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Analysis of Myogenic and Candidate Disease Biomarkers in FSHD Muscle Cells

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Et al.

Title: Analysis of myogenic and candidate disease biomarkers in FSHD muscle cells.

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Abstract: The UMMS Wellstone Program is a foundation and NIH-funded cooperative research center focusing on identifying biomarkers for facioscapulohumeral muscular dystrophy (FSHD) to gain insight into the molecular pathology of the disease and to develop potential therapies. FSHD is characterized by progressive wasting of skeletal muscles, with weakness often initiating in facial muscles and muscles supporting the scapula and upper arms. While the genetics associated with FSHD are complex, the major form of the disease, FSHD1, is linked to contraction of the D4Z4 repeat region located at chromosome 4q. Recently, a transcript encoded at the distal end of the repeat region, Dux4-fl, normally expressed in embryonic stem cells and germ cells, was also detected in differentiated muscle cells and biopsies from FSHD subjects, giving rise to the hypothesis that DUX4-FL function contributes to muscle weakness.

We established a repository of high quality, well-characterized primary and immortalized muscle cell strains from FSHD and control subjects in affected families to provide biomaterials for cell and molecular studies to the FSHD research community. qPCR and immunostaining analyses demonstrate similar growth and differentiation characteristics in cells from FSHD and control subjects within families. We detected Dux4-fl transcript and protein in FSHD cells as recently described; interestingly, we also detected Dux4-fl in muscle cells from a subset of control individuals, suggesting that any Dux4-fl-mediated myopathy would require additional modifying elements. Microarray analysis of FSHD and control muscle cells demonstrated that several genes were upregulated in FSHD cells, including genes that were concurrently identified as downstream targets of Dux4-fl and as candidate FSHD disease genes. Future studies will further characterize the RNA and protein expression of candidate disease genes in cells from FSHD and control subjects, including nonmanifesting subjects with the D4Z4 lesion but no muscle weakness, and utilizing whole transcriptome sequencing (RNAseq) to identify additional candidates.