Neuromuscular Disorders xxx (xxxx) xxx

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Meeting report: The 2023 FSHD International Research Congress

Jamshid Arjomand[a], Davide Gabellini[b], Nicol Voermans[c,*], on behalf of the 2023 FSHD International Research Congress Program Committee[#]

[a] FSHD Society, 75 North Main Street, Suite 1073, Randolph, MA 02368 USA
[b] Division of Genetics and Cell Biology, IRCCS Ospedale San Raffaele, Milano 20132, Italy
[c] Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands

ARTICLE INFO

Article history:
Available online xxx

ABSTRACT

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common inherited muscular dystrophies. As part of the FSHD Society's commitment to promote global communication and collaboration among researchers, the Society collaborated with FSHD Europe and convened its 30th annual International Research Congress (IRC) on June 15–16, 2023, in the city of Milan, Italy. Over 240 researchers, clinicians, patients and pharmaceutical company representatives from a wide geographical background participated to hear about the latest developments and breakthroughs in the field. The meeting was structured to provide a mix of basic and clinical research in five sessions: 1. Discovery research & genetics; 2. Outcome assessments; 3. Disease mechanisms & interventional strategies; 4. Clinical studies & trial design; and 5. Pediatric FSHD. The keynote speakers were Professor Baziel van Engelen (on the importance of incorporating the patient's voice to help refine and improve basic laboratory and clinical research) and Dr. Bénédict Chazaud (on the role of the immune system in normal muscle regeneration and in Duchenne muscular dystrophy). The FSHD IRC was preceded by the Industry Collaborative for Therapeutic Development in FSHD meeting and followed by the World FSHD Alliance network of national patient groups and advocacy organizations for FSHD summit. The Congress concluded with the announcement for the 2024 International Research Congress, which will take place on June 13–14, 2024 in Denver, Colorado, USA, and followed by the FSHD Society's flagship educational conference for the FSHD community, the Patient Connect Conference, on June 15–16, 2024.

1. Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is a myopathy characterized by slowly progressive muscle weakness, leading to increasing impairments over the lifetime of patients. It is estimated to affect one million people worldwide, making it one of the most common inherited muscular dystrophies. As part of the FSHD Society's commitment to promote global communication and collaboration among researchers, the Society collaborated with FSHD Europe and convened its 30th annual International Research Congress (IRC) on June 15–16, 2023, in the city of Milan, Italy. This year's organizing committee reflected the diversity of the conference participants and included members from Argentina, Belgium, Croatia, Italy, the Netherlands, Turkey, and the United States. Over 240 researchers, clinicians, patients and pharmaceutical company representatives registered to attend the meeting in person and virtually to hear from FSHD experts on the latest developments and breakthroughs in the field. In addition to the 26 oral presentations and panel discussion summarized below, 73 additional research studies and projects were presented during the poster sessions. The meeting was structured to provide a mix of basic and clinical research on each day of the two-days congress. The FSHD IRC was preceded by the Industry Collaborative for Therapeutic Development in FSHD meeting and followed by the World FSHD Alliance network of national patient groups and advocacy organizations for FSHD summit.

2. Keynote presentations

One of the themes of the 2023 IRC was "Pediatric FSHD," and the meeting began with a moving presentation by an FSHD patient, Jaya Motta, a 22-year-old college student in bioengineering. Born in Nepal, Jaya was adopted by an Italian family and was diagnosed with infantile-onset FSHD. He shared his experiences, support system, and hopes for the future, as he completes his studies and looks to use his engineering skills to help others.

Professor Baziel van Engelen, MD PhD followed with a keynote address underlining the importance of incorporating the patient's

* Corresponding author.
E-mail address: nicol.voermans@radboudumc.nl (N. Voermans).
Listed at the end of this report.

https://doi.org/10.1016/j.nmd.2023.10.018
0960-8966

Please cite this article as: J. Arjomand, D. Gabellini and N. Voermans, Meeting report: The 2023 FSHD International Research Congress, Neuromuscular Disorders, https://doi.org/10.1016/j.nmd.2023.10.018

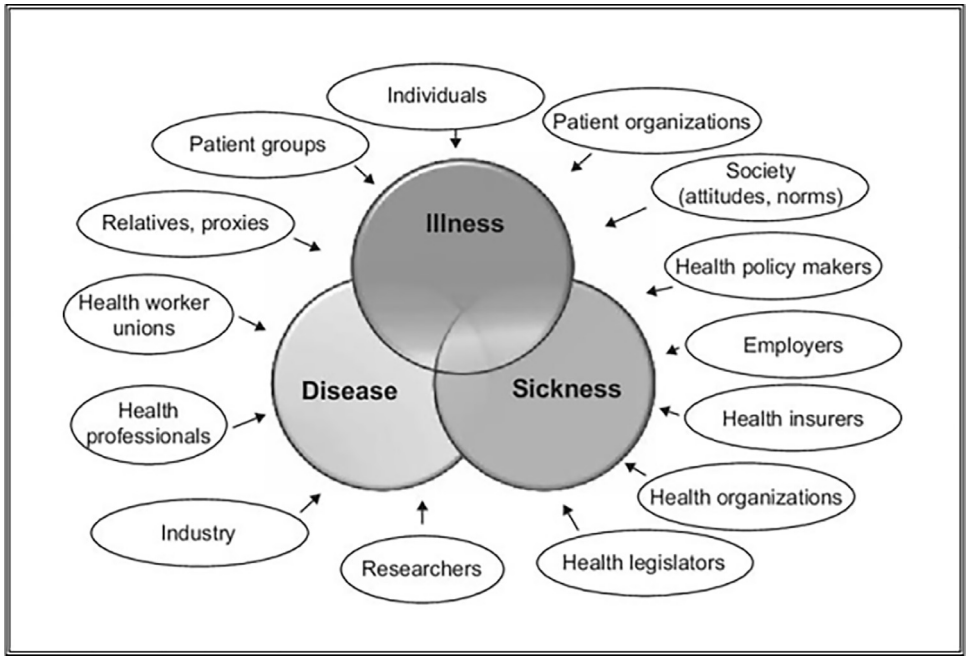

Fig. 1. Perspectives from different stakeholders more accurately capture the complexity of the disease and its impact on the patient.

voice to help refine and improve basic laboratory and clinical research. As head of the Clinical Division of Neuromuscular Disease at Radboud University, Nijmegen Medical Center in the Netherlands, his presentation provided an overview of the cutting-edge work that has been carried out by Dutch researchers, with input from the patient community, in laboratory and clinical investigations of FSHD to date. Prof. van Engelen highlighted the importance of incorporating the viewpoints from the many different stakeholders involved to ensure a comprehensive and balanced model of FSHD [Fig. 1] .

The second day of the IRC featured a keynote address by Dr. Bénédict Chazaud, director of the NeuroMyoGène Institute in Lyon (France). Dr. Chazaud presented her extensive research on the role of the immune system in normal muscle regeneration and in Duchenne muscular dystrophy. Her studies focused on macrophages, which initially exhibit pro-inflammatory properties to clean damaged muscle tissue and later switch to a regeneration-favoring type through cytokine and growth factor secretion. A growing body of evidence suggests that these mechanisms may also be altered in FSHD.

3. Session 1: Discovery research & genetics

Drs. Gabellini and Bosnakovski co-chaired the first scientific session on early stage discovery research, with Dr. Darko Bosnakovski (University of Minnesota) presenting data on the characterization of a novel FSHD mouse model, iDux;HSA, that tunably expresses mouse Dux in myofibers to study Dux's gain of function *in vivo* and compare them to current FSHD mouse models based on human *DUX4* gene expression. Initial studies revealed that high levels of Dux induce rapid myofiber damage followed by expansion of fibroadipogenic progenitors and muscle infiltration by inflammatory cells, leading to muscle fibrosis and impaired muscle function. Hence, despite some differences in the target genes induced by Dux and DUX4, these data indicate that the two proteins drive similar pathological pathways *in vivo*, further supporting the relevance of human *DUX4* transgenic mouse models.

Dr. Florian Full (University Medical Center, Freiburg) discovered an interplay between DUX4 and herpesviruses *in vitro* and *in vivo*. Herpes viral infection leads to the activation of DUX4, DUX4-target genes and endogenous retroelements. Intriguingly, DUX4 directly binds to the virus genome upon infection and supports viral gene expression and viral replication. Given that herpesviruses infect skeletal muscle very inefficiently, the potential relevance for herpes viral infection in modulating FSHD pathogenesis is unclear.

Dr. Amelia Fox (Saint Louis University) discovered that the SIX family of transcription factors facilitate *DUX4* transcription during myogenic differentiation. Furthermore, they showed evidence of a negative feedback loop between DUX4 and SIX1, 2 and 4. She concluded that SIX proteins are key regulators of *DUX4* gene expression and could be potential therapeutic targets for FSHD. A different study from Dr. Emanuele Mocciaro (San Raffaele Scientific Institute) showed that WDR5 chromatin remodeling protein is necessary for the expression of both DUX4 and its target genes. WDR5 silencing or pharmacological inhibition rescue cell viability and myogenic differentiation of FSHD muscle cells pointing to WDR5 as another potential druggable target for FSHD [1].

Dr. Dongxu Zheng (Leiden University) combined two sequencing methods (PacBio long-read and Illumina short-read) to investigate the full-length transcriptome in DUX4 expressing myocytes and reported on 652 previously unknown intergenic loci activated by DUX4, of which, half contained potential DUX4 binding sites. These findings can be utilized to identify potential novel biomarkers for disease diagnosis, progression, and therapeutic intervention.

Dr. Joel Chamberlain (University of Washington) presented work on the identification of a novel FSHD biomarker, initiated by gene expression profiling of a mouse model in which muscles were injected with adeno-associated viruses expressing DUX4. Among the altered pathways, neutrophil activation was identified. When compared to human plasma samples, similar patterns were also seen in FSHD patients compared to controls.

Lastly, Dr. Richard Lemmers (Leiden University) presented results on FSHD molecular testing conducted in India under the umbrella of the International center for Genomic Medicine in Neuromuscular Diseases (ICGNMD). In total, 57 FSHD families

were tested, and the results suggest that people of Indian descent have lower clinical susceptibility than Europeans based on the size of the FSHD1 allele repeat. While cultural aspects concerning disease perception might be a confounding factor, larger epidemiological studies could inform on potential factors affecting FSHD susceptibility among different populations.

4. Session 2: Outcomes assessments

Moderated by Drs. Kate Eichinger and Mauro Monforte, the studies presented in this session provided an overview of different techniques being developed to assess the severity and progression of FSHD. Dr. Sanne Vincenten (Radboud University Medical Center) compared two widely used muscle imaging methods (*i.e.* ultrasound and MRI) in a longitudinal study. Results suggest better performances of ultrasound in detecting early changes, while MRI appears better at evaluating and tracking changes of intermediately and severely affected muscles. Dr. Mauro Monforte (Fondazione Policlinico Universitario A. Gemelli IRCCS) summarized the findings of a 24-month longitudinal study that evaluated the changes of clinical scales, qualitative and quantitative MRI sequences in a large cohort of FSHD patients. Several clinical scales and the radiological burden of the disease changed over the study period, but with great variability. Promising correlations between clinical and MRI assessments were found, and the presence of edema at the baseline MRI confirmed its impact on the prediction of future disease worsening.

Michaela Walker (University of Kansas Medical Center) presented an overview and baseline results from a multi-site natural history study MOVE (Motor Outcomes to Validate Evaluations) and MOVE+, a sub-study that includes additional assessments including MRI, Reachable Workspace and blood and saliva collection. The goals of these projects are to hasten drug development by examining the predictive value of motor outcomes and biomarkers on disease progression milestones. In an analysis of medical claims data, Dr. Elizabeth (Lisa) Ackerman (Avidity Biosciences) presented on the medical procedures and healthcare utilization of individuals with FSHD and compared this to matched controls. Not surprisingly, individuals with FSHD were found to have higher utilization of medical services, higher medical costs, more days of care, more mobility related care and durable medical equipment, signifying the disease burden and need for targeted treatments. Finally, Dr. Yi-Wen Chen (Children's National Medical Center) focused on circulating biomarkers, describing differentially expressed proteins and microRNAs between patients and controls in a cohort of early-onset FSHD subjects. The process to discover pharmacodynamics and monitoring biomarkers that respond to DUX4 repression by *in vitro* experiments was also presented. A number of promising candidates were identified, and their validation is pending.

5. Session 3: Disease mechanisms & interventional strategies

The subsequent session focusing on the pathophysiology of FSHD and therapeutic strategies was moderated by Drs. Alexandra Belayew and Alberto L. Rosa. Two studies highlighted the potential role of the immune system in FSHD. Dr. Beatrice Biferali (San Raffaele Scientific Institute) first presented that DUX4 activates inflammatory pathways. Dr. Katelyn Daman, (UMass Medical School) presented a complex mouse model using human umbilical cord blood-derived cell lineages involved in the innate immune response. In this model, a xenograft of FSHD muscle cells, but not healthy control cells, activated the human complement pathway, possibly contributing to muscle cell death in FSHD.

Dr. Elise Engquist (King's College London) investigated muscle regeneration during disease progression in FSHD biopsies. Transcriptomic and histological analyses revealed deregulations of mitochondria and fibroadipogenic precursors (FAPs) before overt muscle inflammation. Clinical severity correlated with markers of quiescent satellite cells and early myogenesis, but not late myogenesis, suggesting incomplete muscle regeneration in FSHD patients.

Dr. Clothilde Claus (University of Mons) explored protein partners that co-purify with DUX4 or its homologue DUX4c, which is expressed in healthy muscles. C1qBP was identified as the major common partner, and interactions of this multifunctional protein with DUX4 or DUX4c were detected in small atypical fibers co-stained for regeneration markers in FSHD muscle biopsies. These interactions suggest abortive attempts at regeneration, and it was proposed that DUX4 competition for DUX4c protein partners might be a new toxicity mechanism in FSHD. Moriya Slavin (Hebrew University) also searched for DUX4 protein partners and identified an E3 ubiquitin ligase of the RFPL4 family. By point mutagenesis, specific interacting residues have been mapped, suggesting that DUX4 could be ubiquitinated and degraded by the proteasome.

The session concluded with a presentation by Dr. Scott Harper (Nationwide Children's Hospital) on the development of a CRISPR complex comprising of dead Cas13 that targets RNA instead of DNA. When fused to ADAR, a base modifying enzyme, the authors aimed to introduce stop codons into the DUX4 mRNA, thereby preventing the synthesis of the toxic DUX4 protein.

6. Session 4: Clinical studies & trial designs

In the next session, moderated by Drs. Nicol Voermans and Piraye Oflazer, four studies were presented which were either on-going trials or planned trial designs in FSHD.

Drs. Leo Wang (U Washington) and Marie-Helene Jouvin (Fulcrum Therapeutics) jointly presented the results of the ReDUX4 trial with Losmapimod, a p38a/b MAPK inhibitor, sponsored by Fulcrum Therapeutics. The duo provided the details from 48-week placebo controlled and follow-on 48-week Open Label Extension of the Phase 2 trial with oral dosing at 15 mg. In addition to quantifying DUX4-gene regulated expression from open muscle biopsies and monitoring changes in muscle MRI, the range of upper extremity movement in space was also measured using Reachable Work Space (RWS). As reported, a total of seventy-six patients and controls were followed for 96-weeks and changes in RWS in dominant and non-dominant arms of patients indicated slowing of disease progression. A phase 3 placebo controlled 48-week trial (REACH) has since been launched, with the primary endpoint of RWS and secondary end points of Muscle Fat Fraction, Muscle Fat Infiltration through MRI, as well as patient reported outcomes.

Dr. Amy Halseth (Avidity Biosciences) presented the trial design for the FORTITUDE clinical study with AOC1020, an Antibody-Oligonucleotide Conjugates consisting of a DUX4 targeting siRNA linked to a humanized anti-transferrin receptor-1 antibody. The trial is a double-blind Phase 1/2 trial in 72 genetically confirmed FSHD1 and FSHD2 adult patients. Designed as a dose-escalation study, the first two groups of participants will receive an initial transfusion at increasing doses, followed by booster at 6 weeks and subsequent quarterly dosing for up to 12 months. Based on safety and tolerability parameters of these initial studies, a final cohort will be treated with the optimal dose to allow more comprehensive analytics. The primary endpoints of the study are safety and tolerability, while exploratory biomarker readouts such as MRI and DUX4 regulated gene panels, as well as clinical endpoints consisting of RWS and various functional, mobility and strength measurements will be used.

Study design for GYM329, a long-lasting monoclonal anti-myostatin antibody targeting the myostatin receptor was presented

by Dr. Giorgio Tasca (Newcastle University) on behalf of Roche Pharmaceuticals. Named MANEUVRE, the trial is a Phase 2, placebo controlled, double blind study in ambulatory adults with genetically confirmed FSHD1 and FSHD2. Study participants will be monitored for 4 weeks during a pre-treatment period and then administered the drug subcutaneously every 4 weeks for a total period of 52 weeks. Assessments include pharmacokinetic measures for safety and tolerability with primary endpoint of changes in contractile muscle tissue as measured by MRI, as well as exploratory functional endpoints such as RWS. Recruitment to this trial is still on-going.

Dr. Dalila Laoudj-Chenivesse (INSERM) presented results from personalized nutraceutical studies aimed at mitigating the oxidative stress response seen in FSHD [2]. Their pilot trial in 54 FSHD patients showed that oxidative stress proteins increased in blood samples of patients. Patient-adjusted and personalized combinations of antioxidant treatment in this trial reduced markers of oxidative stress, increased endogenous antioxidant defenses and improved functional outcomes, such as 2-minute walk test, maximum isometric voluntary contraction of quadriceps muscle and endurance of quadriceps muscle. In a three-year longitudinal study (PERSPECTYV), half of the participants ($N = 74$) who maintained the regiment of supplements showed stabilization across some of these functions. Currently, a software platform is being developed to help with the customization of supplements on an individual basis.

7. Session 5: Pediatric FSHD

The 2023 Congress included a special session on Pediatric FSHD, a neglected area of research with significant potential impact on future drug development. The session, moderated by Drs. Nicol Voermans and Piraye Oflazer began with a presentation by Dr. Corrie Erasmus (Radboud University Medical Center) highlighting a multi-year longitudinal effort carried out in the Netherland to address gaps in the identification of patients under 18 years of age, understanding of pediatric natural history and the development of suitable pediatric outcome measures. In a two-year study, 95% of pediatric patients manifested facial weakness, 40% showed scapular weakness along with additional extra-muscular manifestations, such as impaired hearing and/or irregular EKGs [3]. Still needed in the field are better measures of functional capacity for the upper limbs, muscle fatigability/endurance as well as quality of life (QoL) measures to determine the overall impact of the disease during this critical stage of development. Results from a five-year follow-up are being prepared for publication and an eight-year study is being planned. Katy de Valle (Royal Children's Hospital) presented her work on the development of relevant pediatric outcome measures to account for the confounds of natural growth in this population. Her approach included adaptation of FSHD-COM, a composite measure of various motor components in adults(FSHD-COM Peds) [4]. Showing high test-retest reliability, their study showed promising and significant correlations with other functional, imaging and QoL measures. FSHD-COM Peds was also shown to successfully discriminate between FSHD and control volunteers. Longitudinal validation and clinical interpretation of these measures are ongoing. This session concluded with a panel discussion fielding questions on the status and priorities for advancing the understanding of pediatric FSHD. Panelists included the session speakers, as well as Dr. Jildou Dijkstra, resident in neurology (Radboud University Medical School), Dr. Ian Woodcock, a pediatric neurologist (Royal Children's Hospital), Dr. Jeff Statland, professor of neurology (University of Kansas Medical Center). Feedback from the audience supported the need for more extensive work in this area.

8. Conclusions & future directions

On the final day of the meeting, delegates voted and awarded the best poster to Dr. Joost Kools (Radboud University Medical Center) titled "Assessment of the burden of outpatient clinic and MRI-guided needle biopsies as reported by patients with FSHD" [5]. In addition, two awards for the rising stars in the field were awarded to Dr. Lorena Di Pietro (Università Cattolica del Sacro Cuore) and Dr. Ceren Hangül (Akdeniz University Faculty of Medicine). The Congress concluded with the announcement for the 2024 International Research Congress, which will take place in June 13–14, 2024 in Denver, Colorado.

Declaration of Competing Interest

None.

Acknowledgments

We would like to thank the following sponsors for supporting this congress: AFM Téléthon, Andrew Graham and Friends, Armatus Bio, Avidity Biosciences, Dyne Therapeutics, FSHD Europe, FSHD Global, FHSD Stichting, Fulcrum Therapeutics, James Chin, Sr. Scholarship Fund, Kate Therapeutics, miRecule, Muscular Dystrophy Association, National Institute of Health, Roche, Sanofi, The Chris Carrino Foundation for FSHD, University of Massachusetts Medical School Wellstone Center for FSHD Research, Ultragenyx, Vita Therapeutics.

2023 FSHD International Research Congress Program Committee

Jamshid Arjomand, FSHD Society, Randolph, MA, USA

Alexandra Belayew, Research Institute for Health Sciences and Technology, University of Mons, 6, Avenue du Champs de Mars, B-7000, Mons, Belgium

Darko Bosnakovski, Lillehei Heart Institute and Department of Pediatrics, Medical School, University of Minnesota, Minneapolis, MN, USA

Katy Eichinger, Department of Neurology, University of Rochester, Rochester NY, USA

Davide Gabellini, Division of Genetics and Cell Biology, IRCCS Ospedale San Raffaele, 20132 Milano, Italy

Mauro Monforte, UOC di Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Piraye Oflazer, Department of Neurology, Koç University Hospital Muscle Center, Koç University Medical Faculty, Topkapı, Istanbul, Turkey

Alberto Luis Rosa, Laboratorio de Genética y Biología Celular y Molecular, Departamento de Farmacología Otto Orsingher, IFEC-CONICET, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba

Nicol Voermans, Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, the Netherlands

References

[1] Mocciaro E, Giambruno R, Micheloni S, Cernilogar FM, Andolfo A, Consonni C, et al. WDR5 is required for DUX4 expression and its pathological effects in FSHD muscular dystrophy. Nucleic Acids Res 2023;51:5144–61. doi:10.1093/NAR/GKAD230.
[2] Amzali S, Wilson VD, Bommart S, Picot MC, Galas S, Mercier J, et al. Nutritional status of patients with facioscapulohumeral muscular dystrophy. Nutrients 2023;15. doi:10.3390/NU15071673.
[3] Dijkstra JN, Goselink RJM, van Alfen N, de Groot IJM, Pelsma M, van der Stoep N, et al. Natural history of facioscapulohumeral dystrophy in children: a 2-year follow-up. Neurology 2021;97:E2103–13. doi:10.1212/WNL.0000000000012882.

[4] de Valle K, Dobson F, Woodcock I, Carroll K, Ryan MM, Heatwole C, et al. Reliability and validity of the FSHD-composite outcome measure in childhood facioscapulohumeral dystrophy. Neuromuscul Disord 2021;31:706–15. doi:10.1016/J.NMD.2021.05.011.

[5] Kools J, Aerts W, Niks EH, Mul K, Pagan L, Maurits JSF, et al. Assessment of the burden of outpatient clinic and MRI-guided needle muscle biopsies as reported by patients with facioscapulohumeral muscular dystrophy. Neuromuscul Disord 2023;33:440–6. doi:10.1016/J.NMD.2023.04.001.