Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 27 (2017) 782–790

www.elsevier.com/locate/nmd

Workshop report

225th ENMC international workshop: A global FSHD registry framework, 18–20 November 2016, Heemskerk, The Netherlands

Karlien Mul [a], June Kinoshita [b], Hugh Dawkins [c], Baziel van Engelen [a], Rossella Tupler [d,*] on behalf of the FSHD Consortium

[a] *Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands*
[b] *FSH Society, Lexington, USA*
[c] *Department of Health, Office of Population Health Genomics, Public Health Division, Government of Western Australia, Perth, Western Australia, Australia*
[d] *Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy*

Received 27 February 2017

1. Introduction

On 18–20 November 2016, the 225th ENMC Workshop on *'A global FSHD Registry framework'* took place in Heemskerk, the Netherlands. Twenty-two participants from 11 different countries gathered, including clinicians, researchers, policy makers and representatives from patient advocacy groups and industry.

Facioscapulohumeral muscular dystrophy (FSHD) is an inherited muscle disorder, characterized by weakness of the facial and shoulder girdle muscles followed by the leg and trunk muscles [1,2]. There is a large variability in the severity of symptoms, ranging from asymptomatic to wheelchair bound individuals.

Approximately 95% of FSHD patients carry one allele with a reduced number (1–10) of D4Z4 repeat units on chromosome 4q35 associated with specific haplotypes (FSHD1) [3]. Of the remaining 5% of patients with FSHD phenotype (FSHD2), most cases have been explained by heterozygous mutations in the *SMCHD1* (Structural Maintenance of Chromosomes flexible Hinge Domain containing-1) gene [4]. These two different (epi)genetic mechanisms lead to chromatin relaxation of the D4Z4 repeat in somatic tissue and subsequent expression of the *DUX4* gene in myogenic cells. DUX4 is thought to be the major contributor to FSHD pathology, although the exact pathophysiological mechanism is still largely unknown [5].

Expansion of our knowledge on the (epi)genetic mechanism underlying FSHD has led to advances in identifying (targeted) therapeutic strategies. Consequently it is now important to develop a 'clinical trial toolbox', consisting of patient registries, biomarkers and clinical outcome measures to ensure resources are utilized effectively [6]. The wide phenotypic expression in rare diseases, such as FSHD, means that patient registries are particularly important for clinical trial readiness. The aims of this workshop were to analyze the experience and results of the existing FSHD patient registries, update the Treat-NMD recommended dataset for FSHD, increase collaboration among established research groups and patient advocacy organizations and create the foundation on which to establish a global registry for FSHD.

1.1. Session 1: FSHD overview

Rossella Tupler started with an overview on the adult FSHD phenotype. The first description of FSHD was of an infantile onset case in 1884 by Landouzy and Dejerine. Even in this first report, the wide spectrum of clinical presentation was evident, describing familial cases with later onset and without facial weakness. Phenotypic variability was further expanded upon in a case report of a large family in Utah in the 1950s that included the observation of minimally affected individuals. In the 1980s, Padberg examined multiple large FSHD families and established diagnostic criteria for individuals to be included in linkage analyses (Table 1), setting the gold standard for FSHD [1,7]. This led to the discovery of the D4Z4 repeat contraction as the cause of FSHD1 in 1992, enabling highly sensitive and specific genetic testing for FSHD [8]. A rough inverse correlation between the number of D4Z4 repeat units (1–10) and clinical severity has been proposed [9].

In recent studies on patients included in the Italian FSHD registries, again wide variability in disease severity, including among members of the same family, has been demonstrated. The 'comprehensive clinical evaluation form' was introduced as a novel tool for categorizing patients and their relatives based on typical and/or atypical features for the FSHD phenotype

* Corresponding author. Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy.
E-mail address: rossella.tupler@unimore.it (R. Tupler).

http://dx.doi.org/10.1016/j.nmd.2017.04.004

[10]. A number of videos with examples of different FSHD phenotypes were shown during the presentation.

In the first workshop discussion session, it was agreed to first focus on discriminating typical from atypical phenotypes, because this distinction seems most relevant for future clinical trials on therapeutic approaches. Additionally, atypical phenotypes are rare and potential modifiers of the phenotype are still largely unknown.

Angela Berardinelli presented an overview of the infantile form of FSHD, starting with the criteria for infantile FSHD set by Brouwer and Padberg: signs and symptoms of facial weakness by the age of five and shoulder girdle weakness by the age of ten (Table 1) [11].

In the literature, the infantile form is considered a very severe and rapid form of FSHD. It makes up a small proportion (around 4%) of the total FSHD population [11]. Within this group, disease course is reported to be more homogeneous. One remarkable characteristic of this group is that the onset of pelvic girdle weakness can occasionally precede the shoulder girdle weakness by 1.5–2 years. The infantile form is also more frequently associated with extra-muscular manifestations such as mental retardation, epilepsy, severe exudative retinopathy, hearing loss and severe respiratory problems in some cases requiring (non-invasive) ventilation. This severe form is often associated with very short D4Z4 repeat fragments of 1–3 repeat units.

Results were shown of a multicenter retrospective study aiming to investigate the prognostic significance of very short 4q35 alleles of 1–3 repeat units [12]. A total of 66 index cases (40 de novo and 26 familial cases) were included through the Italian National Consortium for FSHD.

In this cohort of patients carrying 1–3 repeat units, there was wide clinical variability in the severity of symptoms. Additionally, infantile onset of symptoms did not always predict a very severe clinical outcome. In this retrospective study, no evidence of pre- or perinatal onset of the disease was found. The results indicate that the presence of a very short repeat fragment does not always associate with a severe phenotype, thus supporting the hypothesis that additional factors other than the repeat size must contribute to FSHD disease severity.

In the workshop discussion that followed, other clinicians noted that in their experience young onset FSHD is not necessarily predictive of a very severe disease course. In retrospect, quite a proportion of FSHD patients may have had unnoticed mild facial weakness at young age.

Table 1
Padberg and Brouwer clinical criteria for diagnosing (infantile) FSHD.

Main criteria for clinical diagnosis of FSHD by Padberg et al.
1. Onset of the disease in facial or shoulder girdle muscles; sparing of the extra-ocular, pharyngeal and lingual muscles and the myocardium
2. Facial weakness in more than 50% of the affected family members
3. Autosomal dominant inheritance in familial cases
4. Evidence of myopathic disease in EMG and muscle biopsy in at least one affected member without biopsy features specific to alternative diagnosis
Main criteria for clinical diagnosis of infantile FSHD by Brouwer et al.
1. Signs and symptoms of facial weakness by the age of five
2. Shoulder girdle weakness by the age of ten

Nicole Voet presented the results of a clinical trial on aerobic exercise and cognitive behavioral therapy to reduce chronic fatigue in FSHD through tackling fatigue perpetuating factors [13]. After 16 weeks of intervention and 12 weeks of follow-up, both treatments were effective in reducing chronic fatigue. Additionally, MRI imaging of the upper leg muscles showed a significantly smaller increase in the percentage of fatty infiltration in the muscles of patients in the intervention groups compared to a control group [14].

In the workshop discussion that followed, it was agreed that physical activity or exercise could potentially be a modifier of disease severity, which may be of particular relevance in the design of future clinical trials.

Silvère van der Maarel summarized what is currently known on FSHD on a molecular level and elucidated current knowledge in the context of his extensive experience in the molecular characterization of the disease. Briefly, 95% of all FSHD patients carry a repeat contraction of the D4Z4 repeat on chromosome 4q35, whereas most of the other 5% have a mutation in the *SMCHD1* gene. Both mechanisms result in chromatin relaxation of the D4Z4 repeat in somatic tissue and subsequent expression of the *DUX4* transcription factor in skeletal muscle. Only specific 4qA haplotypes provide the necessary polyadenylation signal to stabilize the DUX4 transcript and are thus disease-permissive. An exception is the 4qA166 haplotype, which for unknown reasons appears to be less likely to be disease-causing than other 4qA haplotypes. DUX4 is a transcription factor normally expressed in the luminal cells of the testis and suppressed in somatic cells. The exact pathways by which DUX4 expression leads to muscle weakness is currently unknown, but it is believed to influence, amongst others, pathways involved in apoptosis, expression of stem cell genes, alterations of RNA processing in muscle atrophy and inhibition of muscle regeneration.

Because of the observation that in individuals with shorter repeat sizes, the disease is more likely to be symptomatic, an oligogenic model is proposed in which individuals with longer repeat sizes are more dependent on additional modifiers for the disease to become symptomatic. This oligogenic model could also explain the variability in onset and progression of FSHD and the high frequency of non-penetrant mutation carriers in the population. Modifiers could be environmental factors or (epigenetic) factors working in *cis,* such as the repeat length or the polyadenylation signal, or in *trans,* like SMCHD1. Recently, a new *trans*-acting factor was found through the identification of two FSHD families with a mutation in the *DNMT3B* gene [15]. Research continues on finding additional modifiers.

1.2. Session 2: current landscape

Betsy Bogard introduced different registry models from the perspective of the industry as well as from patient advocacy groups. She explained the “original” registry model in rare diseases: a longitudinal registry focused on one disease and owned by a drug company. These registries have historically

been clinician-centered, with data input only through clinicians and no or limited feedback directly to the participating patients. Over the last 5–7 years 'patient-driven' registries have evolved. These are more frequently cross-sectional, patient-reported and provide direct feedback to patients. An example of a global 'one registry' for fibrodysplasia ossificans progressiva (FOP) was shown. In this registry example, there is input by both clinicians and patients through different portals of the same registry. In general, it was pointed out to be aware of de-centralized registry ownership, because it can lead to registry fragmentation and thus complicate data consolidation. Although registries provide valuable information, no registry could replace natural history studies and clinical trials.

Armelle Richiardi outlined the relevance of patient registries for the industry. From an industry perspective, registries are mostly used in the setting of clinical trials for obtaining disease knowledge (clinical trial endpoints, long term disease progression, treatment impact) and patient knowledge (patient profile and identification for clinical trials, post marketing surveillance). An example of a successful collaboration of the industry with a registry was given: a registry and natural history study for early onset FSHD including patients from twelve different hospitals worldwide. Longitudinal data on this cohort will be collected in the upcoming years.

June Kinoshita presented an overview of the existing FSHD patient registries from an international perspective. Currently, there are FSHD registries in 13 different countries comprising data on over 3000 patients. While the current registries include a large number of patients, this is still only a fraction of the total number of FSHD patients worldwide. Furthermore, of those registered, data are not uniformly collected and is consequently difficult to aggregate or compare. Therefore, it is critical for the FSHD community to establish a global core dataset that collects patient-reported information in a way that it can be anonymized, aggregated and analyzed. There are still a number of logistic issues to be solved before establishing a global federated registry.

1.3. Session 3: the registry paradigm

Five different national FSHD registries and their results so far were discussed.

Baziel van Engelen presented the Dutch FSHD registry, a patient-centered online registry that currently contains 275 participants. Patients register themselves online, sign an informed consent form to collect genetic data and then fill out online questionnaires. In addition to the standardized and internationally agreed Treat-NMD core data set (Table 2), a number of validated questionnaires are included, for example on fatigue, depression, pain and quality of life. These additional questionnaires serve as patient reported outcome measures (PROMS) to enable researchers to learn more about the impact of the disease.

The Dutch registry envisions a two-way registry, in which patients not only provide input but also receive feedback about their successive data over time or in comparison to the total group. Additionally, the registry is structured to enable participants to make suggestions with regard to researched items. This registry has already proven useful in the recruitment of patients for a recent clinical trial.

Teresinha Evangelista presented the UK (United Kingdom) FSHD patient registry. The UK FSHD Patient Registry is an online patient-initiated registry combining patient reported outcomes with clinically verified details [16]. Genetic confirmation is obtained through a clinician specialist or directly from the laboratory that is performing the test. The registry contains the Treat-NMD core data set and a set of additional questionnaires, for example on pain, quality of life and scapular fixation. Since 2013 over 700 participants have registered, 576 of whom have a confirmed genetic diagnosis. Longitudinal data are collected through annual updates. The registry has proven its utility with the recruitment of patients for a natural history study of infantile onset FSHD and the validation of a newly developed Rasch-built patient reported outcome measure.

The US (United States) National Patient Registry was presented by *Rabi Tawil.* It is the oldest FSHD registry established in 2000 as a combined registry for FSHD and myotonic dystrophy [17]. Participants sign a consent form that allows the registry to obtain medical records for review. There are currently 876 patients registered and 88 unaffected family members. Paper questionnaires are filled out by the participants and all medical records are reviewed by one clinician and participants are categorized by diagnostic certainty. All data are then entered into an electronic data base. About 60% of all participants are genetically confirmed. There is a yearly follow-up to track disease progression and longitudinal data up to 14 years is available. The registry captures hard endpoints such as age at first use of assistive devices and use of wheelchair and includes a functional questionnaire that allows tracking of disease progression [18]. Newsletters and recruitment letters about studies are sent out regularly by the registry to participants. Researchers utilize the registry to either to help recruit patients for clinical studies or to analyze anonymized data. To date, the registry has received application for 19 applications.

Rossella Tupler presented the Italian FSHD registry; it is a multi-center clinician reported registry. Fourteen neuromuscular clinics and two diagnostic laboratories participate in the 'Italian National Registry for FSHD'. The registry includes a standardized clinical examination and molecular testing of index cases and relatives. The registry now includes 1093 index cases with 2131 D4Z4 carrier relatives and 399 single cases. The patients are categorized based on the phenotype into classical and atypical or complex phenotypes [10]. The registry has been used for a prospective observational study of 246 subjects with a follow-up period of five years. Over those five years, the mean FSHD score [19] increased from 4.4 ± 3.7 SD to 5.6 ± 4.3 SD and 4% of patients lost ambulation. Approximately a quarter of the 45% asymptomatic relatives became symptomatic during the five years of follow-up, decreasing the percentage of asymptomatic relatives to 34%.

Sabrina Sacconi introduced the French FSHD registry, which includes a total of 682 patients. It is a combined patient- and doctor-reported registry with a self-reported form and a clinical evaluation form respectively. Patients and doctors can view data for a specific patient online by using a personal

Table 2
Updated treat-NMD core dataset for FSHD.

	Item	Self-report example
	Mandatory items	
1a.	**Personal data**	**Your* personal data**
	Biological sex at birth	Biological sex at birth
	First name	First name
	Middle name	Middle name
	Last name	Last name
	Date of birth	Date of birth
	City of birth	City of birth
	Country of birth	Country of birth
	Current Address Zip/post code Country	Current Address Zip/post code
	Telephone	Country
	Email	Telephone
		Email
		*Or FSHD patient's, if you are a parent/guardian or caregiver registering on behalf of a patient
1b.	**Alternative contact**	**Alternative contact should you be unavailable**
	Next of kin	Next of kin
	First name	First name
	Last name	Last name
	Current address	Current address
	Zip/post code	Zip/post code
	Country	Country
	Telephone	Telephone
	Email	Email
1c.	**Diagnosing physician**	**Physician who diagnosed you with FSHD**
	First name	First name
	Last name	Last name
	Medical institution	Medical institution
	Address	Address
	Zip/post code	Zip/post code
	Country	Country
	Telephone	Telephone
	Email	Email
2.	**Genetic test result**	**What is your genetic test result?**
	○ Confirmed FSHD1 (D4Z4 contraction 1–10 repeats + 4qA)	○ I have been told I have genetically confirmed FSHD and I can provide a copy of my genetic test result [UPLOAD]
	○ FSHD2 (no contraction + 4qA + SMCHD1 mutation)	○ I have been told I have genetically confirmed FSHD but I do not have my genetic test result. [FOLLOW-UP: OBTAIN GENETIC TEST REPORT FROM DIAGNOSING PHYSICIAN]
	○ Not FSHD (homozygous for 4qB)	○ I have been tested but I haven't received the result yet
	○ Result pending	○ I have not been tested but wish to be tested
	○ Not tested	○ I have not been tested and do not wish to be tested
3.	**Clinical diagnosis**	**Which of these symptoms do you have? (Select all that apply)**
	○ Facial weakness	○ Facial weakness
	○ Periscapular shoulder weakness	(weakness of muscles in the face causing e.g. inability to smile, to whistle, or to close your eyes fully at night)
	○ Foot dorsiflexor weakness	○ Shoulder weakness
	○ Hip girdle weakness	(weakness of the muscles around the shoulder blades causing e.g. shoulder blades to protrude; inability to raise your arms sideways above the level of your shoulder).
	○ Asymptomatic (patients has no complaints, but physician detects signs)	○ Foot or ankle weakness
	○ Non-penetrant (no signs)	(weakness of the muscles that help you lift your feet up, causing e.g. foot drop (where the foot tends to hang with the toes pointing down), steppage gait (lifting the feet high when walking), or frequent tripping)
		○ Hip girdle weakness
		(weakness of the muscles of the pelvis and top of the legs, causing e.g. difficulties in going up stairs or ladders, rising from a chair or getting up from the floor)
		○ I have none of the signs or symptoms described above
4.	**Current best motor function**	**Which of the following options describes the best motor function you are currently able to achieve?**
	○ Ambulatory (unassisted)	○ I can walk unaided always
	○ Ambulatory (assisted)	○ I can walk unaided most of the time
	○ Non-ambulatory	○ I can walk with an assistive device for some distance
		○ I can walk with an assistive device for a short distance
		○ I cannot walk

(*continued on next page*)

Table 2 (*continued*)

	Item	Self-report example
5.	**Wheelchair use** ○ No ○ Part-time (start date year) ○ Full-time (start date year)	**Do you use a wheelchair? (please select all that apply)** ○ I don't use a wheelchair. ○ I started using an assistive device from [YEAR] ○ I started using a wheelchair part-time from [YEAR] ○ I use a wheelchair all the time since [YEAR]
6a.	**Pulmonary function test** ○ No ○ Yes	**Has your respiratory capacity ever been evaluated (for example pulmonary function testing)?** ○ No ○ Yes ○ I don't know
6b.	**Non-invasive ventilation** ○ None ○ Part-time (start date year) ○ Full-time (start date year)	**Do you regularly use a non-invasive (mask) ventilation device?** ○ No, never ○ Yes, but only part-time, e.g. at night, since [YEAR]) ○ Yes, all day since [YEAR]
6c.	**Invasive ventilation** o None o Part-time (start date year) o Full-time (start date year)	**Do you use invasive ventilation (requiring surgery, e.g. tracheostomy)?** ○ No ○ Yes, part-time since [YEAR] ○ Yes, full-time since [YEAR]
7.	**Age of onset for selected FSHD symptoms (taken from question 3)** ○ Facial weakness (start date year) ○ Periscapular shoulder weakness (start date year) ○ Foot dorsiflexor weakness (start date year) ○ Hip girdle weakness (start date year)	**At what age did you first notice symptoms related to your FSHD? Give approximate year for all that apply** ○ Facial weakness, first occurred in [YEAR] ○ Shoulder weakness, first occurred in [YEAR] ○ Ankle/foot weakness, first occurred in [YEAR] ○ Hip girdle weakness, first occurred in [YEAR]
8.	**Retinal vascular disease attributable to FSHD** ○ No ○ Yes (start date year) ○ Unknown	**Have you been diagnosed with retinal problems or abnormal blood vessels at the back of your eye that your doctors think may be related to your FSHD? ("Coat's disease," retinal vascular disease)** ○ No ○ Yes, first occurred in [YEAR], but with no visual impairment ○ Yes, first occurred in [YEAR], and has caused visual impairment ○ I don't know
9.	**Hearing loss** ○ No ○ Yes (start date year) ○ Unknown	**Do you have hearing loss?** ○ No ○ Yes, first occurred in [YEAR], but I don't use a hearing aid ○ Yes, first occurred in [YEAR], and I use a hearing aid ○ I don't know
10.	**Scapular fixation** ○ No ○ Yes, unilateral (surgery date year) ○ Yes, bilateral (surgery dates year)	**Have you had scapular fixation (an operation to fix your shoulder blade to your ribcage)?** ○ No ○ Yes, in one shoulder [LEFT/RIGHT], operated in [YEAR] ○ Yes, both shoulders, operated in [YEAR] and [YEAR]
11.	**Pregnancy (only females)** ○ No ○ Yes ○ Number of pregnancies	**(For women only) Have you ever been pregnant? Select all that apply.** ○ No ○ Yes, ____ time(s) in [YEARS]
12.	**Family history** ○ Affected mother ○ Affected father ○ Affected offspring ○ Affected sibling(s) ○ Other affected relative ○ No ○ Unknown	**Has anybody else in your family been diagnosed with FSHD (select all that apply)?** ○ Yes, mother ○ Yes, father ○ Yes, one or more children ○ Yes, one or several of my siblings (brothers and sisters) ○ Yes, further relatives (other than parents and siblings) ○ No ○ I don't know
13.	**Epilepsy** ○ No ○ Yes	**Do you have a history of seizures/convulsions?** ○ No ○ Yes
14.	**Mental retardation** ○ No ○ Yes	**Do you have a history of delayed cognitive development or cognitive impairment?** ○ No ○ Yes

(*continued on next page*)

Table 2 (*continued*)

	Item	Self-report example
	Non-mandatory	
15.	**Ethnic origin**	**How would you describe your ethnic origin?**
	○ Pulldown menu [SPECIFIC TO EACH COUNTRY'S REQUIREMENTS]	○ Pulldown menu [SPECIFIC TO EACH COUNTRY'S REQUIREMENTS]
	○ Other	○ Other
	○ Declined to answer	○ I choose not to answer this question
16.	**Other registry**	**Have you signed up for any other FSHD registry or studies?**
	○ Yes (specify)	○ Yes (if yes, please specify: PULLDOWN MENU or OTHER)
	○ No	○ No
	○ Unknown	○ I don't know

patient identification number. More recently, the motor function measure has been included as an outcome measure in the registry.

After these five registries were presented, the workshop participants discussed some of the challenges faced by current registries. The proportion of registered patients is still low compared to the total number of potential participants. The inclusion rates could be improved by actively involving patients and patient advocacy groups, improving accessibility of the registries and actively inviting patients to be involved, for example at the time of diagnosis. Since no registry will be able to capture data on every aspect of the disease, a core dataset with optional additional data collection on specified topics is desired. Data collection needs to be standardized to enable assembly of data globally. Additionally, different topics could be addressed in different registries to complement one another.

1.4. Session 4: examples from other disease areas

Hugh Dawkins shared the experiences from the federated global registry for Duchenne muscular dystrophy (DMD). The Duchenne Foundation, in close partnership with Australian umbrella neuromuscular disease patient organizations, initiated a nationwide campaign for a National DMD Registry to collate clinical and genetic data. Patients and patient advocacy groups have been involved in the development of the registry throughout the entire process. This 'patient voice' has helped to get policymakers engaged and thus accelerate registry design. Because accuracy of the data was considered a critical success factor, a clinician-centered registry was chosen. The Treat-NMD core dataset was the starting point for data collection. After successfully rolling out a DMD registry, other registries for neuromuscular diseases were developed as well, resulting in an overarching neuromuscular disease registry structure that is open source, secured and interoperable with other registries. The Australian Duchenne registry is now also participating in a global registry supported by Treat-NMD, which is a federated global registry of multiple national registries.

Jacqui van Rens summarized experiences from the European Cystic Fibrosis Society Patient Registry. Since its initiation in 2003, the registry has included over 40,000 genetically confirmed patients in 30 countries, including longitudinal data since 2008. It is a highly secured web-based and open-source registry containing anonymized data. Data are collected through cystic fibrosis centers as well as through national registries. Patient encounters are entered into the registry and annual summaries are sent to the federated European registry. It is possible to extract reports per patient, center or country, which enables comparisons over time or between centers or countries. Applications for aggregated data can be made by researchers, patient organizations and industry. Important lessons learned include: aim for clear definitions, start with a pilot study, organize funds, share online data-collection platform and collaborate with existing (inter)national registries and patient advocacy groups.

In a workshop discussion that followed this session, it was emphasized that anonymized (aggregated) data should be easily accessible wherever possible to facilitate and accelerate research projects.

1.5. Session 5: beyond the dataset

June Kinoshita reported the results of a survey conducted by the FSH Society on patients' views and priorities with regard to registries. Three hundred twenty-six patient responses were received. The main outcomes indicated that patients often misunderstand the purpose and/or intention of registries and have difficulty discriminating between registries and other research studies. Additionally, registry participants appreciate some forms of interaction or feedback in return for their efforts. Regular communication from registries and active involvement of patients and patient advocacy groups will help to keep them engaged.

Chad Heatwole presented the design of the FSHD Health Index (FSHD-HI), a disease-specific patient-reported outcome measure intended to measure a patient perception of the total disease burden. It was developed based on the Food and Drug Administration (FDA) guidelines starting from qualitative interviews of patients followed by a national cross-sectional validation study. The questionnaire contains 116 questions in 14 subscales that can be answered in approximately 15 minutes. The FSHD-HI was tested and compared to traditional outcome measures in a 12-month longitudinal study including 41 participants. The questionnaire showed good reliability and correlation with traditional outcome measures like the FSHD clinical score, 6-minute walking test and manual muscle testing. Further analyses will be performed regarding responsiveness and minimally clinically important differences.

Betsy Bogard emphasized the value of registries for the pharmaceutical industry in a drug development process. Briefly

she explained how the role of a registry evolves along the drug development path. It starts with gathering disease and patient knowledge, connecting patients and researchers and identifying patients for clinical trials in the preclinical development phase and the clinical trial phase. Later in the process, in the regulatory approval phase and the commercial phase, registries can support post-marketing commitments, provide data supportive of trial findings, support label expansion and advance the understanding of treatment response.

The existing Treat-NMD core dataset for international FSHD registries was introduced by *Rabi Tawil* and *Baziel van Engelen*. The dataset currently comprises five mandatory items and ten highly encouraged items, including personal data, genetic data and data on clinical aspects. It includes one column with items in medical terms and another one with the same items in layman terms to be included in patient-reported registries. All items were introduced and discussed shortly in preparation for the final core dataset in the discussion session.

1.6. Session 6: structured discussions on areas of the dataset

For the first part of the discussion, the workshop participants were separated into three groups: clinicians, patient advocates and geneticists. Conclusions of each group were discussed and key issues and recommendations were crystallized during the plenary session.

The clinicians discussed the diagnostic criteria for FSHD as formulated by Padberg et al. in 1991 [7]; they agreed that these criteria are still accurate and continue to be highly relevant (Table 1). Although pharyngeal and tongue muscles can be involved in very severe forms of FSHD, involvement of these particular muscles was considered so rare that the current criteria were presumed to apply to practically all FSHD patients. In the future, when longitudinal (registry) data become available, the criteria may be revised or expanded. Additionally, the criteria by Brouwer et al. for infantile FSHD were still supported by the group [11].

In relation to the core dataset for international FSHD registries, the workshop participants confirmed that all the current data items were considered highly relevant. The infantile form should be considered a severe form in the total spectrum of FSHD, and it was agreed that most of the current items capture data that is also applicable to infantile cases. Regarding extra-muscular manifestations of FSHD, the workshop participants agreed that it would be useful to add items on the involvement of the central nervous system. Based on existing the literature, it was decided to add two items about epilepsy and cognitive delay as highly encouraged items (Table 2).

The patient advocates reviewed the design and formulation of the Treat-NMD common dataset for FSHD. All participants agreed on a number of textual changes to make item descriptions clearer and to remove any ambiguity. Conceptual changes were made so that for every item, the drop down or radio-button lists for responding to the options start with the least severe symptoms/characteristics first (Table 2). An expansion of the personal data elements was suggested to enable the possibility of Privacy-Preserving Record linkage that could include the need to assign patients a unique global identifier code, thus opening up possibilities for the data to be used in a global dataset. Again it was emphasized that additional questionnaires can be used along with the core dataset in national registries. All agreed that further iterations of the group, followed by industry engagement and wider FSHD testing and feedback are desired to design an optimal dataset.

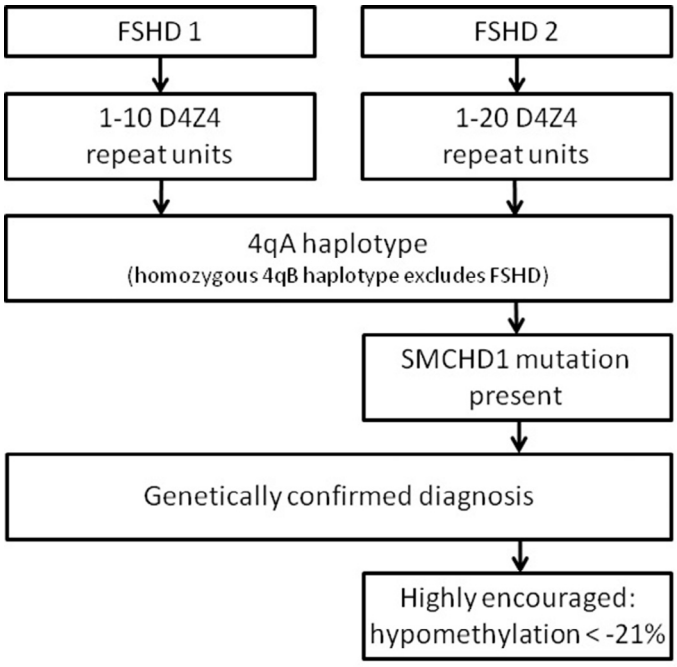

Fig. 1. Graphical representation of currently known genetic mechanisms used in molecular diagnosis of FSHD1 and FSHD2.

The geneticists proposed a genetic testing workflow for diagnosing FSHD (Fig. 1). For a molecular diagnosis of FSHD, the number of D4Z4 repeat units should be determined. A range of 1–10 repeat units is compatible with FSHD1, but only on a *DUX4* polyadenylation signal containing chromosome, usually the 4qA haplotype. In the absence of this polyadenylation site, homozygous 4qB haplotypes typically exclude the diagnosis of FSHD.

For FSHD2, repeat size should be in the range of 1–20 D4Z4 units, although some patients have been reported with repeat sizes that exceed the 20 units. Again, a 4qB haplotype is not compatible with FSHD and the haplotype should always be determined. A mutation in the SMCHD1 gene confirms the diagnosis. Assessment of hypomethylation is strongly encouraged, but not essential for the genetic diagnosis of FSHD, although this may render the interpretation of *SMCHD1* variants cumbersome.

2. Conclusions

FSHD is a rare condition for which potential interventions and targeted therapies are on the near horizon. Patient registries are valuable instruments to efficiently recruit patients for clinical trials and also to provide knowledge on many aspects of FSHD to doctors, researchers and patients. A global registry would allow for a greater number of participants and

subsequently bigger data sets. Since there are already multiple national registers for FSHD in place, the most suitable way would be to create a one federated global registry consisting of different national registries. Such a federated registry should have a common general data set, but should also leave room for national registries to expand and have their own approaches. Along these lines, the existing common data set by Treat-NMD was updated. Additionally, two items were added concerning central nervous system involvement, especially relevant for early onset cases.

Accurate diagnosis is essential for the patients to receive best care and for capturing useful genotype–phenotype data. The clinical diagnostic criteria as proposed by Padberg et al. were still considered highly relevant and accurate. A genetic test flow for genetic diagnosis for FSHD1 and FSHD2 was designed.

Patient empowerment, as well as engagement of industry and policy makers was considered critical for optimal design and use of patient registries.

2.1. Future plans

During the meeting the 'FSHD Consortium' was formed to initiate and maintain an international effort to initiate and maintain one federated global FSHD registry. The consortium will be formalized and a charter will be written. The first consortium goal will be a pilot study to collect curated data of the minimal core dataset of the existing 13 national registries toward the global registry. The global registry could be used to further define the FSHD phenotype and genotype, and to collect longitudinal data. The registry could also be used as a basis for international surveys and research into the benefit of exercise and cognitive behavioral therapy, the use of pharmaceutical and other (non-prescription) drugs, pregnancy-related issues, and to evaluate and deploy patient reported outcome measures like the FSHD-HI. Further iteration of the registry design and especially of the content of the common minimal data set will be required, not only by clinicians and researchers, but also by industry and patient advocates.

2.2. Workshop participants

Dr. Verònica Alonso Ferreira (Madrid, Spain)
Prof. Shahram Attarian (Marseille, France)
Dr. Angela Berardinelli (Pavia, Italy)
Ms. Betsy Bogard (USA)
Prof. Hugh Dawkins (Australia)
Prof. Baziel van Engelen (Nijmegen, the Netherlands)
Dr. Teresinha Evangelista (Newcastle, UK)
Mr. Kees van der Graaf (the Netherlands)
Dr. Chad Heatwole (Rochester, USA)
Ms. June Kinoshita (USA)
Prof. Silvère Van der Maarel (Leiden, the Netherlands)
Dr. Jean Mah (Calgary, Canada)
Dr. Karlien Mul (Nijmegen, the Netherlands)
Dr. Jacqui van Rens (Leuven, Belgium)
Dr. Armelle Richiardi (France)
Dr. Richard Roxburgh (New Zealand)
Prof. Sabrina Sacconi (Nice, France)
Prof. Rabi Tawil (Rochester, USA)
Prof. Rossella Tupler (Modena, Italy)
Ms. Diana van der Meij-Kim (the Netherlands)
Dr. Nicole Voet (Nijmegen, the Netherlands)
Dr. Stanislav Vohánka (Brno, Czech Republic)

Acknowledgments

This workshop was made possible, thanks to the financial support of the European Neuromuscular Centre (ENMC) and ENMC main sponsors: Association Française contre les Myopathies (France), Deutsche Gesellschaft für Muskelkranke (Germany), Telethon Foundation (Italy), Muscular Dystrophy Campaign (UK), Muskelsvindfonden (Denmark), Prinses Beatrix Fonds (Netherlands), Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland), Telethon Foundation (Italy), Spierziekten Nederland (The Netherlands), and Associated member: Finnish Neuromuscular Association (Finland). Also, we would like to thank FSH Society, Friends of FSH Research and FSHD Stichting for their support to this workshop.

References

[1] Padberg GW. *Facioscapulohumeral disease.* 1982, University of Leiden.
[2] Mul K, Lassche S, Voermans NC, Padberg GW, Horlings CG, van Engelen BG. What's in a name? The clinical features of facioscapulohumeral muscular dystrophy. Pract Neurol 2016;16:201–7.
[3] Lemmers RJ, van der Vliet PJ, Klooster R, Sacconi S, Camaño P, Dauwerse JG, et al. A unifying genetic model for facioscapulohumeral muscular dystrophy. Science 2010;329:1650–3.
[4] Lemmers RJ, Tawil R, Petek LM, Balog J, Block GJ, Santen GW, et al. Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. Nat Genet 2012;44:1370–4.
[5] Ricci G, Zatz M, Tupler R. Facioscapulohumeral muscular dystrophy: more complex than it appears. Curr Mol Med 2014;14:1052–68.
[6] Tawil R, Padberg GW, Shaw DW, van der Maarel SM, Tapscott SJ, Participants FW. Clinical trial preparedness in facioscapulohumeral muscular dystrophy: clinical, tissue, and imaging outcome measures 29–30 May 2015, Rochester, New York. Neuromuscul Disord 2016;26:181–6.
[7] Padberg GW, Lunt PW, Koch M, Fardeau M. Diagnostic criteria for facioscapulohumeral muscular dystrophy. Neuromuscul Disord 1991;1:231–4.
[8] Wijmenga C, Hewitt JE, Sandkuijl LA, Clark LN, Wright TJ, Dauwerse HG, et al. Chromosome 4q DNA rearrangements associated with facioscapulohumeral muscular dystrophy. Nat Genet 1992;2:26–30.
[9] Tawil R, Forrester J, Griggs RC, Mendell J, Kissel J, McDermott M, et al. Evidence for anticipation and association of deletion size with severity in facioscapulohumeral muscular dystrophy. The FSH-DY Group. Ann Neurol 1996;39:744–8.
[10] Ricci G, Ruggiero L, Vercelli L, Sera F, Nikolic A, Govi M, et al. A novel clinical tool to classify facioscapulohumeral muscular dystrophy phenotypes. J Neurol 2016;263:1204–14.
[11] Brouwer OF, Padberg GW, Wijmenga C, Frants RR. Facioscapulohumeral muscular dystrophy in early childhood. Arch Neurol 1994;51:387–94.
[12] Nikolic A, Ricci G, Sera F, Bucci E, Govi M, Mele F, et al. Clinical expression of facioscapulohumeral muscular dystrophy in carriers of 1–3 D4Z4 reduced alleles: experience of the FSHD Italian National Registry. BMJ Open 2016;6:e007798.
[13] Voet N, Bleijenberg G, Hendriks J, de Groot I, Padberg G, van Engelen B, et al. Both aerobic exercise and cognitive-behavioral therapy reduce chronic fatigue in FSHD: an RCT. Neurology 2014;83:1914–22.

[14] Janssen B, Voet N, Geurts A, van Engelen B, Heerschap A. Quantitative MRI reveals decelerated fatty infiltration in muscles of active FSHD patients. Neurology 2016;86:1700–7.
[15] van den Boogaard ML, Lemmers RJ, Balog J, Wohlgemuth M, Auranen M, Mitsuhashi S, et al. Mutations in DNMT3B modify epigenetic repression of the D4Z4 repeat and the penetrance of facioscapulohumeral dystrophy. Am J Hum Genet 2016;98:1020–9.
[16] Evangelista T, Wood L, Fernandez-Torron R, Williams M, Smith D, Lunt P, et al. Design, set-up and utility of the UK facioscapulohumeral muscular dystrophy patient registry. J Neurol 2016;263:1401–8.
[17] Hilbert JE, Kissel JT, Luebbe EA, Martens WB, McDermott MP, Sanders DB, et al. If you build a rare disease registry, will they enroll and will they use it? Methods and data from the National Registry of Myotonic Dystrophy (DM) and Facioscapulohumeral Muscular Dystrophy (FSHD). Contemp Clin Trials 2012;33:302–11.
[18] Statland JM, Tawil R. Risk of functional impairment in facioscapulohumeral muscular dystrophy. Muscle Nerve 2013;49:520–7.
[19] Lamperti C, Fabbri G, Vercelli L, et al. A standardized clinical evaluation of patients affected by facioscapulohumeral muscular dystrophy: the FSHD clinical score. Muscle Nerve 2010;42:213–17.