From ChIP-seq data of a single transcription factor towards understanding of molecular mechanisms involved in disease

Hands-on training April 18,2017

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

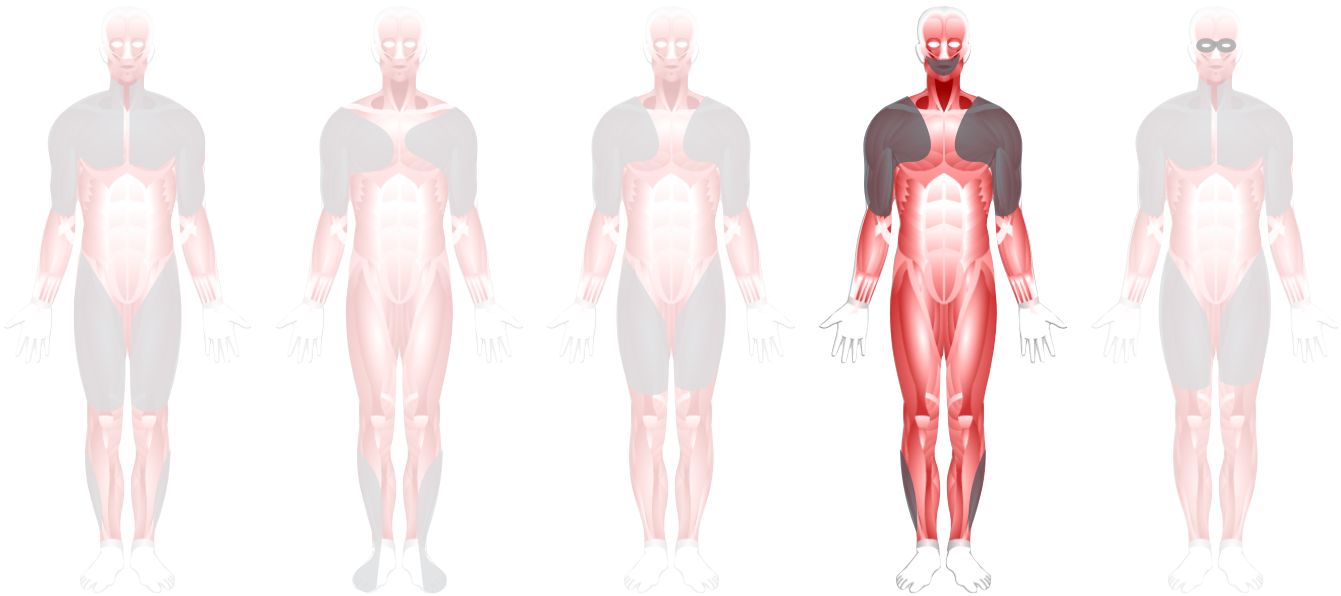
Facioscapulohumeral dystrophy (FSHD)

Muscular dystrophy affecting mainly the face, shoulder blades, and upper arms

Onset usually in early adulthood

Third most common genetic disease of skeletal muscle

Estimated 870,000 affected worldwide



Main areas of muscle weakness in different types of dystrophy

FSHD: genetic cause

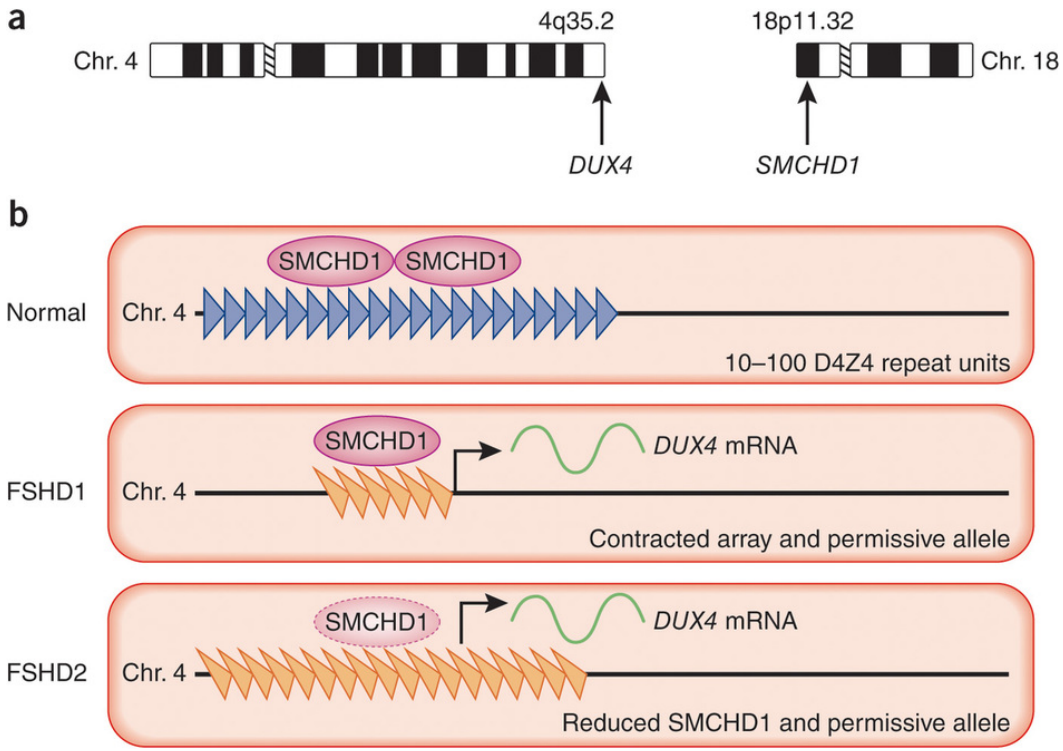
Ectopic expression of usually silenced DUX4 TF retrogene in skeletal muscle

FSHD1: deletion in D4Z4 macrosatellite repeat in subtelomeric region of chr 4

Normal: 11-100 repeats; FSHD1: 1-10 repeats

FSHD2: normal D4Z4 repeat length, reduced SMCHD1 level

Effect in both cases: hypomethylation, euchromatic DNA, DUX4 expression



Lupski,Nat Genet 2012

FSHD model

Published online 6 March 2016

Nucleic Acids Research, 2016, Vol. 44, No. 11 5161–5173
doi: 10.1093/nar/gkw141

DUX4 recruits p300/CBP through its C-terminus and induces global H3K27 acetylation changes

Si Ho Choi[1,2,3], Micah D. Gearhart[4], Ziyou Cui[1,2], Darko Bosnakovski[1,2], Minjee Kim[3], Natalie Schennum[1,2] and Michael Kyba[1,2,*]

[1]Lillehei Heart Institute, University of Minnesota, 312 Church St. SE, Minneapolis, MN 55455, USA, [2]Department of Pediatrics, University of Minnesota, 312 Church St. SE, Minneapolis, MN 55455, USA, [3]Research Center, Dongnam Institute of Radiological & Medical Sciences (DIRAMS), Busan, South Korea and [4]Department of Genetics, Cell Biology and Development, University of Minnesota, 312 Church St. SE, Minneapolis, MN 55455, USA

Model system: immortalized human myoblasts

Doxycycline-inducible DUX4 transgene

Data used in example: differential expression (RNA-Seq) and DUX4 ChIP-Seq

Subsampled data for reducing run times

Chip-Seq and downstream analysis workflow