = 1616 U/L. Western blot: normal dystrophin expression levels but reduced size (360 kDa). Negative family history.	ECG showed R/S>1. Holter ECG showed isolated monomorphic PVCs (Lown grade 1). Normal LA volume. LV EDV = 63 mL/ m^2. EF = 69%. Normal LV wall motion. RV EDV = 60 mL/ m^2. RVEF = 68%. Normal RV wall motion.	10	3

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
SL1198	45-51	BMD	UDP	Age of skeletal muscle symptom onset: 1 year. Diagnosis: 2 years. Skeletal muscle symptoms are present. Developmental delay. Vignos Scale (8 years): upper = 1/ lower = 1.	SF = 38.6%	8	
SL54	45-51	BMD	UDP	Age of skeletal muscle symptom onset: 4 years. Diagnosis: 11 years. Myalgia, cramping. Vignos Scale (13 years): upper = 1 / lower = 1. Positive family history.	EF = 65%, SF = 34%.	13	3
185	45-52	BMD	[2] (Patient A18)	Age at consultation: 29 years. Cramps, myalgia, myoglobinuria, calf hypertrophy. CK = 2100 U/L. Western blot: normal dystrophin amount but reduced size (360 kDa).	Normal ECG. LVEDV = 53 mL/ m^2. EF = 61%.	29	3
162	45-55	BMD	[16] (Patient 2)	Onset of skeletal muscle symptoms: 59 years. Mild but progressive weakness affecting both arms and legs, difficulty climbing hills and stairs, difficulty lifting luggage and standing from a sitting or crouching position. Age at consultation: 69 years. Neurological exam: moderate proximal muscular atrophy and weakness, especially in the lower limbs, positive Gower's sign, waddling gait, no calf hypertrophy. CK = 669 U/L. Biopsy showed fiber size variation, opaque fibers and proliferated connective tissues. Dystrophin staining: faint and discontinuous patchy pattern. Negative family history.	No cardiac symptoms. Negative cardiac failure, cardiomegaly on chest X-ray. ECG showed prominent R wave in V1. No LV hypokinesis, LVEDd = 56mm, LVEDs = 38mm. EF = 60%, SF = 32.1%.	69	3

ID	Deleted Exons	Dx	Source	Clinical information	Cardiac information	Age* (Years)	Group
178	45-55	BMD	[2] (Patient A5)	Age at consultation: 12 years. Clinical Severity: Mild. Cramps, myalgia, myoglobinuria, calf hypertrophy. CK = 6000 U/L. FVC normal. Western blot: reduced dystrophin amount (40%) and reduced size (340 kDa). Negative family history.	ECG showed R/S>1 and incomplete LBBB. Holter ECG showed isolated monomorphic PVCs (Lown grade 1). Normal LA volume. LV EDV = 50 mL/ m^2. EF = 61%. Normal LV wall motion. RV EDV = 63 mL/ m^2. RVEF = 60%. Normal RV wall motion.	12	3
204	48-51	BMD	[5]	Onset of skeletal muscle symptoms: 5 years. Age at consultation: 9 years. Calf hypertrophy and mild proximal muscle weakness. CK = 3,000 U/L. Grandson of #203.	Normal echocardiography.	9	3
AH08	49-51	BMD	MDAc	Onset of skeletal muscle symptoms and diagnosis: 4 years. CK = 551 U/L. Normal pulmonary function. Brother of #AH9. Positive family history.	SF = 37%, EF = 59%, LVEDd = 1sd.	5	3
AH09	49-51	BMD	MDAc	Onset of skeletal muscle symptoms: 7 years. Weakness and muscle pain. CK = 1096 U/L. Brother of #AH8. Positive family history.	SF = 42%, EF = 62%, no mitral regurgitation.	8	3
202	50-51	BMD	[6]	Onset of skeletal muscle symptoms: 2 years. Age at consultation: 4 years. CK =1300 U/L. Normal EMG. Biopsy showed rhabdomyolysis without features of muscular dystrophy. Immunolabelling for dystrophin, merosin and dysferlin were normal. Western blot: reduced size of dystrophin and slightly reduced amount of dystrophin, α and γ-sarcoglycan.	Normal echocardiography.	4	3
SL896	50-53	BMD	UDP	Onset of skeletal muscle symptoms: 5years. Diagnosis: 6.5 years. Symptom of weakness. Vignos Scale (13 years): upper = 1 / lower = 1. Positive family history.	SF = 39%.	4	3

* Age refers to the age in years of the patient at the last reported cardiac evaluation with cardiac findings that fulfill our criteria for a classification of non-affected with cardiomyopathy.

Abbreviations:
BMD: Becker muscular dystrophy; **CK:** creatine kinase; **Dx:** diagnosis; **ECG:** electrocardiogram; **EDV:** end diastole volume; **EF:** ejection fraction (left ventricular unless otherwise specified); **EMG:** electromyography; **EPSS:** E-point septal separation; **FVC:** forced vital capacity; **LA:** left atrium; **LBBB:** left branch bundle block; **LV:** left ventricle; **LVEDd:** left ventricular end-diastolic diameter; **MDAc:** muscular dystrophy clinics of Nationwide Children's Hospital and The Ohio State University Medical Center; **PVC:** premature ventricular contraction; **RBBB:** right branch bundle block; **RV:** right ventricle; **SF:** shortening fraction; **UDP:** United Dystrophinopathy Project.

Normal values for measured parameters:
CK: 200 U/L (unless otherwise stated); **EF:** above or equal to 55%; **EPSS:** below 5 mm; **FVC:** 80%-120% predicted; **LVEDd:** below 58 mm, 2 z scores, or 2 SD; **SF:** above or equal to 32%; **Vignos Scale:** described in *JAMA* (1963), 184:89-96.

Published sources:

1. Melacini P, Fanin M, Danieli GA, Fasoli G, Villanova C, Angelini C, Vitiello L, Miorelli M, Buja GF, Mostacciuolo ML, et al.: Cardiac involvement in Becker muscular dystrophy. *J Am Coll Cardiol* 1993, 22:1927-1934.

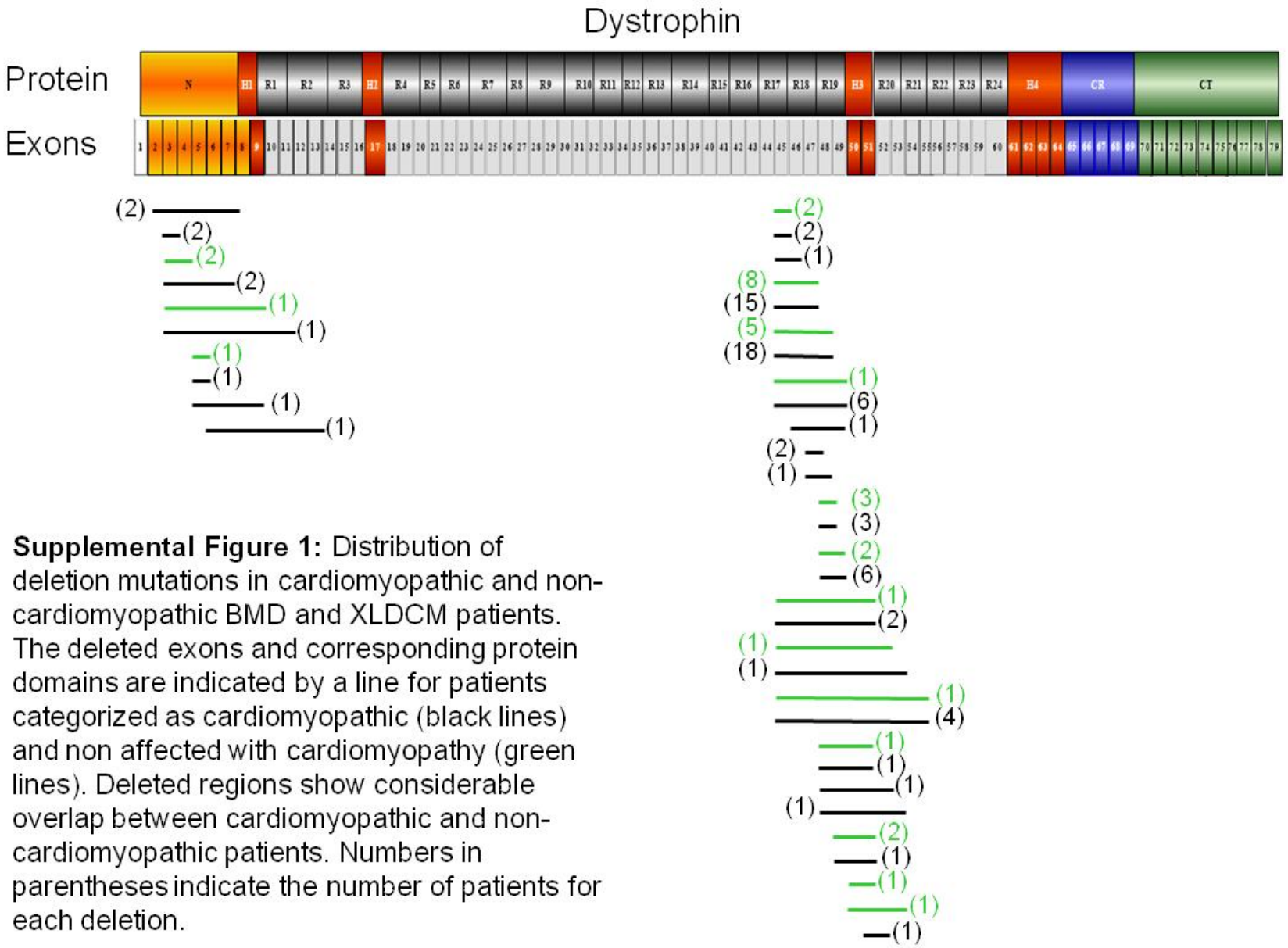
2. Melacini P, Fanin M, Danieli GA, Villanova C, Martinello F, Miorin M, Freda MP, Miorelli M, Mostacciuolo ML, Fasoli G, et al.: Myocardial involvement is very frequent among patients affected with subclinical Becker's muscular dystrophy. *Circulation* 1996, 94:3168-3175.

3. Siciliano G, Fanin M, Angelini C, Pollina LE, Miorin M, Saad FA, Freda MP, Muratorio A: Prevalent cardiac involvement in dystrophin Becker type mutation. *Neuromuscul Disord* 1994, 4:381-386.

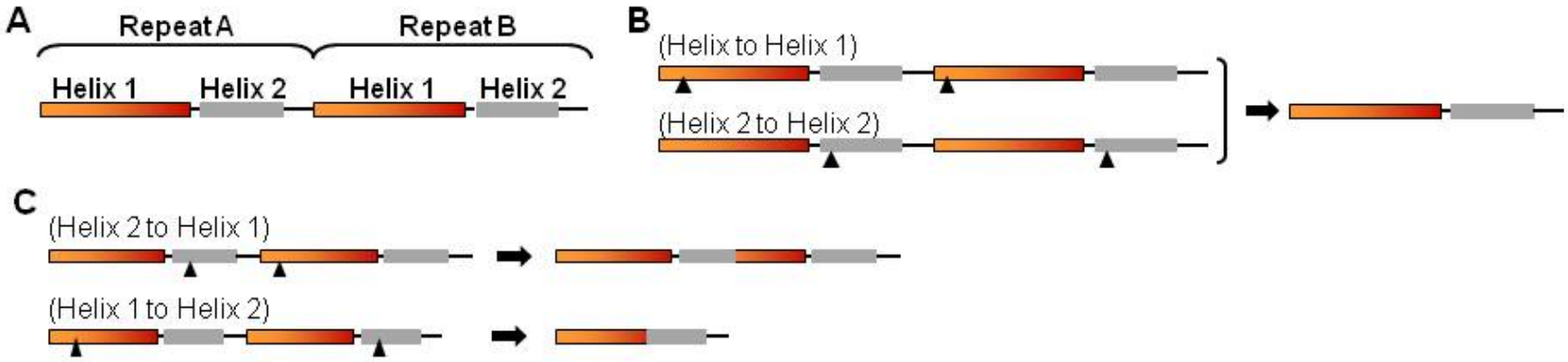
4. Ramelli GP, Joncourt F, Luetschg J, Weis J, Tolnay M, Burgunder JM: Becker muscular dystrophy with marked divergence between clinical and molecular genetic findings: case series. *Swiss Med Wkly* 2006, 136:189-193.

5. Palmucci L, Mongini T, Chiado-Piat L, Doriguzzi C, Fubini A: Dystrophinopathy expressing as either cardiomyopathy or Becker dystrophy in the same family. *Neurology* 2000, 54:529-530.

6. Lesca G, Testard H, Streichenberger N, Pelissier JF, Lestra C, Burel E, Jonveaux P, Michel-Calemard L: [Family study allows more optimistic prognosis and genetic counselling in a child with a deletion of exons 50-51 of the dystrophin gene]. *Arch Pediatr* 2007, 14:262-265.



Supplemental Figure 1: Distribution of deletion mutations in cardiomyopathic and non-cardiomyopathic BMD and XLDCM patients. The deleted exons and corresponding protein domains are indicated by a line for patients categorized as cardiomyopathic (black lines) and non affected with cardiomyopathy (green lines). Deleted regions show considerable overlap between cardiomyopathic and non-cardiomyopathic patients. Numbers in parentheses indicate the number of patients for each deletion.



D

Exon Deletion	Spectrin repeat phasing	Joins	To
45	*Out-of-phase*	*SR17 H2*	*SR18 H1*
45-46	In-phase	SR17 H2	SR18 H2
45-47	*Out-of-phase*	*SR17 H2*	*SR19 H1*
45-48	In-phase	SR17 H2	SR19 H2
45-49	*Out-of-phase*	*SR17 H2*	*SR20 H1*
46-49	In-phase	SR18 H1	SR20 H1
47	*Out-of-phase*	*SR18 H2*	*SR19 H1*
47-48	In-phase	SR18 H2	SR19 H2
48	*Out-of-phase*	*SR19 H1*	*SR19 H2*
48-49	In-phase	SR19 H1	SR20 H1

Abbreviations: SR: Spectrin Repeat; H1: Helix 1; H2: Helix2

Supplemental Figure 2: Spectrin repeat phasing and deletion mutations in the exon 45 to 49 region. **A.** Basic structure of the dystrophin spectrin repeats. A long alpha-helical segment (Helix 1, orange-red) alternates with a short Helix 2 (grey). Linker sequences of variable length connect the helical segments. **B.** In phase mutations shorten the rod domain without disrupting the basic structure of spectrin repeats. Arrow-heads indicate beginning and end sites of deletions. **C.** Out-of-phase deletion mutations joining a Helix 2 to a Helix 1 and vice versa, with loss of a flexible linker sequence. Arrow-heads indicate beginning and end sites of deletions. **D.** Patient exon deletions that result in in-phase and out-of-phase modifications of the exon 45 to 49 region.