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Magnetic resonance imaging in facioscapulohumeral muscular dystrophy

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The past decade has seen steady growth in the body of literature describing magnetic resonance imaging (MRI) features in facioscapulohumeral muscular dystrophy (FSHD). This may be surprising given that MRI is not routinely used in the diagnosis and management of hereditary muscle disorders. Nonetheless, there are more studies and more patients reported in MRI studies of FSHD than for any hereditary muscle disease except Duchenne muscular dystrophy (DMD).¹ One of the reasons for this may be the relatively high prevalence of FSHD compared to other muscular dystrophies,² but this phenomenon also reflects the need for clinical outcomes to match the pace of basic science discovery in FSHD.

Among the muscular dystrophies, FSHD is one of the most complex, with both genetic and epigenetic causes that have only recently been described.^{3, 4} Our improved understanding of FSHD genetics has led to the identification of multiple therapeutic targets for novel genetic technologies, including gene silencing and gene editing.^{5, 6} Because there is no curative treatment for this debilitating illness, there is great eagerness in the research and patient community to develop these potential therapies and accelerate their progression into human clinical trials.⁷

One of the anticipated obstacles to these trials is the lack of appropriate disease biomarkers and surrogate outcome measures for genetic myopathies. The limitations of currently available outcome measures have been made apparent by our collective experience in DMD, where multiple therapeutic trials have already taken place and are still ongoing. Several publications on these trials have reported that the variability of the primary outcome measure

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(the six-minute walk distance) within the study population was larger than anticipated.^{8, 9} Unanticipated high variability can greatly impact the interpretability of trial results, and we may not discover until the end of the trial that we are unable to agree upon whether the absence of a statistically significant effect is due to underpowering or true ineffectiveness of the intervention. The inability of a trial to answer its prospective scientific question carries multiple costs, including loss of participant time, consumption of limited investigator resources, and potential divisiveness within a rare disease field where collaboration is instrumental to success.^{10, 11} The impact of unexpected variability seen in DMD trials is concerning for those who seek to develop clinical trials for FSHD, which has even greater phenotypic variability than DMD. Using existing biomarkers and outcome measures, FSHD trials may ultimately require prohibitively large numbers of patients and long duration to achieve adequate power to detect meaningful treatment effects.

A number of characteristics of MRI scanning offer solutions to some of the limitations of current outcome measures. MRI is highly sensitive to fat infiltration and intramuscular edema, which are common features in myopathies. MRI scanning is not dependent on effort or cooperation in the way that strength and timed function tests are, which may make it less vulnerable to inconsistent cooperation and learning effects. Non-contrast scanning is non-invasive and non-irradiating, which makes repeated measurements safe, and it can be used to assess both ambulatory and non-ambulatory patients. For these reasons, multiple investigators have identified the development of MRI biomarkers as a priority for future clinical trials.

In this issue of *Muscle & Nerve*, Ferguson et al. report findings related to changes in fat infiltration and intramuscular edema in a cohort of patients with FSHD.¹² This study represents a significant next step in pathophysiologic discovery and clinical trial preparedness in FSHD. An important point that this study addresses is the need for longitudinal imaging studies to adequately characterize the radiographic natural history of FSHD. In addition to the variability in baseline severity of disease, the authors show early evidence of variability in the rate of disease progression, as only a minority of participants showed detectable worsening of intramuscular fat infiltration (over 6.9 to 13.8 months) while most remained stable. The authors further provide evidence that the rate of progression may be associated with deletion size, with faster deterioration occurring in participants with smaller numbers of D4Z4 repeats.

The work of Ferguson et al. is one of several recent reports describing longitudinal changes in both imaging and clinical outcomes (such as strength testing and quality of life) in large cohorts of FSHD patients.^{13, 14} All of these studies were able to detect progression of fat infiltration in muscle. However, the associations between changes in intramuscular fat and changes in clinical outcomes were often not significant. This is a relevant and concerning finding in terms of clinical trial development, as biomarkers not only need to be measurable and sensitive to change, but also predictive of clinical disease characteristics that are relevant to patient function.^{15, 16} The lack of association is likely due in part to the fact that the clinical outcomes did not change over the relatively short observation periods of these studies (ranging from approximately seven months to two years); it is also probably related to the variability of these outcomes, which makes the detection of statistically significant

effects more difficult. As such, longer periods of observation are needed to record clinical progression in enough patients to assess the ability of MRI to detect clinical change in FSHD and to establish its feasibility as a disease biomarker.

Beyond the immediate pragmatic goal of clinical trial readiness, the increasing number of studies on imaging in FSHD reflects new discoveries about the disease itself. Early clinical reviews of the FSHD population reported a slowly progressive cephalo-caudal pattern of weakness, and clinical studies have likewise shown slowly progressive weakness over years.^{17, 18} MRI studies of FSHD have enriched this phenotype by demonstrating that lower extremity and trunk muscles can be involved early in FSHD and that extensive involvement of individual muscles may occur before observable weakness.¹⁹

Prior studies that included both T1-weighted and fluid-sensitive [in this case, short tau inversion recovery (STIR)] MRI sequences have compelled researchers to further revise models of disease progression in FSHD. While fat infiltration is the predominant finding in affected muscles in FSHD, muscles in an intermediate stage of fat infiltration are unexpectedly rare, suggesting a more rapid phase of fat replacement than was previously suspected.²⁰ Furthermore, a minority of the muscles are also found to be hyperintense on fluid-sensitive sequences. Biopsy studies targeting these STIR hyperintense muscles have shown evidence of active inflammatory cell infiltration.^{21, 22} The identification of these inflammatory changes has led to revised conceptual models of disease progression in FSHD; instead of a slow continuous pattern of progression, new models indicate long periods of stability punctuated by active inflammation and rapid fat infiltration of individual muscles with the cumulative effect of gradual weakness over time. The presence of an early inflammatory phase of FSHD also offers new potential targets for drug therapy.²³

The findings of Ferguson et al. also challenge previous studies that have shown fat infiltration of muscle preceded by STIR hyperintensity. By comparing the T1 and STIR characteristics of individual muscles over time, the authors were able to identify a small number of muscles that showed increased fat infiltration without preceding STIR hyperintensity. These findings complement prior work by this group, which identified STIR hyperintense muscles that did not develop increased fat infiltration on subsequent scanning.²⁴ While these findings may prove to be rare exceptions, they also hint at alternative pathways or phases of fat infiltration that should be further explored.

This study has some limitations, the most salient of which is its small sample size. Given the known variability of the FSHD population, larger studies are needed to fully capture the spectrum of muscle involvement in this disease. Larger studies are also needed to adequately sample subgroups based on important disease modifiers, such as gender and deletion size. Understanding the variability in imaging outcomes between and among these disease subgroups will help inform power and sample size calculations for future trials utilizing MRI as an outcome measure for FSHD.

The findings of this and other MRI studies in FSHD provide direction for future MRI research in this population. One of the most important is incorporation of fully quantitative imaging techniques and the standardization of methods to characterize heterogeneous fat

infiltration within muscles. Another is the development of analytic techniques that integrate data from multiple MRI sequences (e.g. fat infiltration from T1 and intramuscular edema from STIR sequences). In taking these next steps, we seek to move incrementally closer not only to the creation of more efficient biomarkers, but also to a better understanding of the relationship between the genetic underpinnings of FSHD and its complex phenotype.

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List of abbreviations

FSHD	facioscapulohumeral muscular dystrophy
DMD	Duchenne muscular dystrophy
MRI	magnetic resonance imaging
STIR	short tau inversion recovery

References

1. Leung DG. Magnetic resonance imaging patterns of muscle involvement in genetic muscle diseases: a systematic review. *J Neurol*. 2017; 264:1320–1333. [PubMed: 27888415]
2. Mah JK, Korngut L, Fiest KM, Dykeman J, Day LJ, Pringsheim T, et al. A Systematic Review and Meta-analysis on the Epidemiology of the Muscular Dystrophies. *Can J Neurol Sci*. 2016; 43:163–177. [PubMed: 26786644]
3. 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; 44:1370–1374. [PubMed: 23143600]
4. Jones TI, King OD, Himeda CL, Homma S, Chen JC, Beermann ML, et al. Individual epigenetic status of the pathogenic D4Z4 macrosatellite correlates with disease in facioscapulohumeral muscular dystrophy. *Clin Epigenetics*. 2015; 7:37. [PubMed: 25904990]
5. Himeda CL, Jones TI, Jones PL. CRISPR/dCas9-mediated Transcriptional Inhibition Ameliorates the Epigenetic Dysregulation at D4Z4 and Represses DUX4-fl in FSH Muscular Dystrophy. *Mol Ther*. 2016; 24:527–535. [PubMed: 26527377]
6. Lim JW, Snider L, Yao Z, Tawil R, Van Der Maarel SM, Rigo F, et al. DICER/AGO-dependent epigenetic silencing of D4Z4 repeats enhanced by exogenous siRNA suggests mechanisms and therapies for FSHD. *Hum Mol Genet*. 2015; 24:4817–4828. [PubMed: 26041815]
7. Tawil R, Padberg GW, Shaw DW, van der Maarel SM, Tapscott SJ. Clinical trial preparedness in facioscapulohumeral muscular dystrophy: Clinical, tissue, and imaging outcome measures 29–30 May 2015, Rochester, New York. *Neuromuscul Disord*. 2016; 26:181–186. [PubMed: 26627872]
8. Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP, et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle Nerve*. 2014; 50:477–487. [PubMed: 25042182]
9. Goemans N, Mercuri E, Belousova E, Komaki H, Dubrovsky A, McDonald CM, et al. A randomized placebo-controlled phase 3 trial of an antisense oligonucleotide, drisapersen, in Duchenne muscular dystrophy. *Neuromuscul Disord*. 2017
10. Kesselheim AS, Avorn J. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. *JAMA*. 2016; 316:2357–2358. [PubMed: 27775756]
11. Mullard A. EMA reconsiders ‘read-through’ drug against Duchenne muscular dystrophy following appeal. *Nat Biotechnol*. 2014; 32:706. [PubMed: 25101726]
12. Ferguson MR, Poliachik SL, Budech CB, Gove NE, Carter GT, Wang LH, et al. MRI change metrics of facioscapulohumeral muscular dystrophy: STIR and T1. *Muscle Nerve*. 2017

13. Andersen G, Dahlqvist JR, Vissing CR, Heje K, Thomsen C, Vissing J. MRI as outcome measure in facioscapulohumeral muscular dystrophy: 1-year follow-up of 45 patients. *J Neurol*. 2017; 264:438–447. [PubMed: 28000006]
14. Fatehi F, Salort-Campana E, Le Troter A, Lareau-Trudel E, Bydder M, Foure A, et al. Long-term follow-up of MRI changes in thigh muscles of patients with Facioscapulohumeral dystrophy: A quantitative study. *PLoS One*. 2017; 12:e0183825. [PubMed: 28841698]
15. FDA-NIH_Biomarker_Working_Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring (MD): 2016. Monitoring Biomarker.
16. Katz R. Biomarkers and surrogate markers: an FDA perspective. *NeuroRx*. 2004; 1:189–195. [PubMed: 15717019]
17. Tawil R, Figlewicz DA, Griggs RC, Weiffenbach B. Facioscapulohumeral dystrophy: a distinct regional myopathy with a novel molecular pathogenesis. *FSH Consortium. Ann Neurol*. 1998; 43:279–282. [PubMed: 9506542]
18. The FSH-DY Group. A prospective, quantitative study of the natural history of facioscapulohumeral muscular dystrophy (FSHD): implications for therapeutic trials. *Neurology*. 1997; 48:38–46. [PubMed: 9008491]
19. Leung DG, Carrino JA, Wagner KR, Jacobs MA. Whole-body magnetic resonance imaging evaluation of facioscapulohumeral muscular dystrophy. *Muscle Nerve*. 2015; 52:512–520. [PubMed: 25641525]
20. Janssen BH, Voet NB, Nabuurs CI, Kan HE, de Rooy JW, Geurts AC, et al. Distinct disease phases in muscles of facioscapulohumeral dystrophy patients identified by MR detected fat infiltration. *PLoS One*. 2014; 9:e85416. [PubMed: 24454861]
21. Frisullo G, Frusciante R, Nociti V, Tasca G, Renna R, Iorio R, et al. CD8(+) T cells in facioscapulohumeral muscular dystrophy patients with inflammatory features at muscle MRI. *J Clin Immunol*. 2011; 31:155–166. [PubMed: 21063901]
22. Tasca G, Pescatori M, Monforte M, Mirabella M, Iannaccone E, Frusciante R, et al. Different molecular signatures in magnetic resonance imaging-staged facioscapulohumeral muscular dystrophy muscles. *PLoS One*. 2012; 7:e38779. [PubMed: 22719944]
23. McKew J, Ashlock M, Ogilvie K, Nangle L, Taylor K, Chiang K, et al. Resolaris, a potential therapeutic for rare myopathies with an immune component. *Neuromuscular Disorders*. 2015; 25:S215–S216.
24. Friedman SD, Poliachik SL, Otto RK, Carter GT, Budech CB, Bird TD, et al. Longitudinal features of STIR bright signal in FSHD. *Muscle Nerve*. 2014; 49:257–260. [PubMed: 23720194]