European LGMDR9 Community Conference

SATURDAY 25TH MAY 2024

Natural history studies in LGMDR9

Andreas D. Rosenberger

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Natural history studies in LGMDR9

LGMDR9 European Patient Day 25.05.24

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Synopsis

What is a natural history study, and why conduct them?

Insights from selected studies

What is it- and why conduct a natural history study?

Definition: "*The natural history of a disease* is traditionally defined as the course a disease takes in the absence of intervention in individuals with the disease, from the disease's onset until either the disease's resolution or the individual's death. *A natural history study* is a preplanned observational study intended to track the course of a disease."
Purpose of a natural history study: To identify demographic, genetic, environmental, and other variables (e.g. treatment modalities, concomitant medications) that correlate with the disease's development and outcomes.

(FDA 2019)

What is it- and why conduct a natural history study?

Uses of a natural history study:

A. Drug development

1. Identifying the patient population
2. Identification or development of clinical outcome assessments (clinician reported, PROMs, performance outcome etc.)
3. Identification or development of biomarkers

B. Other uses

-"To benefit patients by establishing communication pathways, identifying disease-specific centers of excellence, facilitating the understanding and evaluation of the current standard of care practices, and identifying ways to improve patient care" (FDA 2019)

Examples of natural history studies

ACTIVE, NOT RECRUITING

Natural History Study of Patients With Limb-Girdle Muscular Dystrophy 2I

ClinicalTrials.gov ID NCT03842878

Sponsor Genethon

Information provided by Genethon (Responsible Party)

Last Update Posted 2023-04-06

ACTIVE, NOT RECRUITING

Limb-Girdle Muscular Dystrophy Type 2I in Norway

ClinicalTrials.gov ID NCT03930628

Sponsor University Hospital of North Norway

Information provided by University Hospital of North Norway (Responsible Party)

Last Update Posted 2022-11-07

COMPLETED

Biomarker Development in LGMD2i (MLB-01-001)

ClinicalTrials.gov ID NCT04202627

Sponsor ML Bio Solutions, Inc.

Information provided by ML Bio Solutions, Inc. (Responsible Party)

Last Update Posted 2023-03-29

The Iowa Wellstone Muscular Dystrophy Specialized Research Center

Welcome | About the Centers | Research | Cores | Resources for Patients and Researchers | People | News and Events

Research Projects

Project 1 | Project 2

RECRUITING

Clinical Trial Readiness for the Dystroglycanopathies

ClinicalTrials.gov ID NCT00313677

Sponsor Katherine Mathews

Information provided by Katherine Mathews, University of Iowa (Responsible Party)

Last Update Posted 2024-04-09

Different insights

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Natural history of limb girdle muscular dystrophy R9 over 6 years: searching for trial endpoints

Correction(s) for this article

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RESEARCH ARTICLE | VOLUME 33, ISSUE 2, P119-132, FEBRUARY 2023

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Synnøve M. Jensen • Kai Ivar Müller • Svein Ivar Mellgren • ... Øivind Nilssen • Marijke Van Ghelue • Kjell Arne Arntzen • Show all authors

Open Access • Published: November 25, 2022 • DOI: https://doi.org/10.1016/j.nmd.2022.11.005 •

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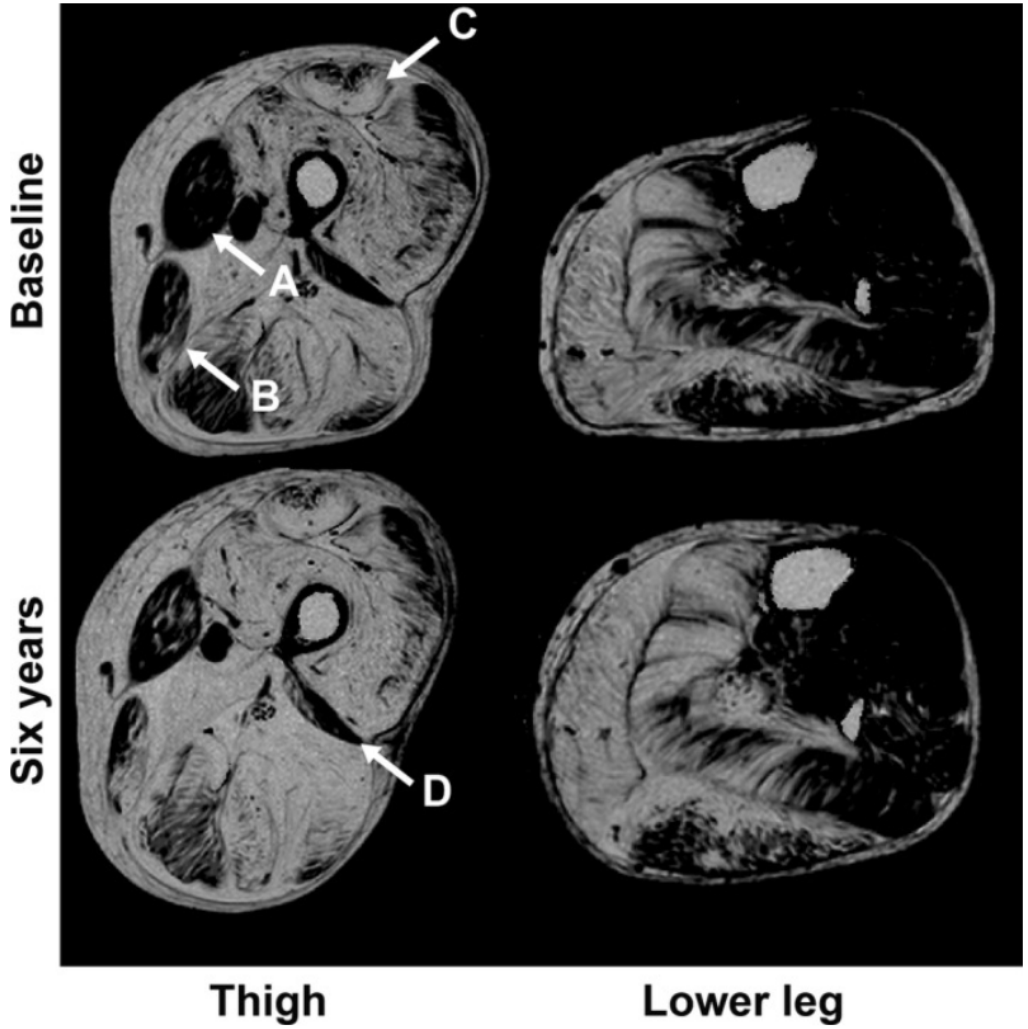

Table 2

Median muscle fat fractions at baseline and 6-year follow up

Muscle group	Median baseline (range), %	Median 6 years (range), %	*P* value	SRM
Rectus femoris[b, c]	10.8 (0.9–81.9)	19.9 (0.4–92.2)	<0.001[a]	0.90
Vastus medialis	21.0 (1.1–86.6)	44.4 (2.5–87.9)	<0.001[a]	0.83
Vastus lateralis[c]	13.7 (1.5–65.2)	36.1 (2.8–81.7)	<0.001[a]	0.92
Sartorius[c]	20.9 (1.7–89.8)	34.2 (5.4–88.3)	<0.001[a]	0.98
Gracilis[b]	18.4 (3.7–81.0)	32.4 (4.5–90.2)	<0.001[a]	1.04
Biceps femoris long head[c]	69.4 (2.2–97.7)	78.6 (4.8–100)	0.001[a]	0.81
Biceps femoris short head	21.3 (3.2–94.5)	32.5 (4.6–84.3)	0.002[a]	0.53
Semitendinosus[c]	35.6 (2.1–100)	69.6 (4.1–100)	<0.001[a]	0.83
Semimembranosus[c]	25.7 (0.5–95.1)	53.4 (4.6–99.2)	<0.001[a]	0.90
Tibialis anterior	5.2 (0.9–25.3)	7.1 (1.1–27.1)	0.002[a]	0.67
Peroneus longus	15.8 (3.0–46.2)	18.0 (4.6–65.2)	0.001[a]	0.88
Soleus	7.5 (1.8–67.4)	16.7 (3.1–70.1)	<0.001[a]	1.17
Lateral gastrocnemius[c]	19.4 (0.9–76.1)	35.8 (3.1–75.2)	<0.001[a]	0.91
Medial gastrocnemius[c]	19.9 (1.1–91.8)	48.0 (2.8–84.2)	<0.001[a]	0.95

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The median change in functional assessments over the follow-up of 6 years

Functional assessment	Median baseline (range)	Median 6 years (range)	*P* value	SRM
Forced vital capacity sitting (%)[c]	77 (55–94)	64 (31–86)	0.001[a]	−1.29
Forced vital capacity lying (%)[d]	70 (36–90)	54 (21–84)	0.002[a]	−1.06
Hip flexion (kg)	7.7 (0.0–36.8)	6.4 (0.0–24.3)	0.13	−0.35
Hip adduction (kg)	6.1 (0.7–26.7)	4.2 (0–23.9)	0.02[a]	−0.59
Hip abduction (kg)	8.3 (0.6–25.0)	7.2 (2.2–25.3)	0.76	−0.01
Knee extension (kg)	11.1 (2.0–40.3)	12.0 (1.5–39.1)	0.15	−0.26
Knee flexion (kg)	8.4 (0.9–30.0)	4.8 (0–37.9)	0.21	−0.12
Ankle dorsiflexion (kg)	14.7 (2.5–38.6)	13.9 (2.4–26.3)	0.07	−0.42
Six-minute walk (meters)	391 (67–625)	286 (0–750)	0.001[a]	−0.85
Timed up and go velocity ($msec^{-1}$)[e]	0.5 (0.0–1.7)	0.3 (0.0–1.6)	0.007[a]	−0.48
Ten-meter walk or run velocity ($msec^{-1}$)[e]	1.2 (0.5–4.4)	0.8 (0.0–3.9)	<0.001[a]	−1.02
Stair ascent velocity (steps/sec)[e]	0.7 (0.0–4.4)	0.4 (0.0–3.0)	0.001[a]	−0.46
Stair descent velocity (steps/sec)[e]	1.2 (0.0–4.4)	0.4 (0.0–3.3)	0.008[a]	−0.47
Chair rise (sec)[b], [c]	2.6 (0.3 to ∞)	9.8 (0.5 to ∞)	0.001[a]	N/A

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Results

At 6 years, all 14 muscle groups assessed demonstrated significant increases in fat fraction, compared to eight groups in the 1-year follow-up study. In direct contrast to the 1-year follow-up, the 6-min walk test, 10-m walk or run, timed up and go, stair ascend, stair descend and chair rise demonstrated significant decline. Among the functional tests, only FVC significantly declined over both the 1- and 6-year studies.

Interpretation

These results further support fat fraction measurements as a primary outcome measure alongside functional assessments. The most appropriate individual muscles are the vastus lateralis, gracilis, sartorius, and gastrocnemii. Using composite groups of lower leg muscles, thigh muscles, or triceps surae, yielded high standardized response means (SRMs). Over 6 years, quantitative fat fraction assessment demonstrated higher SRM values than seen in functional tests suggesting greater responsiveness to disease progression.

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Clinical characteristics and demographics	Patient Groups						
	Non-genetically confirmed patients	All genetically confirmed patients	All genetically confirmed LGMDR9 patients	Homozygous common in LGMDR9	Heterozygous common in LGMDR9	Homozygous unique in LGMDR9	Heterozygous unique in LGMDR9
Patients (n)	343	320	-	-	-	-	-
Sex (f/m, n)	183/160	177/143	-	-	-	-	-
LGMD R9 patients (n)	-	-	305	207	87	3	8
Sex (f/m, n)	-	-	168/137	117/90	45/42	1/2	5/3
Diagnosis							
Mean age of genetically confirmed diagnosis (years ±SD, n) *(at time of diagnosis)*	-	29.9 ± 17.5 (259) F(141): 30.8 ± 16.5 M(118): 29.0 ± 18.6	30.1 ± 17.3 (251) F(138): 31.1 ± 16.4 M(113): 28.8 ± 18.3	34.8 ± 15.9 (164) F(90): 35.1 ± 15.2 M(74): 34.5 ± 16.8	20.7 ± 16.5 (76) F(42): 23.2 ± 16.2 M(34): 17.5 ± 16.5	19.2 ± 7.4 (3) F(1): 17.6 M(2): 20.0 ± 10.3	26.1 ± 16.6 (8) F(5): 29.3 ± 17.4 M(3): 20.7 ± 17.0
Disease onset							
Mean age of symptom onset (years ±SD, n)	9.0 ± 6.4 (4) F(1): 7.0 M(3): 9.7 ± 7.6	14.8 ± 12.3 (155) F(88): 14.2 ± 11.0 M(67): 15.7 ± 13.9	15.1 ± 12.3 (152) F(86): 14.5 ± 10.9 M(66): 15.9 ± 13.9	19.0 ± 12.4 (102) F(61): 17.6 ± 10.6 M(41): 21.0 ± 14.5	6.8 ± 7.3 (44) F(22): 6.4 ± 7.2 M(22): 7.2 ± 7.5	5.8 ± 0.4 (2) F(1): 5.5 M(1): 6.0	12.0 ± 9.3 (4) F(2): 12.5 ± 10.6 M(2): 11.5 ± 12.0

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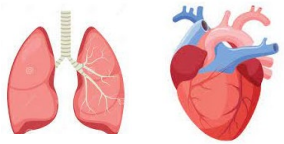
-LGMDR9 patients who are homozygous for the common mutation (c.826C > A) are more likely to have milder phenotype

-Variable walking abilities across range of ages- not possible to detect age ambulation is lost

-Fifty-five genetically confirmed LGMDR9 patients (55/303, 18.2%) required ventilation, and 30/129 (23.3%) reported a heart condition. Standards of care and follow up in routine care is needed.



ARTICLE

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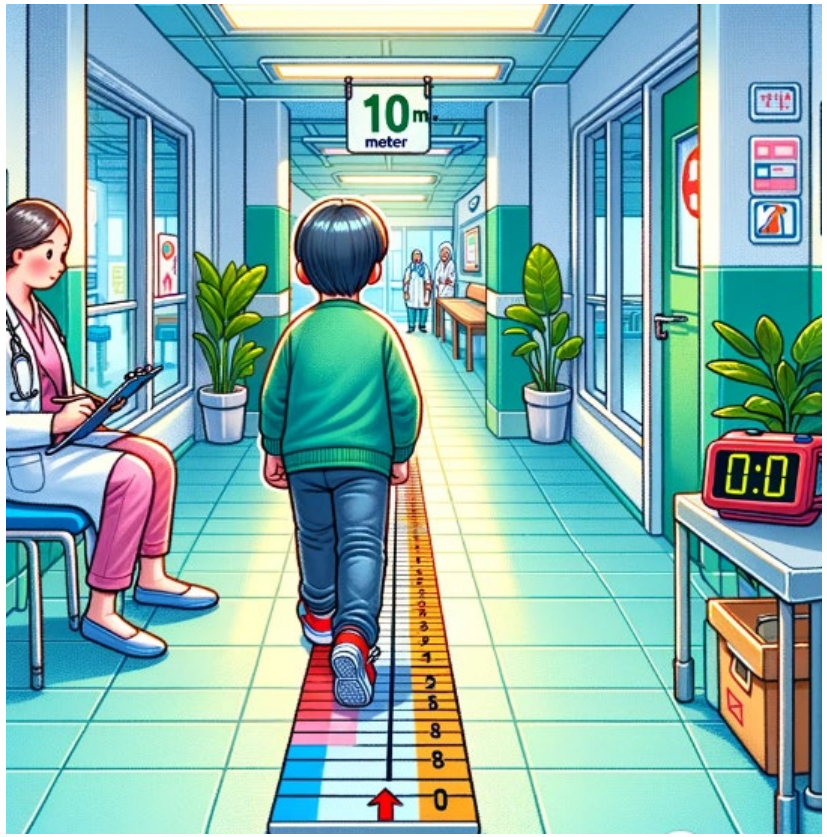
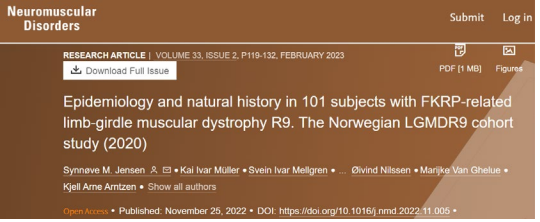


Conclusions

There is a slow annual decline in motor function in adults with *FKRP* mutations that can be detected with standard motor outcome measures, while the results in the pediatric population were more variable and affected by genotype. Overall, these analyses provide a framework for development of future clinical trials. The dystroglycanopathies natural history study (Clinical Trial Readiness for the Dystroglycanopathies) may be found on clinicaltrials.gov (NCT00313677).



Clinical features

***FKRP* genotype**	**c.826C>A / c.826C>A (n = 88)**	**Other (n = 13)**
Onset symptom(s) n (%)		
Lower limb weakness	51/88 (58.0)	4/13 (30.8)
Exertional pain, stiffness or cramps	33/88 (37.5)	2/13 (15.4)
Exertional fatigue	9/88 (10.2)	2/13 (15.4)
Exertion-induced myoglobinuria	8/88 (9.1)	0/13 (0)
Upper limb weakness	5/88 (5.7)	1/13 (7.7)
Delayed motor development	4/88 (4.5)	2/13 (15.4)
Toe walking	2/88 (2.3)	1/13 (7.7)
General fatigue	2/88 (2.3)	1/13 (7.7)
Symptomatic cardiac failure	1/88 (1.1)	0/13 (0)

Diff.diagnosis.: metabolic myopathy

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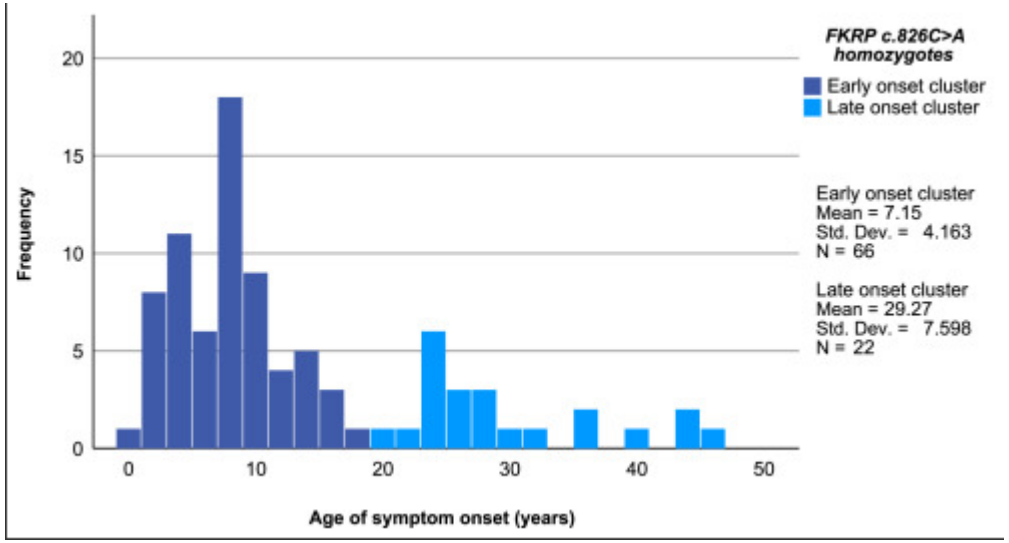

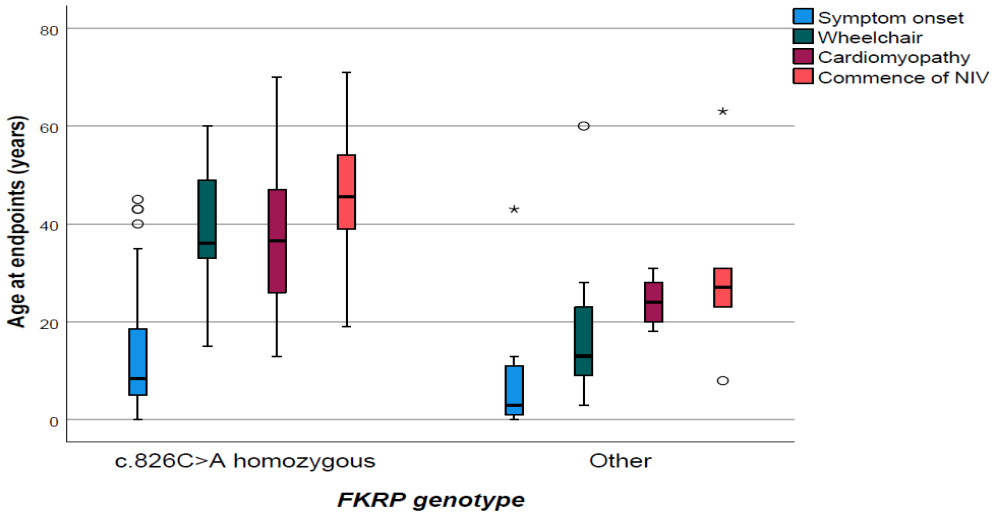

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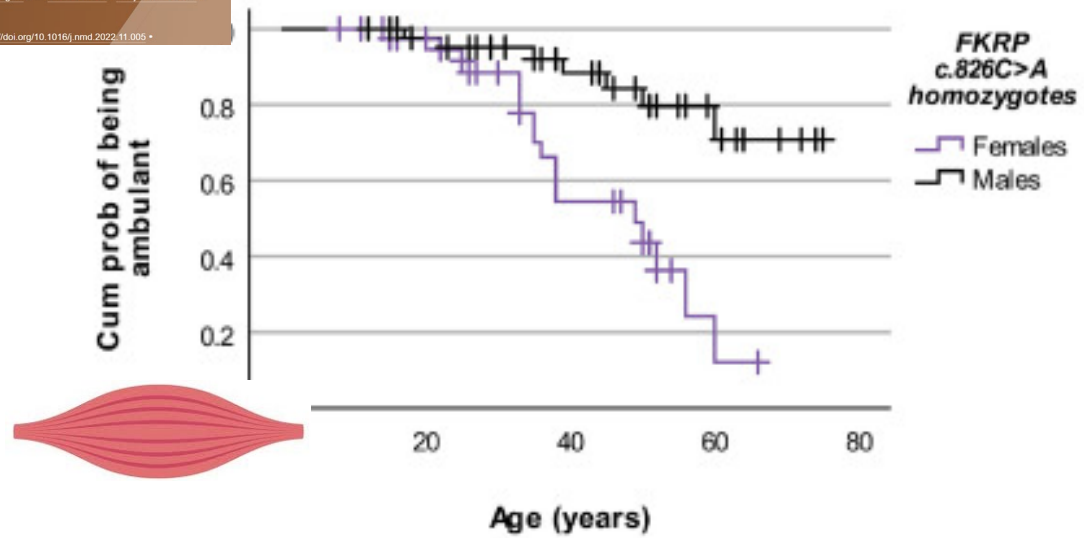

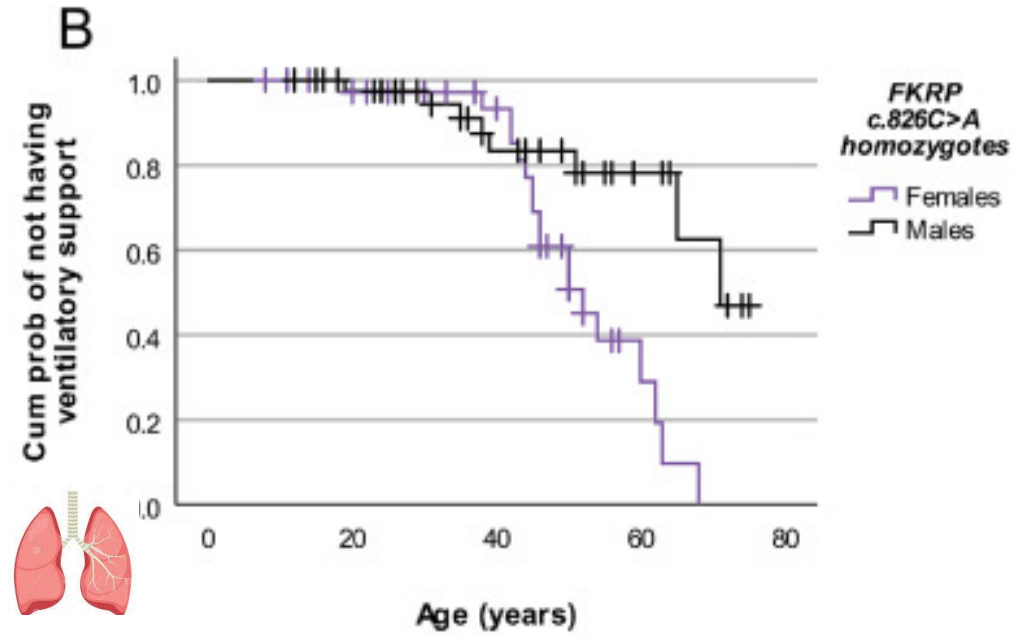

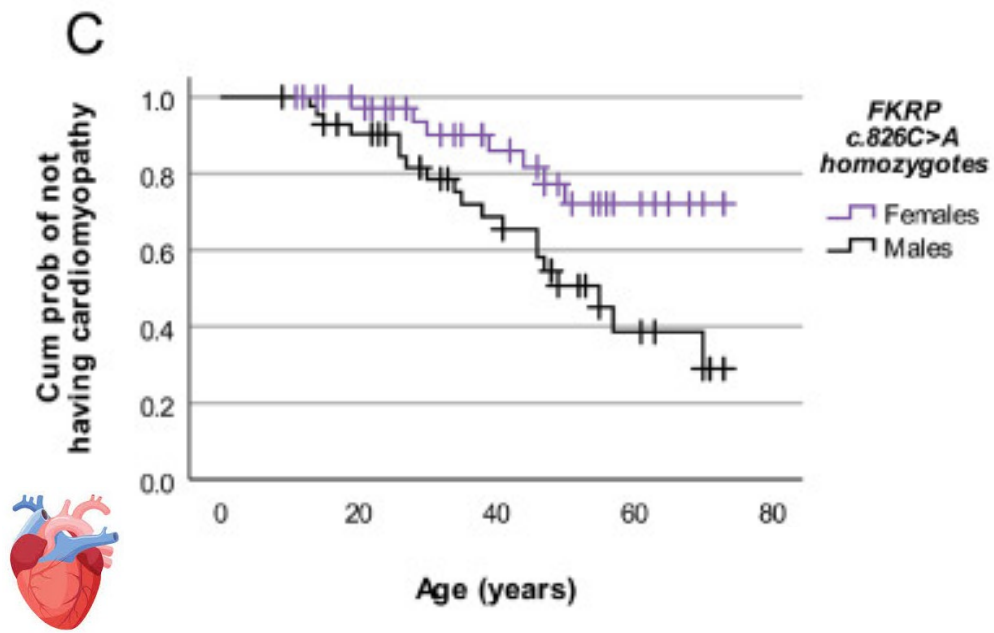

Journal of Neuromuscular Diseases 11 (2024) 59–74
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IOS Press

Research Report

Health-Related Quality of Life in FKRP-Related Limb-Girdle Muscular Dystrophy R9

The Norwegian LGMDR9 cohort study (2020)

Synnøve M. Jensen[a,b,*], Oddgeir Friborg[c], Svein Ivar Mellgren[a,b], Kai Ivar Müller[a,b,d], Svein Bergvik[c] and Kjell Arne Arntzen[a,b]

Aim: investigate HRQoL in the Norwegian LGMDR9 cohort over 14 months and relation to fatigue and sleep quality.

Conclusions:

-Physical, emotional, and social aspects of HRQoL were impaired, which advocates for a multi-disciplinary care.

-In c.826 C > A homozygotes, perceived muscle weakness and disease burden deteriorated during the study

- Females reported a higher burden among homozygous

-Associations suggest that myalgia and mental distress are potential targets for the treatment of fatigue

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