FSHD 101 and research overview

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NMD4C

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Disclosures

Consultancy or research support for research and clinical trials:

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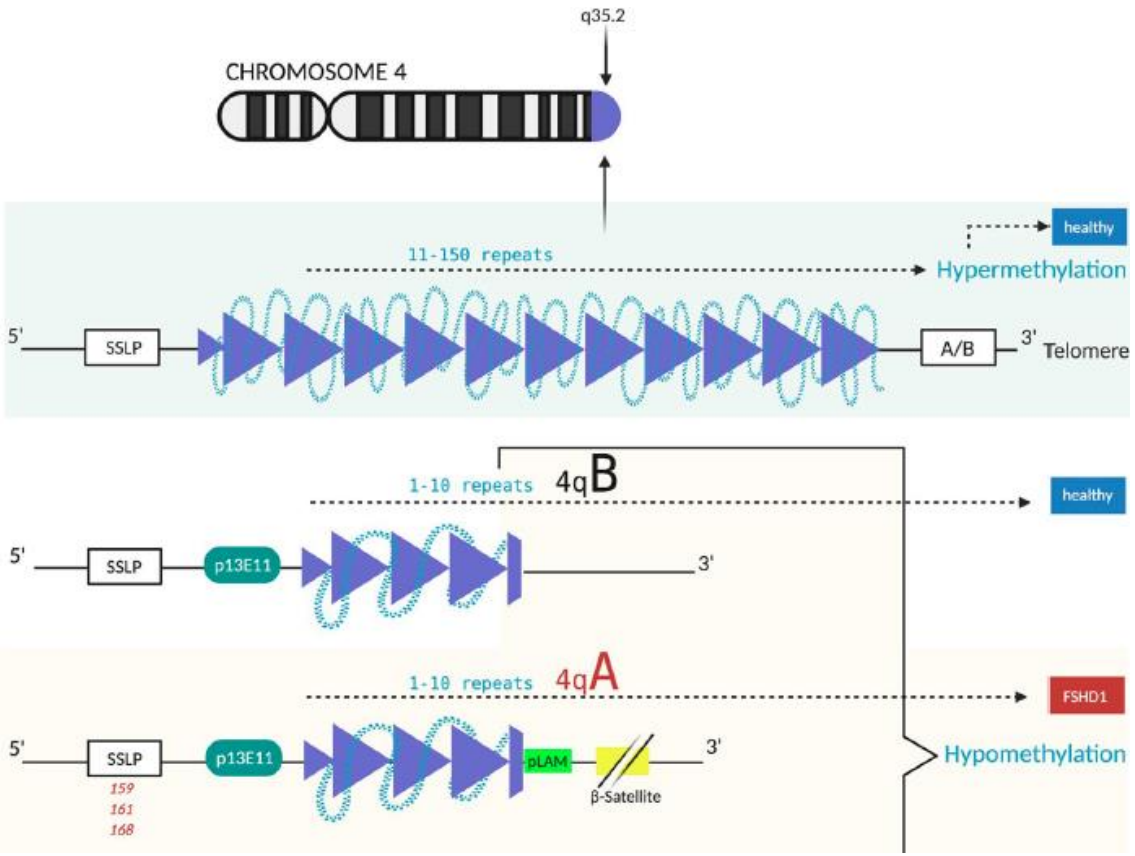
Investigator of sponsored clinical research (regulated trials) at CHEO and at TOH

Editor-in-chief of the Journal of Neuromuscular Disease (IOS Press)

Pathophysiology of FSHD

FSHD is caused by ectopic expression of the germline transcription factor *DUX4* in skeletal muscle cells.



Contraction of the D4Z4 subtelomeric region

(chr 4q35 – repeated unit 1 to 9)

↓

Hypomethylation

↓

Chromatin relaxation + Permissive allele A

↓

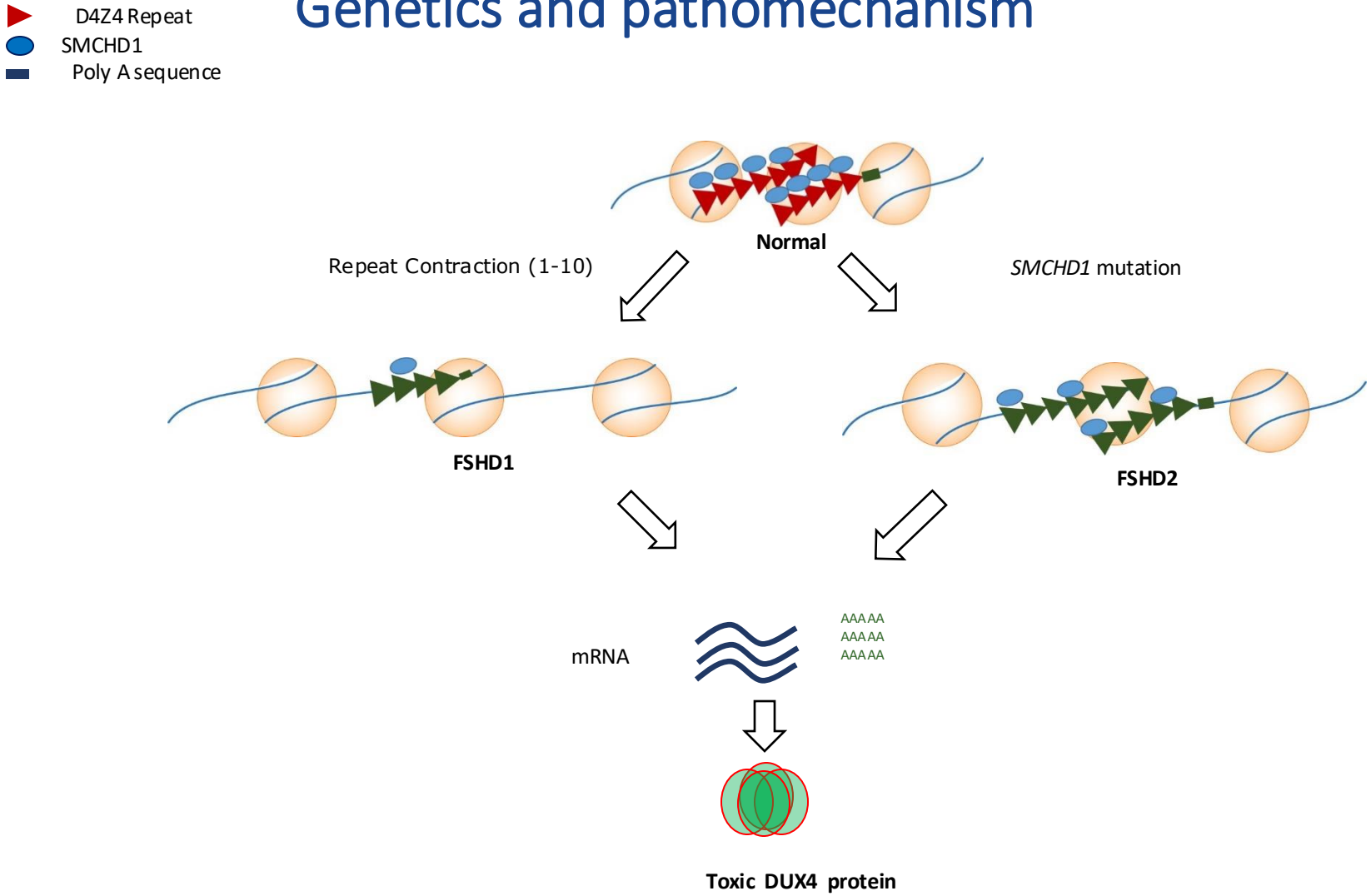
Expression of the toxic *DUX4* gene

↓

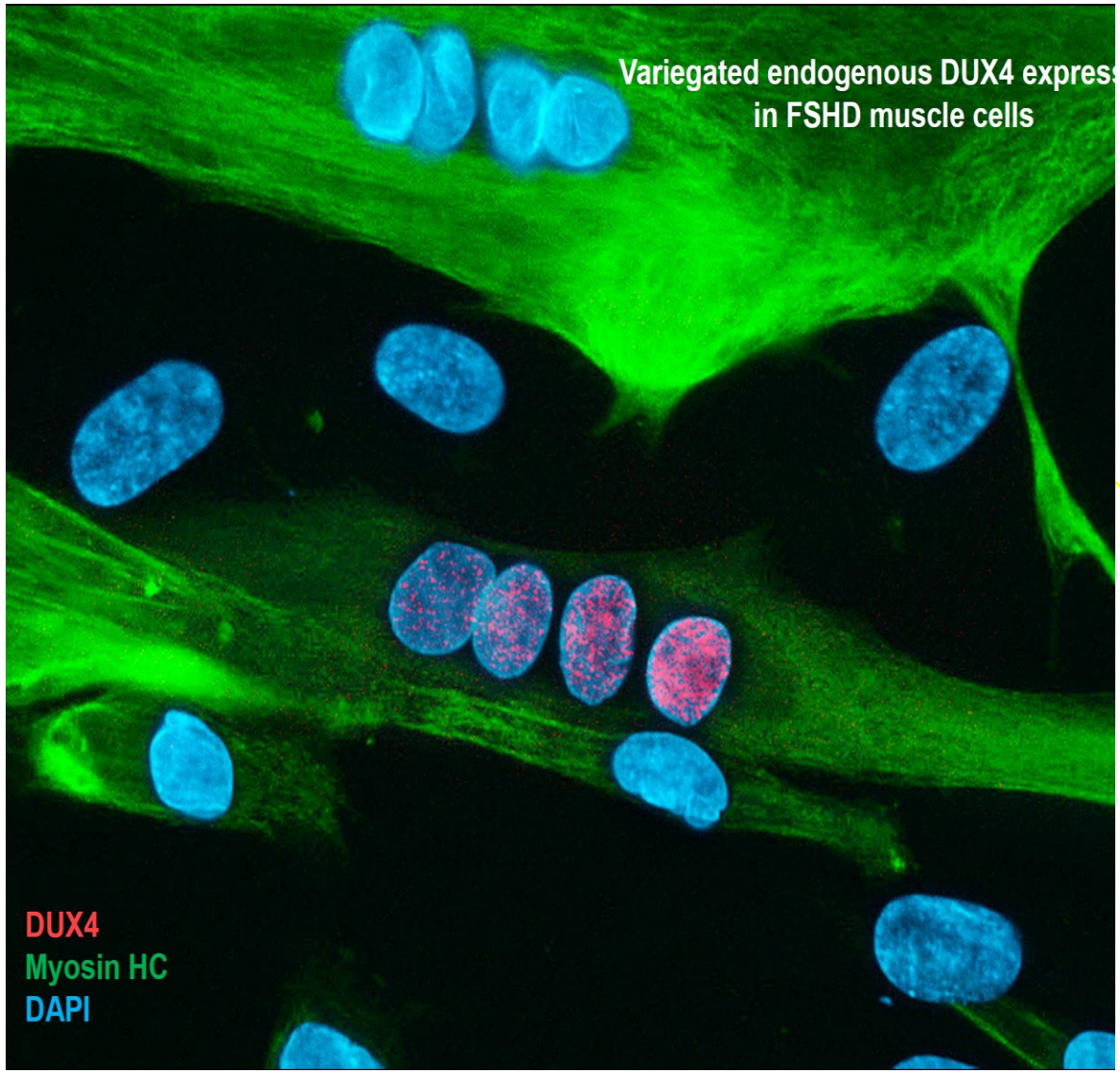
Expression of *DUX4* target genes

Adapted from Schätz et al, Orphanet J Rare Dis, 2021

Genetics and pathomechanism



Slides kindly provided by Dr Tawil, Rochester



Potential Therapeutic Targets

FSHD1:Repeat Contraction

FSHD2: SMCHD1 mutation

Increase SMCHD1

A

Enhance Epigenetic Repression

Antisense oligos

AAV mediated RNAi

mRNA

DUX4 Protein

Reduce DUX4 protein

Downstream Effects

Targeting DUX4 effects

Challenges to Therapeutic development in FSHD

- Rare disease
- Slowly progressive*
- Wide spectrum of clinical severity
- Need new outcome measures that are more clinically relevant
- Need for biomarkers for early phase studies
  - MRI
  - Tissue biomarker

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Thanks!

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uOttawa Faculté de médecine Faculty of Medicine

CIHR IRSC Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

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