The Facioscapulohumeral Muscular Dystrophy Functional Composite Outcome Measure

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Abstract

Introduction—We developed an evaluator-administered functional composite outcome measure (FSHD-COM) comprised of patient-identified areas of functional burden for future clinical trials.

Methods—We performed a prospective observational study of 41 FSHD participants at 2 sites. The FSHD-COM includes functional assessment of the legs, shoulders and arms, trunk, hands, and balance/mobility. We determined the test-retest reliability and convergent validity as compared to established FSHD disease metrics.

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Author's Contributions

Jeffrey Statland, Chad Heatwole, Katy Eichinger, Wendy King, Lindsay Baker, Stanley Iyadurai, Nuran Dilek, William B Martens, John Kissel and Rabi Tawil contributed to drafting/revising the manuscript for content; study concept or design; analysis or interpretation of data; acquisition of data; and statistical analysis.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosures

Jeffrey Statland's work on this project was supported by an NCATS grant awarded to the University of Kansas Medical Center for Frontiers: The Heartland Institute for Clinical and Translational Research # KL2TR000119. Dr. Statland is a consultant for Acceleron, Strongbridge Biopharma, Regeneron, and Sanofi.

Stanley Iyadurai is the PI on projects related to treatment of FSHD (aTyr) and Sub-PI on projects related to treatment of FSHD (Acceleron). Dr. Iyadurai is on the Advisory Board for Alnylam, CSL Behring, Genzyme, Pfizer and receives an honorarium as a Continuum author.

Chad Heatwole, M.D., MS-CI: has received grant funding from the NIH, FDA, and Cure SMA foundation. He is the founder and CEO of the Neuromuscular Quality of Life Institute. He receives royalties for the Myotonic Dystrophy Health Index, the FSHD-HI, the CMT-HI, and the SMA-HI. He has provided expert testimony for neuromuscular cases unrelated to this research. He has provided consultation to Biogen Idec, Ionis Pharmaceuticals, Regeneron Pharmaceuticals, aTyr Pharma, and Acceleron Pharma.

John Kissel is the co-PI PI on projects related to treatment of FSHD (aTyr and Acceleron). He is on the AveXis receives an honorarium as a Continuum author.

Rabi Tawil is a consultant for Acceleron and aTyr, and served on the DSMB for Novartis for a non FSHD trial.

The remaining authors have no conflicts of interest.

Results—The FSHD-COM demonstrated excellent test-retest reliability (intraclass correlation coefficient [ICC] 0.96; subscale ICC range: 0.90–0.94). Cross sectional associations between the FSHD-COM and disease duration, clinical severity, and strength were moderate to strong (Pearson correlation coefficient range: |0.51–0.92|).

Discussion—The FSHD-COM is a disease-relevant, functional composite outcome measure suitable for future FSHD clinical trials, which shows excellent test-retest reliability and cross sectional associations to disease measures. Future directions include determining multi-site reliability, sensitivity to change, and the minimal clinically important change in the FSHD-COM.

Keywords

Muscular dystrophy; Facioscapulohumeral Muscular Dystrophy; Functional Testing; Composite Measures; Outcome Measures

INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most prevalent muscular dystrophies, with a world-wide prevalence range of 2–7:100,000.¹ It is often thought of as a slowly progressive condition; however, it can result in significant lifetime morbidity, with approximately 20% of individuals requiring a wheelchair or becoming disabled due to FSHD.^{2,3} Advances in the genetic understanding of FSHD have identified the aberrant expression of the gene *DUX4* as a potential target for therapy, which has shifted focus in the research community towards clinical trial planning.^{4,5}

A prior natural history study developed procedures and tested the reliability and validity of measures of strength, and separate individual functional outcome measures (e.g. Go 30 feet, time to climb 4 stars), which have been used in clinical trials.^{6–8} Despite this, no individual functional outcome assessment has demonstrated sensitivity to disease progression in FSHD, and no individual functional measure captures the full range of patient-identified disability.⁹ A performance-based functional composite outcome measure which combines multiple functional domains and individual evaluator-administered items into one measure and captures key components of patient-identified disease burden could help hasten drug development by documenting functionally relevant changes in FSHD with therapy, putting small changes in composite strength or biomarkers in a clinically meaningful context, and supporting drug registration applications.

Here we describe a new evaluator-administered FSHD functional composite outcome measure (FSHD-COM), and determine test-retest reliability and convergent validity of this instrument compared to existing FSHD disease metrics, including disease severity, strength testing, and patient-reported functional burden.

METHODS

We performed a prospective cross sectional study across 2 sites (the University of Rochester Medical Center and The Ohio State University Wexner Medical Center) between February

2013 and November 2016. The protocol was approved by the human subject research committees at both institutions, and all individuals provided written and informed consent.

Participants between 18–75 years of age, genetically confirmed, clinically affected, and able to walk at least 30 feet without assistance of another person (assistive devices and bracing allowed) were eligible to participate in this study.^{10,11} Participants with other medical conditions which could interfere with safe performance of study procedures could be excluded at the discretion of the investigator (no participant was excluded for this reason). Consecutive willing participants were recruited from clinic, or from the URM neuromuscular research data base, or the National Registry of FSHD Patients. The inclusion criteria was designed to match the most likely criteria used for clinical trials – which would be genetically defined and clinically affected individuals with FSHD who are still ambulatory.

Outcomes and Measures

Participants completed a half day baseline visit in the Clinical Research Center, and local participants or those able to return for a second visit returned within 3 weeks for test-retest reliability testing (University of Rochester only). In addition to basic demographics, and FSHD medical history, disease severity was assessed using a clinical severity scale, which documents muscle involvement in the face, shoulders, arms, abdomen, and legs (0 = unaffected; and 15 = severely affected/non-ambulatory).¹² Time since onset of symptoms and time since diagnosis of FSHD were recorded separately as measures of disease duration.

The FSHD-COM is an 18 item evaluator administered instrument. The items chosen for the FSHD-COM represent body areas impacted by the disease and were based on: 1) consensus expert opinion about muscle involvement and progression; 2) muscle involvement and functional limitations seen in a prior natural history study; 3) patient-reported surveys and registry data; and 4) patterns of muscle involvement seen on MRI studies (Supplemental figure 1).^{9,13–17} The functional tasks are standardized, evaluator-administered and reported in the literature. The body regions represented are leg function; shoulder and arm function; trunk function, hand function; and balance/mobility. Each component is scored on a 0–4 scale, with 0 representing unaffected/normal performance, and the divisions based on healthy population normative values and standard deviations (where available), or the relative degree of ability to perform the functional task (Table 1, Supplemental methods). The total scale has 72 points, with more items chosen for the two most frequently patient-cited areas of functional motor concern – leg function and shoulder and arm function. The FSHD-COM takes approximately 35 minutes to complete, including a 10 minute rest prior to the six minute walk test (6MWT).

Leg function—The leg subscale is composed of 6 different continuous measures which are converted to a 0–4 ordinal scale using divisions as described above, for a possible total of 24 points. The leg function tasks test a range of different abilities, from power, to endurance, to balance and climbing. The timed sit to stand tests proximal lower extremity strength and core strength by having subjects stand from a standard height chair.^{18,19} The 6MWT is a measure of functional exercise capacity that requires both strength and physical endurance.

It assesses how far an individual can walk in 6 minutes and is used widely in studies involving neuromuscular disease.^{20–22} Self-selected gait speed is used as measure of overall health status in the elderly and was previously used in a study of dynamic motion in FSHD.^{23,24} The 30 Foot Go test is a measure of speed and strength where subjects are asked to traverse 30 feet as fast as they can safely, including running. The time to ascend 4 stairs is a functional activity that requires proximal leg strength; both the 30 Foot Go and the time to ascend 4 stairs are predictors of loss of ambulation for Duchenne muscular dystrophy.^{22,25}

Shoulder and arm function—The shoulder and arm function category tests proximal to mid arm tasks, and the ability to coordinate upper extremity function across a variety of muscle groups. The shoulder/arm subscale includes 7 items for 28 points. The tasks are an adaptation of the activities contained in the Brooke upper extremity scale, where a weight is added to mimic functional activities such as lifting a gallon of milk, and for elbow function, to mimic lifting groceries.^{9,25,26} The time to don and doff a coat is a more complex task that incorporates functional use of both proximal and mid-limb muscles.²⁷

Trunk function—There are no specific functional tasks designed to measure trunk function in FSHD so we have chosen practical tasks which will reflect changes in core truncal muscle groups. This subscale includes 3 items (12 points). Picking a penny up off the floor tests the ability to bend and straighten, but also balance and the ability of lower extremity muscles to compensate for core weakness, and has been used in the elderly.²⁷ The ability to sit up from lying supine and the timed supine to sitting at edge of bed test reflects core muscle strength and coordination.²⁸ The ability to get out of a bed was one of the most frequently patient-identified areas of functional loss over 6 years.²

Hand function—Hand grip strength has widely been reported as an independent predictor of morbidity and mortality in aging populations, is intrinsically related to performing daily activities, is abnormal in individuals with FSHD, and was the most sensitive strength measure in assessing a response to albuterol in a randomized controlled trial.^{6,7,29,30} Hand grip is measured bilaterally and contributes 4 points to the FSHD-COM score.

Balance function—Balance and mobility are assessed by using the Timed Up and Go (TUG), a standard outcome measure for the elderly, and also increasingly being used in neuromuscular disorders. Participants are asked to rise from a chair, walk 3 meters, turn 180 degrees and return to a seated position in the chair. It assesses strength, mobility, and balance.^{31–33} This task is timed and then scored 0–4.

Standard manual muscle testing was performed on 14 bilateral muscle groups (shoulder abductors and external rotators; elbow flexors and extensors; wrist flexors and extensors; hip flexors, abductors, adductors and extensors; knee flexors and extensors; ankle dorsiflexors and plantar flexors) and neck flexors and extensors. Muscles were graded using a modified Medical Research Council scale (MRC, 5=normal strength, 5–, 4+, 4, 4–, 3, 3–, 2, 1, 0=no contraction). Muscles scores were averaged to create whole body, or body region subscores (e.g. lower extremity). Quantitative myometry was performed using a fixed myometry testing system (QMA, Gainesville, GA) on 8 bilateral muscle groups (shoulder abductors and external rotators, elbow flexors and extensors, knee flexors and extensors, ankle

dorsiflexors, and handgrips).⁷ Scores were standardized using regression equations based on normative data to yield the number of standard deviations from predicted normal strength, after accounting for age, gender, and height, and averaged to create composite total body or regional scores.³⁴

Patient-reported functional burden and the emotional and social impact of FSHD on daily life were determined using standard previously validated scales, including the SF-36 Short Form, the PROMIS 57, and the Facial Disability Index.^{35–37}

Manual muscle testing, quantitative myometry, and the FSHD-COM were performed by physical therapists with experience testing individuals with FSHD. Standardized testing procedures were created and used by both sites. Test-retest reliability was performed by the same evaluating therapist.

Statistical Considerations

Sample characteristics were presented using means, standard deviations, minimum and maximum values, or frequency and percent. Reliability was determined by comparing the baseline testing to testing at 3 weeks using intraclass correlations coefficients (ICC) determined from a linear mixed effects model. Correlations between the FSHD-COM and other FSHD disease metrics of interest (clinical severity, disease duration, strength testing, or patient-reported disability) were determined by Pearson correlation coefficient. Internal consistency of the FSHD-COM was assessed using item-total correlations and Cronbach's alpha. Additionally, correlations between scored items of the FSHD-COM were determined using Spearman rank analysis. Floor effect was determined by the frequency of participants scored with the minimal value of a scale; ceiling effect as the frequency of participants scored as the maximal scale value. The slope of the FSHD-COM compared to clinical severity (and 95% confidence interval) was determined from a linear model with the FSHD-COM as the dependent variable and the FSHD clinical severity score, age, and gender as the independent variables. The minimal detectable change beyond which we can be 90% certain a true change occurred (MDC90) was calculated from the intraclass correlation and mean square error.^{38,39} Differences between groups (male or female, genetic mutation, disability or employment status) were determined by two sample t-tests. A P-value of <0.05 was considered significant and all testing was two-sided. The Holm method was applied for multiple comparisons.⁴⁰ Statistical testing was performed using SPSS (IBM, version 22), or STATA (version 11.2, STATA Corp).

RESULTS

Forty-one individuals with FSHD (FSHD1=85%) participated in this study. Participants were mostly male (63%), middle aged, but represented the full range of adult age (22–70 years old, Table 2). Overall, participants were moderately affected with an average FSHD clinical severity of 7.1, which roughly equates to face, shoulder, and the beginnings of lower extremity involvement. However, participants demonstrated the full range of ambulatory severity. The individuals in this study were able to complete all tasks and tolerated all testing well.

The mean, range and standard deviation of all of the scored FSHD-COM items are summarized in Table 3. The reliability of the total score and the subscale components of the FSHD-COM were excellent (ICCs 0.90–0.96, Table 4). The Cronbach's alpha for the entire scale was 0.79 and for the subscales ranged from 0.70 to 0.80, demonstrating good internal consistency. Inter-item correlations were overall moderate (Supplemental Table 1). The test-retest reliability of the continuous subcomponents of the FSHD-COM was good to excellent (intraclass correlation coefficients [ICC] 0.69–0.99, Supplemental Table 2).

The sample mean for the overall FSHD-COM of 25.44 (range 3–51; standard deviation 14.30) is not quite mid-scale, which would be consistent with a population who are still ambulatory and moderately affected. Using the standard deviation and ICC the MDC90 was determined to be 6.67, or a change of 9.3% on the FSHD-COM total scale. Ceiling or floor effects were not seen with the overall FSHD-COM.

Correlations of the FSHD-COM to disease severity, duration, and strength were moderate to strong (Pearson correlation coefficients range: $|0.63–0.91|$, Table 5). The associations were equally strong whether looking at upper extremity or lower extremity summary strength scores – which would be expected for a scale with a relatively equal weight for leg, shoulder, and arm function. From the linear model: for each increase of 1 in the FSHD clinical severity score, the FSHD-COM increased by 4.3 (95 % confidence interval 3.5, 5.2), after adjusting for gender and age.

Correlations to patient-reported disease burden were strong for physical components (the SF-36 Physical Composite, and the PROMIS 57 physical score), but not for emotional components (Table 6). There was a moderate association between the FSHD-COM and the PROMIS 57 social satisfaction subscore.

The FSHD-COM was able to distinguish between participants based on disability and employment status, with participants who are disabled or unemployed being more severely affected (Table 7).

DISCUSSION

We based our conceptual framework for the FSHD-COM on expert opinion about FSHD progression, natural history studies, MRI studies, and patient surveys and registries. Recent MRI studies have revealed early involvement of muscles of the shoulder girdle and arms, but also the trunk, pelvic girdle, and thigh.^{13,14,17} Open-ended interviews revealed the most commonly quoted functional motor limitations to be problems with mobility and ambulation, arm, and shoulder limitations.¹⁵ The most frequently reported functional motor limitations over 6 years in the US National FSHD Registry were difficulty getting up from lying down in bed and difficulty using arms for activities of daily living.² From a practical standpoint, this means that improving gait and mobility, trunk or arm function would be meaningful to patients, and outcomes that reflect these functional domains are important for FSHD clinical trials.

The classic clinical model for FSHD suggests a descending muscular progression affecting first the mimetic muscles of the face, the scapular fixators, and humeral muscles, followed

by muscles of the abdomen and paraspinal region, and later muscles of the lower extremity in a scapulo-peroneal pattern.^{3,16} In actuality, there is considerable variability between individuals, and side to side asymmetry in muscular involvement.¹⁷ In order to capture the descending progression and side to side asymmetry, the FSHD-COM scores the left and right sides separately, and contains subcomponents which match major areas of muscular involvement, with the exception of the face. Although severe facial weakness, when present, can be socially limiting, for most people with FSHD the weakness in the face tends to be relatively static. A prior natural history study could not show changes in the time to drink 6 ounces of water through a straw over follow up periods as long as 3 years.^{7,9} In development of the FSHD-COM we tried a variety of measures of facial function, including a timed reading passage and disdiadokinetic syllable rates, but these did not correlate well to disease severity, showed poor test-retest reliability, and thus were not included in the final instrument.

In a prior natural history study, functional motor tasks including the time to get up from a chair, timed 30 foot go, and time to ascend 4 stairs were reliable and showed good cross sectional associations to disease metrics, but individually were not sensitive to disease progression.⁹ By combining functional tasks from multiple body regions, the FSHD-COM may provide a more thorough perspective on the patient's disease state, and prove more versatile when following a population of patients that have disease progression involving multiple diverse muscle groups.

The FSHD-COM includes ambulatory items chosen to represent different stages in FSHD ambulatory loss, whereby people may still be able to walk after losing the ability to go up or down stairs, or get out of chairs without assistance. In the US National FSHD Registry the frequency of progression to requiring use of a wheelchair over 6 years was 24%.² Participants often remain ambulatory even after requiring a wheelchair for distance, with only 10% using a wheelchair for all mobility. From a practical point of view, when designing a functional composite measure this means the majority of referred clinical trial participants will likely be ambulatory, and the likelihood of these participants losing ambulation in a 1–2 years study is relatively low. As a participant moves closer to requiring a wheelchair for mobility, they will be unable to perform certain FSHD-COM gait or mobility tasks but not all functional tasks (for example they may lose the ability to climb 4 stairs or get up from a chair, before the ability to perform the 30 foot go) thus receiving a score of 4, for unable to perform. While this study only assessed individuals who were ambulatory, individuals who are non-ambulatory would have a minimum score of 24; with the remainder of the FSHD-COM reflecting shoulder, arm and trunk impairment.

Recent MRI studies have challenged some of the clinical preconceptions about the temporal pattern of muscle involvement – revealing early involvement of muscles of the shoulder girdle, as previously described, but also paraspinal, semimembranosus, and rectus femoris muscles.^{13,14,17} The current FSHD-COM is designed to maximize the sensitivity to this early muscle involvement, and the MRI-pattern supports the array of different functional motor tasks designed to tease out different aspects of truncal instability and gait and balance. The strong correlations between the FSHD-COM and disease severity, disease duration, strength, and patient-reported physical impairment support the utility of the scale to measure

something meaningful to patients. The minimal clinical meaningful change is an important concept which helps determine the smallest change in a scale that would be meaningful to patients, usually by using a simple anchor to determine patients who improved (or worsened) a little, then seeing the corresponding average change in the scale. This study was not designed to determine the minimal clinical meaningful change as it was cross sectional. That said, statistical approaches can be used to determine how large a change in the FSHD-COM would be statistically detectable, or would relate to a change in clinical severity: such approaches suggest a change of approximately 7 points (or a change of about 10% on a 72 point scale) would be outside that expected for chance and 4 points would equate to an estimated 1 point change on a FSHD clinical severity scale.

Limitations to the current study include the modest sample size, and recruitment from two centers. The small sample size and cross-sectional nature of the present study limit the ability to comment on sample size requirements and sensitivity to change. Additionally, the small sample size prohibited more sophisticated psychometric analyses to fully assess the ability of items to accurately distinguish between functional domains, or to determine the relative contribution of individual items to the total score (e.g. Rasch or factor analysis). A larger multicenter study is in progress to additionally validate the items of the scale, determine the reliability across multiple sites with multiple evaluators, and to determine the relative responsiveness of the FSHD-COM to disease progression. Such a study may also allow us to examine the contribution of genetic or environmental factors to the variability observed in the present study, as well as determine the minimum clinically important difference.

In conclusion, we present a new FSHD-specific, functional composite outcome measure made up of standard evaluator administered functional motor tasks. We show the FSHD-COM to be reliable on repeated days of testing, and to correlate strongly with a number of other established FSHD disease measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Study Funding: The project described in this publication was supported by the following: the FSH Society grants (FSHS-22013 and FSHS-82012) and NIAMS grant #U01AR065119. Additional support provided by the University of Rochester CTSA award number UL1 RR024160 from the National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health. Dr. Statland's work on this project was supported by a NCATS grant awarded to the University of Kansas Medical Center for Frontiers: The Heartland Institute for Clinical and Translational Research # KL2TR000119.

We wish to thank the patients and family members who are the impetus for this study, and without whom we could not perform our research.

Abbreviations

FSHD	facioscapulohumeral muscular dystrophy
6MWT	six minute walk test

SMCHD1	structural maintenance of hinge domain 1
ICC	intra-class correlation
MMT	manual muscle testing
QMT	quantitative myometry
TUG	Timed Up and Go

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Table 1

Facioscapulohumeral Dystrophy Composite Outcome Measure (FSHD-COM).

	ITEM	Score 0	Score 1	Score 2	Score 3	Score 4	References
LEG FUNCTION	Sit to stand	1 sec	1.1–2 sec	2.1–3 sec	>3 sec	Unable	18,19
	6 MWT	650 m	649–518 m	517–386 m	385–254 m	253 m	20,21
	Self-selected gait speed	139 cm/sec	138.9–123 cm/sec	122.9–107 cm/sec	106.9–89 cm/sec	<88.9 cm/sec	23,24
	Go 30'	4 sec	4.1–8 sec	8.1–12 sec	>12 sec	Unable	25,7
ARM/SHOULDER FUNCTION	Ascend/descend stairs	2 sec	2.1–4 sec	4.1–6 sec	>6 sec	Unable	9,25,7
	Shoulder Abduction (R/L)	2kg weight above head	Antigravity	90 degrees	<90 degrees	<45 degrees	9,26,25
	Shoulder Forward Flexion (R/L)	2kg weight above head	Antigravity	90 degrees	<90 degrees	<45 degrees	26,25,9
	Elbow Flexion (R/L)	3kg weight	Antigravity	90 degrees	<90 degrees	<10 degrees	26,25,9
	Don/doff Coat	10 sec	10.1–15 sec	15.1–20	>20	Unable	27
TRUNK FUNCTION	Pick up a penny from floor	2 sec	2.1–4 sec	4.1–6 sec	>6 sec	Unable	27
	Sit up with feet held	Able to do fully	Able to rise >45 degrees	Able to bring shoulders off	Only able to lift head off	Unable	2
	Supine to sit	3 sec	3.1–6 sec	6.1–9 sec	>9	Unable	2,33
HAND FUNCTION	Hand Grip Force Men	Both 35 kg	1 side <35 kg	1 side <25 kg, or 2 sides <35 kg	1 side <20 kg, or 2 sides <25 kg	1 side <15 kg, or 2 sides <20 kg	6,7,29,30
	Hand Grip Force Women	Both 23 kg	1 side <23 kg	1 side <17 kg, or 2 sides <23 kg	1 side <14 kg, or 2 sides <17 kg	1 side <11 kg, or 2 sides <14 kg	6,7
BALANCE	TUG: Timed up and Go	<6 sec	6–8 sec	8.1–10 sec	10.1–12 sec	<12 sec	32,33

R=right, L=left.

Table 2

Demographics and Clinical Characteristics of Study Participants

Item	Value	Standard Deviation
Male/Female	26/15	----
Mean age in years (range)	52.8 (22–70)	11.9
FSHD type 1 (percent)	35 (85.4)	-----
Mean D4Z4 residual fragment kb (range) *	25.29 (13–41)	6.6
Mean age at symptom onset (range)	37.9 (12–60)	11.9
Mean years since diagnosis (range)	15.7 (1–42)	11
Mean years since onset of symptoms (range)	26.9 (4.2–58.6)	14.4
Mean FCS (range)	7.10 (2–13)	2.9

n=32 returned for test-retest reliability testing.

* for patients with FSHD type 1 (n=35).

FCS = FSHD clinical severity score

Table 3

Descriptive Statistics for Scored FSHD-COM Items

Item	Mean	Range	STD
Sit to Stand	.73	0–3	0.95
6 MWT	2.46	0–4	1.03
Self Selected Gait Speed	1.71	0–4	1.63
Go 30 Feet	1.02	0–3	0.85
Ascend 4 Stairs*	1.34	0–4	1.06
Shoulder Abduction Right	2.17	0–4	1.22
Shoulder Abduction Left	2.17	0–4	1.28
Shoulder Forward Flexion Right	1.90	0–4	1.17
Shoulder Forward Flexion Left	1.93	0–4	1.21
Elbow Flexion Right	0.41	0–4	1.09
Elbow Flexion Left	0.23	0–4	0.70
Don/Doff Coat	1.07	0–4	1.17
Pick Up Penny from the Floor*	1.15	0–4	1.13
Supine to Sit	1.10	0–4	1.16
Sit up	1.76	0–3	1.39
Hand Grip Right			
Male	1.69	0–4	1.44
Female	1.07	0–4	1.03
Hand Grip Left			
Male	1.58	0–4	1.33
Female	0.87	0–4	1.06
Timed Up and Go	1.59	0–4	1.32

Table 4

Reliability of the FSHD-COM.

Composite Score	Mean	STD	Floor %	Ceiling %	ICC#	ICC LCLM	Item-Total Correlation	Cronbach's Alpha if Item Deleted
Legs	7.27	4.83	2.4	0	0.94	0.88	0.82	.72
Arms	9.80	5.99	12.2	0	0.90	0.81	0.81	.70
Trunk	4.00	2.83	9.8	0	0.90	0.81	0.79	.76
Hands	2.78	2.43	17.1	9.8	0.90	0.80	0.59	.78
Balance	1.59	1.32	24.4	12.2	0.90	0.81	0.70	.80
Total Score	25.44	14.30	0	0	0.96	0.92		

n=32 returned for test-retest reliability testing.

STD = standard deviation; ICC = intraclass correlation coefficient; LCLM = 95% lower confidence limit.

Table 5

Correlations of the FSHD-COM to Disease Severity and Strength

Item	Pearson r-coefficient	P-value
FCS *	0.89	<0.0001 [†]
Years Since Diagnosis	0.63	0.001 [†]
MMT (34 muscles)	-0.91	<0.0001 [†]
MMT_UEXT	-0.76	<0.0001 [†]
MMT_LEXT	-0.79	<0.0001 [†]
QMT_std#	-0.77	<0.0001 [†]
UEXT QMT_std#	-0.71	<0.0001 [†]
LEXT QMT_std#	-0.71	<0.0001 [†]

* N=40, 1 value missing;

N=31 performed quantitative myometry.

CS = FSHD clinical severity score; MMT = manual muscle testing; UEXT = upper extremity; LEXT = lower extremity; QMT = quantitative myometry; std = standard score.

[†] significant using the Holm criterion.

MMT_UEXT: shoulder abductors and external rotators, elbow flexors and extensors, wrist flexors and extensors; MMT_LEXT: hip flexors, abductors, adductors and extensors, knee flexors and extensors, ankle dorsiflexors and plantar flexors.

QMT_UEXT: shoulder abductors and external rotators, elbow flexors and extensors; QMT_LEXT: knee flexors and extensors, ankle dorsiflexors.

Table 6

Correlations to Patient Reported Measures

Item	Pearson r-coefficient	P-value
SF36 Physical Composite	−0.63	<0.0001 [†]
SF36 Mental Composite	0.02	0.89
Facial Disability Index	−0.27	0.09
FDI Physical Score	−0.43	0.005 [†]
FDI Mental Score	−0.14	0.38
PROMIS 57 Physical *	0.75	<0.001 [†]
PROMIS 57 Anxiety *	0.28	0.12
PROMIS 57 Depression *	0.30	0.10
PROMIS 57 Fatigue *	0.10	0.58
PROMIS 57 Sleep *	0.26	0.15
PROMIS 57 Pain *	0.14	0.6
PROMIS 57 Social Satisfaction *	−0.48	0.006

* N=31 performed the PROMIS 57.

[†] significant using Holm criterion.

SF36 = short form 36; FDI = Facial Disability Index.

Table 7

Differences in the FSHD-COM between genders, genetics, disability and employment

Item	FSHD-COM Group1	FSHD-COM Group2	Mean Difference (95% CI of the Difference)	P-value
Male/Female	27.92 (14.48)	21.13 (3.45)	6.79 (−2.45–16.03)	.15
D4Z4 21 kb versus <21 kb	25.77 (13.10)	27.43 (18.37)	−1.65 (−14.06, 10.74)	.79
Disabled (Yes versus No)**	38.75 (8.91)	21.59 (13.27)	−17.16 (−27.22, −7.09)	.001
Employed (Yes versus No)***	19.58 (14.18)	29.95 (12.66)	10.37 (1.38, 18.96)	0.02

#Female n= 15;

*d4z4<21, n=7;

**disabled n=8;

***employed n=19.