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ORIGINAL ARTICLE

Describing phenotypes in FSHD: an update of the comprehensive clinical evaluation form

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Abstract

Background Facioscapolohumeral muscular dystrophy is characterized by a wide clinical variability; the underlying reasons and the relation between them and the genetic markers are still not clear. In fact, the different phenotypes could show a different disease progression and/or imply distinct genetic mechanisms. As clinical trials are approaching also for FSHD, the correct description and stratification of patients becomes mandatory. To address these matters, in 2016 the Italian Clinical Group for FSHD developed the Comprehensive Clinical Evaluation Form (CCEF), aimed at describing the different observed phenotypes in FSHD.

Methods A working group composed by the former developers of the CCEF and other expert clinicians re-evaluated the whole structure of the CCEF, to develop a simplified version for use in clinical practice; also, other expert clinicians not referring to the Italian Clinical Group for FSHD read and approved the CCEF revised version for its international use.

Results We present the CCEF-R, a revised and simplified version of the CCEF, that while maintaining all the core structure and items of the previous validated version, has been modified with new friendlier graphics, focused on the key anamnestic and neurological examination findings, to facilitate its understanding and use in clinical practice.

Conclusions The phenotypical classification combined with the genetic signature should be considered during the diagnostic work out for guiding genetic analysis and for genotype–phenotype correlations and genetic counseling. The CCEF could have a significant role in the clinical stratification process of patients for clinical trials and in laying the groundwork for evidence-based medical decision making.

Keywords FSHD · Genotype–phenotype correlation · CCEF · Clinical categories · Clinical variability

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Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is typically characterized by young or adult-onset progressive facial, shoulder girdle, and pectoral muscle weakness and atrophy, subsequent involvement of abdominal muscles -manifesting with lumbar hyperlordosis, prominent abdomen and positive Beevor's sign- and of anterior leg muscles with steppage and foot drop. The pattern of weakness distribution is typically asymmetric, and progression is slow over time, with males presenting a lower mean age at clinical onset compared to females [1]. Early-onset FSHD begin in childhood and is the most likely to display extra muscular involvement, such as an exudative retinopathy known as Coat's disease, sensorineural deafness, and cognitive delay [1–4]. Cardiac involvement is not typical, as well as precocious or predominant ventilatory insufficiency, which may be not directly dependent on respiratory muscle involvement but can also derive from axial and abdominal weakness, in general in late stages of disease or in the elderly [5].

However, FSHD patients can display wide clinical variability, even within the same family, as already reported forty years ago in the pre-molecular era [6].

Over the years, the availability of genetic testing seems to have expanded the clinical spectrum of the disease, including presentations that differ significantly from the firstly described phenotype, from pauci-symptomatic cases to severely affected patients, subjects also presenting with extra-muscular features and/or unusual pattern of involved muscles [7–9].

The underlying causes of the wide range of clinical variability and severities and their relationship to the genetic marker remain unclear. This uncertainty complicates genotype–phenotype correlation, hampers accurate prognostication, and poses challenges for effective genetic counseling.

Since genetic testing has become available, it has been clear that the repeat length cannot explain fully this wide variety in clinical presentations. That evidence has led, in the last fifteen years, to understanding that FSHD presents a complex genetic architecture and genetic diagnosis should include the evaluation of the length of the D4Z4 allele, the permissive haplotypes, the level of methylation and the effect of disease modifying genes such as *SMCHD1*, *LRF1* or *DNMT3B* [8]. To date, the molecular diagnosis still needs to be improved in terms of precision, accuracy, time and costs, and the interpretation cannot ignore a careful correlation with the phenotype. The recent guidelines on genetic diagnostics of FSHD [10] further stressed the need for a detailed genotype–phenotype correlation in guiding and interpreting the types and the results of DNA analysis and therefore the necessity of comprehensive clinical information to provide with the genetic test application. Moreover, also the interpretation of genetic modifiers' significance and effect can greatly benefit from a systematic approach in clinical assessment.

The development of a shared, standardized clinical tool that captures key phenotypical features for patient stratification is essential to address the clinical complexity of this disease.. The Comprehensive Clinical Evaluation Form (CCEF), the clinical tool proposed by the Italian Clinical Network for FSHD in 2016 has been designed starting from these premises [11]. The tool allows the recognition and stratification of different clinical subgroups among carriers of the FSHD genetic signature, in addition to measuring the degree of motor disability. However, when the CCEF was created, it was part of a research project funded by Telethon-Italy regarding the genotype–phenotype correlations study of a large cohort of Italian FSHD families, and therefore it included several additional informations useful for the above purposes.

In this paper, we present a revised simplified version of the CCEF (CCEF-R), equipped with user-friendly graphics emphasizing key anamnestic and neurological examination findings. While conserving the fundamental features and core data collection of the previous version, the CCEF-R was built to be a quicker tool for phenotypic characterization, facilitating its use both in clinical practice and for international collaborations.

Methods

The working group was composed by the former developers of the CCEF (G.R., L.V., L.R., M.F., T.M., G.S.) and other members of the Italian Clinical Group for FSHD (F.T., G.G., E.C., E.R., B.R.), including clinicians and one physiotherapist. In July 2023 the group firstly met in person with the aim of re-evaluating the whole structure of the CCEF, to develop a simplified version for use in clinical practice. There were three subsequent meetings of the working group in 2024 to reach a final agreement and finalized the CCEF-R, that was then shared within the Italian Clinical Network. As expert clinicians not referring to the Italian Clinical Group for FSHD T.E., E.B., N.V. and N.D. had finally read and approved the CCEF-R for its international use. No ethics committee approval was necessary based on the nature of the manuscript.

Results

We present a detailed description of the CCEF-R, a simplified version of the CCEF for FSHD, that maintains all the core structure and items; the revised form can be downloaded in the Supplementary Material section.

Sections 1 & 2 (Figs. 1 and 2) briefly investigate the clinical history and evaluate patient's disability, assessing the segmental involvement of fourteen muscle groups using the Medical Research Council (MRC) scale evaluated on both sides, and guiding the FSHD score filling. For obtaining a precise description of the distribution of muscle weakness, the CCEF-R explores the following districts: facial, shoulder girdle, distal upper limb, abdominal, pelvic girdle, distal lower limb, and highlights the typical FSHD signs.

Section 3 (Fig. 3) is a table that summarizes the common features collected during the neurological examination (Sections 1 & 2), including signs not scored by FSHD score, such as orbiculari oris hypokinesia during speech, scapula winging on attempted shoulder abduction or forward flexion, asymmetric winged scapula, horizontal clavicles, forward sloping of the shoulders at rest, horizontal axillary fold (due to weakness and wasting of the sternocostal head of the pectoralis major muscle), "Popeye" arms (as results from the contrast between the atrophied perihumeral muscles and the sparing of the muscles of the forearms and the distal deltoid), and poly-hill sign [1].

Moreover, the Section 3 also lists the "red flag" features not suggestive for the FSHD phenotype, including atypical muscle pattern involvement, presence of cardiac and precocious or predominant respiratory insufficiency, as well as other signs such as myotonia, eyelid ptosis, pes cavus, or early muscle contractures. Also the blood creatine kinase (CK) more than four/five times the normal value or the presence of recurrent macroscopic myoglobinuria are considered as not typical features for FSHD.

Compared to the first version of the CCEF, in this revised version the site of muscle weakness at onset, collected in the anamnestic section, is not considered among the parameters that define the clinical categories in Section 3, since this information is patient-reported and in some cases it could be misleading.

Based on the FSHD score and the combination of the typical/atypical features (CCEF-R Section 3), it is possible to assign patients to different phenotypical categories in Section 4 (Fig. 4), which are better detailed in this revised version as follows:

- *Category A*: subjects with a *typical FSHD phenotype* presenting facial and scapular girdle muscle weakness are assigned to category A and further classified into three subcategories (A1–A3) based on the severity of facial involvement (A1 more severe than A2 than A3).
- *Category B*: subjects with an *incomplete FSHD phenotype*, characterized by muscle weakness limited to only facial or scapular girdle muscles fall into category B. They are further subdivided in category B1 (facial sparing phenotype) or B2 (isolated facial weakness).
- *Category C*: subjects with FSHD score 0, without motor impairment or with minor possibly FSHD-linked signs (for example winging scapula or straight clavicles). Category C1 includes subjects with minor signs, whereas category C2 subjects with a completely normal neurologic examination.
- *Category D*: subjects presenting atypical clinical features not consistent with FSHD are included in this category. Specifically, subjects with FSHD phenotype in association with other uncommon features are classified as D1, while patients with a myopathic clinical picture that do not fulfill the diagnostic criteria for FSHD as D2.

Discussion

It is well known that DNA analysis in FSHD can reveal unanticipated results without a straightforward correlation with the phenotype [7].

A large spectrum of clinical features has been reported in subjects carrying the molecular defect associated with FSHD, including healthy carriers and individuals presenting a partial FSHD picture or myopathic conditions different from the classical phenotype described by Landouzy and Dejerine [12].

The CCEF is a simple tool able to delineate different phenotypical categories within the FSHD spectrum. In the recent updated FSHD genetics guidelines [11] the CCEF has been proposed as a dedicated score useful to clinically characterize patients, useful in defining the phenotype-genotype correlation and promoting a differential diagnosis for patients without a suggestive FSHD phenotype.. Moreover, the description and stratification of patients based on phenotypes is mandatory for appropriate design of the natural history studies, and for the preparation of clinical trials [11]. Category A identifies patients with typical phenotype; the three subcategories (A1–A3) further subdivide patients based on the severity of facial involvement, which seems to discriminate some classical phenotypes. Thus, category A1 includes patients with prominent facial weakness, that is typically observed in some infantile forms or in more severe phenotypes, often observed in association with shorted D4Z4 alleles [13], while most patients with a milder facial involvement fall into Categories A2 and A3. Category B identifies incomplete FSHD phenotype, not presenting a coexisting involvement of facial and scapular girdle muscles without other uncommon features. The category C identifies asymptomatic/pauci-symptomatic carriers with FSHD score 0, allowing a further distinction of asymptomatic subjects with minor signs (such as scapular winging, straight clavicles) suggestive of FSHD (as category C1), and subjects without neuromuscular involvement signs (as category C2).

Revised FSHD Comprehensive Clinical Evaluation Form (CCEF-R) –Evaluation Form Section 1

Referring Hospital: _____ Referring Physician: _____

Compilation Date: _ _/_ _/_ _ _ _

Patient Name: _____ Patient code: _____

Date of birth: _ _/_ _/_ _ _ _ Sex: ○ M ○ F

Part A: ANAMNESTIC DATA

Ethnicity

○ Caucasian

○ Asian (specify _____)

○ Hispanic

○ Black or African American

○ North African

○ Native Hawaiian or Other Pacific Islander

○ American Indian or Alaska Native

Family history

Parents consanguinity: ○ Yes ○ No

Positive family history: ○ Yes ○ No

Notes & Comments

_____

Family tree (page 3)

Age at Onset of motor impairment (patient reported information)

When the patient has noticed the appearance of motor impairment in her/his daily activities:

In her/his_____ decade of life *(first, or second, or…); if available* _____ years old

Where the patient noticed the first muscle impairment:

○ Facial muscles:

○ Shoulder girdle muscles

○ Distal upper limb muscles

○ Abdominal muscles

○ Distal lower limb muscles

○ Pelvic girdle muscles

Asymmetric onset ○ Yes ○ No

When did her/his relatives notice that the patient was sleeping with half-open eyes? If yes, since _____decade

When did the patient notice the appearance of winged scapula? If yes, since _____decade

When has the patient notice the appearance of dropped shoulders? If yes, since _____ decade

Additional anamnestic information

Retinal vasculopathy: ○ Yes ○ No

Sensorineural deafness/auditory problems: ○ Yes ○ No

Developmental delay: ○ Yes ○ No

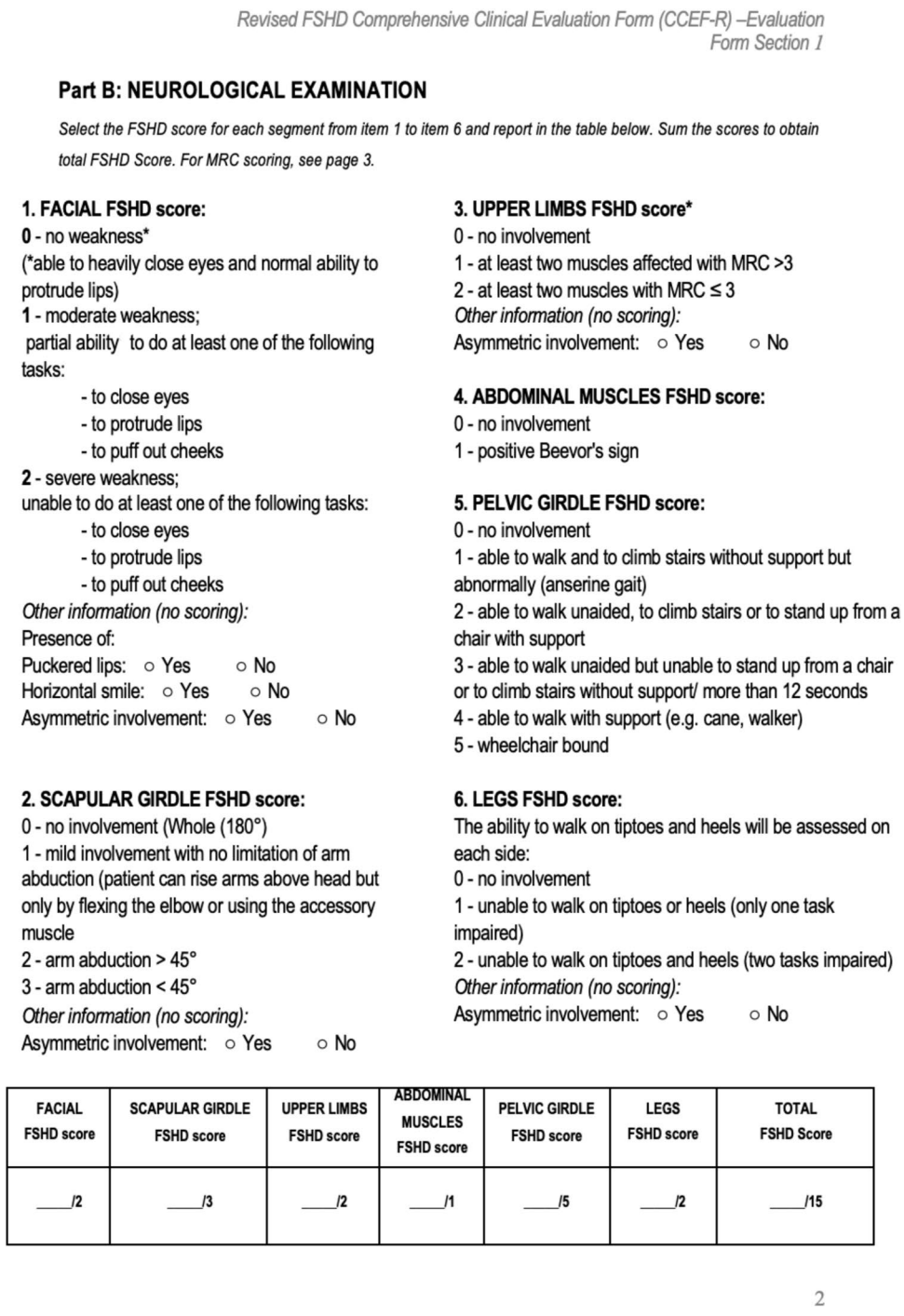
Previous surgery:

○ Scapular fixation

○ Spine surgery

1

Fig. 1 Revised CCEF Section 1 for anamnestic data collection



Revised FSHD Comprehensive Clinical Evaluation Form (CCEF-R) –Evaluation Form Section 1

Part B: NEUROLOGICAL EXAMINATION

Select the FSHD score for each segment from item 1 to item 6 and report in the table below. Sum the scores to obtain total FSHD Score. For MRC scoring, see page 3.

1. FACIAL FSHD score:
0 - no weakness*
(*able to heavily close eyes and normal ability to protrude lips)
1 - moderate weakness;
partial ability to do at least one of the following tasks:
- to close eyes
- to protrude lips
- to puff out cheeks

2 - severe weakness;
unable to do at least one of the following tasks:
- to close eyes
- to protrude lips
- to puff out cheeks

Other information (no scoring):
Presence of:
Puckered lips: ○ Yes ○ No
Horizontal smile: ○ Yes ○ No
Asymmetric involvement: ○ Yes ○ No

2. SCAPULAR GIRDLE FSHD score:
0 - no involvement (Whole (180°)
1 - mild involvement with no limitation of arm abduction (patient can rise arms above head but only by flexing the elbow or using the accessory muscle
2 - arm abduction > 45°
3 - arm abduction < 45°
Other information (no scoring):
Asymmetric involvement: ○ Yes ○ No

3. UPPER LIMBS FSHD score*
0 - no involvement
1 - at least two muscles affected with MRC >3
2 - at least two muscles with MRC ≤ 3
Other information (no scoring):
Asymmetric involvement: ○ Yes ○ No

4. ABDOMINAL MUSCLES FSHD score:
0 - no involvement
1 - positive Beevor's sign

5. PELVIC GIRDLE FSHD score:
0 - no involvement
1 - able to walk and to climb stairs without support but abnormally (anserine gait)
2 - able to walk unaided, to climb stairs or to stand up from a chair with support
3 - able to walk unaided but unable to stand up from a chair or to climb stairs without support/ more than 12 seconds
4 - able to walk with support (e.g. cane, walker)
5 - wheelchair bound

6. LEGS FSHD score:
The ability to walk on tiptoes and heels will be assessed on each side:
0 - no involvement
1 - unable to walk on tiptoes or heels (only one task impaired)
2 - unable to walk on tiptoes and heels (two tasks impaired)
Other information (no scoring):
Asymmetric involvement: ○ Yes ○ No

FACIAL FSHD score	SCAPULAR GIRDLE FSHD score	UPPER LIMBS FSHD score	ABDOMINAL MUSCLES FSHD score	PELVIC GIRDLE FSHD score	LEGS FSHD score	TOTAL FSHD Score
____/2	____/3	____/2	____/1	____/5	____/2	____/15

2

Fig. 2 Revised CCEF Section 2 for the neurological examination with the FSHD score (the section includes the MRC table with muscles to consider for FSHD score)

Category D can facilitate the selection of subjects in which other factors could be involved in determining phenotype and the disease expression, identifying patients presenting some FSHD features in association with other uncommon characteristics suggestive of a possible comorbidity (D1), or patients that do not fulfill the diagnostic criteria for FSHD and can be affected by an alternative disease (D2).

Since the availability of CCEF in 2016, several studies have documented its usefulness for stratifying patients and investigating potential different disease trajectories based on the clinical categories (Table 1).

In Italy, we firstly applied the CCEF to a cohort of 187 probands and 235 relatives from 106 families, carriers of 7–8 D4Z4 reduced alleles (DRAs), reporting that 47.1% of probands did not display the classic FSHD phenotype. Similarly, in another large cohort study of 244 individuals carrying D4Z4 alleles with 9–10 repeats, known as "borderline" alleles, we found that more than half of index cases

Fig. 2 (continued)

Revised FSHD Comprehensive Clinical Evaluation Form (CCEF-R) –Evaluation Form Section 1

Family tree

Medical Research Council (MRC) score

Muscle	Right MRC score	Left MRC score	Atrophy Yes (right or left) / No
Neck extensors			
Pectoralis			
Extrarotator muscles of upper limb* (Infraspinatus, Teres minor)			
Triceps brachii*			
Biceps brachii*			
Finger extensors*			
Wrist extensor*			
Finger flexors*			
Wrist flexors*			
Gluteus maximus			
Ileopsoas			
Biceps femoris			
Quadriceps			
Triceps surae			
Tibialis anterior			

MRC scores range from 0 to 5. In the 3 to 5 range, + and – marks can be attributed to describe muscle strength in detail. * Muscles to be considered for FSHD score "Upper limbs involvement".

3

displayed a classical FSHD phenotype, while about a quarter of the sample showed incomplete phenotype with isolated facial weakness or scapular girdle weakness [7, 9].

A subsequent Italian observational cohort study conducted in 246 FSHD1 patients classified according to the CCEF, showed that 79.1% (38/48) of asymptomatic carriers

Revised FSHD Comprehensive Clinical Evaluation Form (CCEF-R) –Clinical Diagnostic Form
Section 3

	TYPICAL FEATURES	ATYPICAL FEATURES
1. FACIAL INVOLVEMENT	☐ Moderate/severe facial weakness to close eyes and/or protrude lips and/or puff out cheeks (Facial FSHD score ≥1)	☐ Weakness of extra-ocular muscles ☐ Weakness of masticatory muscles ☐ Persistent dysphagia
2. SCAPULAR GIRDLE INVOLVEMENT	☐ Impairment of upper limb abduction with winged scapula or limitation of forward flexion (scapular FSHD score ≥1)	☐ Isolated distal upper limb muscle weakness ☐ Impairment of arms abduction (<90°) without winged scapula at rest and/or on attempted shoulder abduction or forward flexion
3. AXIAL MUSCLES INVOLVEMENT	☐ Hyperlordosis ☐ Beevor's sign ☐ Pectoralis muscles atrophy / weakness	☐ Camptocormia/bent syndrome ☐ Dropped head
4. PELVIC GIRDLE INVOLVEMENT	------	☐ Isolated and/or prevailing pelvic girdle muscle weakness
5. LOWER LIMBS INVOLVEMENT	☐ Weakness of tibialis anterior muscles	☐ Early or prevailing triceps surae atrophy/weakness
6. BLOOD CK LEVEL (at least two samples 1 month apart)	☐ Normal range ☐ < 4/5 x normal value at rest	☐ Value > 4/5 x normal value at rest in at least two evaluation ☐ Recurrent macroscopic myoglobinuria
7. OTHER SIGNS	☐ Orbiculari oris hypokinesia during speech ☐ Scapula winging on attempted shoulder abduction or forward flexion ☐ Asymmetric winged scapula ☐ Horizontal clavicles ☐ Forward sloping of the shoulders at rest ☐ Horizontal axillary fold ☐ "Popeye" arm ☐ Poly-hill sign	☐ Action and/or percussion myotonia ☐ Eyelid ptosis ☐ Pes cavus ☐ Early muscle contractures ☐ Cardiomyopathy (non-ischemic, non-valvular) ☐ Severe early or discordant respiratory restrictive insufficiency ☐ Other_____ (suggestive of other myopathic conditions)

1

Fig. 3 Revised CCEF Section 3, listing typical and atypical clinical features

Fig. 4 Revised CCEF Section 4 for Clinical Categories

FSHD Comprehensive Clinical Evaluation Form (CCEF) –Clinical Categories Section 4

CATEGORY A

Category A1
- Unable both to close eyes and to protrude lips (facial FSHD score 2)
- **Impairment of upper limb abduction** with winged scapula (scapular FSHD score ≥1)
- Absence of uncommon features

Category A2
- Partial ability **both** to close eyes **and** to protrude lips (facial FSHD score 1)
- **Impairment of upper limb abduction** with winged scapula (scapular FSHD score ≥1)
- Absence of uncommon features

Category A3
- Partial ability to close eyes **or** to protrude lips (facial FSHD score 1)
- **Impairment of upper limb abduction** with winged scapula (scapular FSHD score ≥1)
- Absence of uncommon features

CATEGORY B

Category B1
- **No facial weakness** (facial FSHD score = 0)
- **Impairment of upper limb abduction** with winged scapula (scapular FSHD score ≥1)
- Absence of uncommon features

Category B2
- **Facial weakness** (facial FSHD score ≥1)
- **No impairment of upper limb abduction** (scapular FSHD score 0)
- Absence of uncommon features

CATEGORY C

Category C1
- FSHD score = 0
+ at least one sign among the listed typical features (see Section 3)

Category C2
- FSHD score = 0, no other signs

CATEGORY D

Category D1
Subject fulfilling criteria of the above categories
+ at least one uncommon feature

Category D2
Subject not fulfilling criteria of any of the above categories

remained asymptomatic over time, and the progression of motor disability differed between clinical categories [14].

In agreement with these observations, the application of CCEF to retrospectively characterize the UK FSHD registry patients supported the hypothesis of a milder phenotype in patients without facial involvement (clinical category B2) and suggested that the facial-sparing forms do not represent an "initial" form of disease, but a defined phenotype with a different disease progression rate [15].

More recently, the CCEF was applied to a cohort of more than 600 Chinese FSHD patients in a nationwide population-based study [16]. The authors report a similar prevalence of

Table 1 Summary of the studies from literature applying the CCEF in FSHD patient' clinical characterization

Articles	*Cohort of FSHD patients*	*Main results*
Ricci et al., *Muscle Nerve, 2019* [15]	642 patients from UK FSHD Patient Registry	Patients classified as category B2 showed a milder motor disability in comparison with patients with classical phenotype (category A)
Ruggiero et al., *JAMA Netw Open, 2020* [9]	422 carriers of 7–8 DRAs (187 index cases and 235 relatives)- Italian observational cohort study	52.9% of index cases classified as category A, 47.1% presented incomplete or atypical phenotypes
Ricci et al., *Sci Rep. 2020* [7]	244 carriers of 9–10 DRAs (134 index cases and 110 relatives)- Italian observational cohort study	54.5% of index cases classified as category A, 20.1% as category B, 6.7% as category C and 18.7% as category D
Wang et al., *Lancet Reg Health West Pac. 2021* [16]	665 carriers of 1–10 DRAs from a large cohort of Chinese families	69.9% of patients classified as category A, 6.6% as category B, 20.8% as category C and 2.7% as category D
Vercelli et al., *J Neurol. 2021* [14]	246 carriers of 1–10 DRAs—Italian five year follow up study	Nearly 80% of asymptomatic carriers remained asymptomatic over time, and the progression of motor disability differed between clinical categories
Puma et al., *Eur J Hum Genet. 2025* [18]	157 DRAs carriers	27 subjects fell into category D and in 14 patients, FSHD-unrelated genetic causes were identified

the disease to Italy. About 70% of patients fell into category A, with a strong prevalence of the A2 subcategory, and 6.6% (43) were of category B (31 B1, 12 B2). Non-penetrant carriers of DRAs represented 20.8% of the cases and 2.7% had atypical phenotypes, thus belonging to category D. Those percentages slightly differ from the ones identified by the Italian group [16]; notably, the Chinese cohort includes patients with the full DRAs range, while the Italian published data refer to subjects with larger DRAs.

Loonen et al. [17] recently investigated the importance of some clinical features in predicting disease evolution by. They reported that the development of facial weakness appears to progress independently. Moreover, they observed that the forms with a prominent involvement of facial muscles were not related to the disease duration but identified a subgroup of patients (more frequently carriers of very short alleles) with a more severe phenotype that corresponds to CCEF category A1. Also Puma et al. utilized the CCEF to characterize a cohort of 157 FSHD1 patients to identify atypical phenotypes (category D) and further analyze the presence of associated conditions in that subgroup [18].

Overall, these studies support the importance of a detailed phenotypic characterization of FSHD subjects.

Conclusion

The phenotypical classification, together with other clinical parameters such as severity of motor involvement, pattern of muscle magnetic resonance imaging and family history, in combination with the genetic signatures, should be considered during the diagnostic work out for guiding genetic analysis and for genotype–phenotype correlations and genetic counseling. The distinction of the clinical categories can also facilitate the phenotypic classification deserving ad hoc studies for studying genetic modifiers or disease trajectories. Moreover, as we are living in a new therapeutic era in the field of neuromuscular diseases, clinical trials are also rapidly approaching in the FSHD world and CCEF-R can have a significant role in the clinical stratification process of patients and help in having clearer insights into the effects of interventions, laying the groundwork for evidence-based medical decision making.

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