Methods: A subset of 20 adults (10 males, 10 females) from PHENODM1 have been scanned using 3.0T MRI scanner and bilateral lower limb axial T1-weighted and T2-weighted STIR images have been analysed. All pelvic girdle, thigh and lower leg muscles were scored bilaterally according to the Mercuri scale on axial T1-weighted sequences.

In addition to the OMMYD-2 measures described we compared our findings to quantitative strength assessments in the ankle dorsiflexors and plantifl exors, knee extensors and hip fl exors.

The average of the quadriceps and ankle dorsiflexors Mercuri scores were considered for the non-parametric correlations against muscle strength. Kruskal-Wallis Test was utilised to compare the different mean values between the stratified sample.

Results: The mean age at MRI was 41.2±9.9 years with a mean disease duration of 22.2±10.5 years. On T1-weighted images the most severely affected muscles were: gastrocnemius medialis (Mercuri median score: 3), soleus (2b), peroneus longus (1), tibialis anterior (1), flexor digitorum (1), vastus (1), sartorius (1) and biceps femoris (1). STIR abnormalities were detected in 9 patients, mainly in gastrocnemius medialis and soleus. Significant correlation values were identified between sartorius (MRI score) and hip fl exors strength and between ankle dorsiflexors strength and MRI score for dorsiflexors and plantifl exors. Tibialis anterior’s Mercuri score gave indications of discrimination between ankle dorsiflexors strength and MRI score for dorsiflexors and plantifl exors.

Conclusions: This study provides the foundation for MRI assessments as non-invasive biomarker for DM1. Future work on larger cohorts and longitudinal assessments will be required for validation.

D28 Generation of a mouse model of FSHD to reveal the DUX4 expression profile and dynamics

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Background: Facioscapulohumeral muscular dystrophy (FSHD) is characterized by a descending, often asymmetric, skeletal muscle atrophy. The genetic basis of the disease is linked to DNA hypomethylation of D4Z4 macrosatellite repeats on chromosome 4q35. This happens due to either contractions of the D4Z4 repeat array (FSHD1) or mutations of chromatin modifiers (SMCHD1, DNMT3B) in FSHD2, causing aberrant expression of the DUX4 retrogene mapped in each D4Z4 unit. Toxic DUX4 protein is produced from the distal D4Z4 if a 3’ polyA addition site (pLAM region), which stabilizes the mRNA. DUX4 expression is considered the primary cause of FSHD, but its toxicity is a major issue in the development of animal models.

Aims: We aimed to generate mouse models of FSHD to reveal the DUX4 expression profile and dynamics, but avoiding its toxicity. These models will give insight into FSHD pathomechanisms and potential therapeutics.

Methods: To suppress the DUX4 ORF we constructed DUX4p-nlacZ-pLAM with the native human DUX4 promoter and pLAM region flanking a nuclear-localised (n)lacZ reporter gene. To additionally address the role of pLAM UTR region in the expression of native DUX4 locus, we also made a construct that lacks the pLAM region. Using pronuclear injection of these reporter constructs, we generated transgenic mice in which the expression dynamics of the pathogenic locus can be mapped.

Results: We first demonstrated the functionality of the DUX4p-nlacZ-pLAM construct in immortanised marine C2C12 and human myoblasts and myotubes. Comparatively, we discovered that the DUX4p-nlacZ construct without pLAM has a significantly higher level of expression in vitro in the immortalized cell lines. We then generated DUX4p-nlacZ-pLAM transgenic mice by pronuclear injection, and the analysis of the progeny reveals rare nuclei containing β-galactosidase in different groups of skeletal muscle of adult mice. We are now establishing multiple lines of DUX4p-nlacZ mice and will present their detailed analysis at the meeting.

Conclusions: Through generating transgenic reporter mouse lines that carries a native human configuration of DUX4 promoter with or without pLAM region, we aim to create an animal model that could be used for mapping the expression profile and dynamics of DUX4.