FSHD model organisms: FLExDUX4 FSHD-like mouse (Pt 1)

The most widely used FSHD-like model mouse is the FLExDUX4 mouse.

RESEARCH ARTICLE

A cre-inducible *DUX4* transgenic mouse model for investigating facioscapulohumeral muscular dystrophy

Takako Jones[1,2]*, Peter L. Jones[1,2]*

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Transgenic mice expressing tunable levels of DUX4 develop characteristic facioscapulohumeral muscular dystrophy-like pathophysiology ranging in severity

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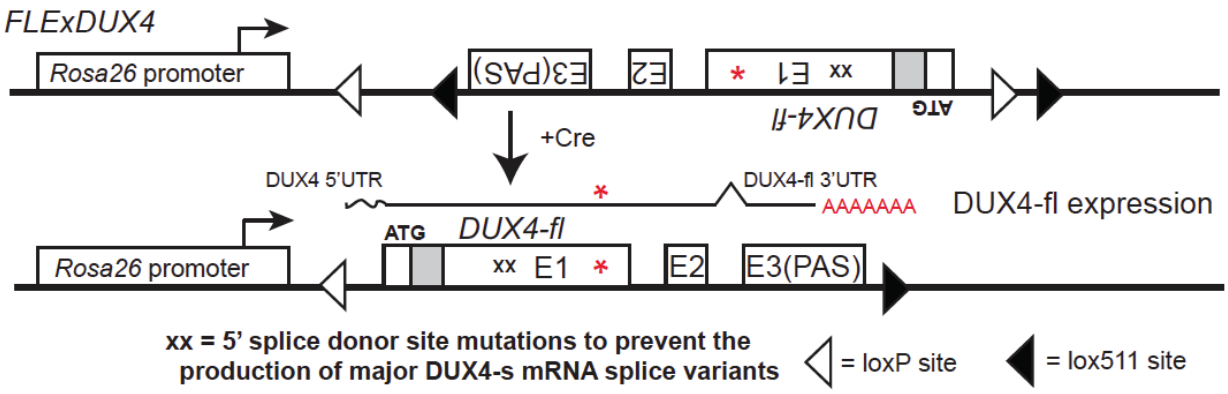
Skeletal Muscle (2020) 10:8

genOway

Made the mice and owns the FLEx technology



The FLExDUX4 mouse is a conditional knock-in line whereby the human *DUX4* gene was inserted into the mouse *Rosa26* locus in the reverse orientation; thus the *DUX4* gene is OFF.

When the cre recombinase is expressed, the *DUX4* transgene flips its orientation and the *DUX4* gene is now ON and expressed from the *Rosa26* gene promoter.

Importantly, the *Rosa26* gene is expressed in all tissues; however, it is not needed. Thus, the *DUX4* gene will be expressed in a cell or tissue that expresses the cre recombinase. For FSHD, we use mice that express cre in skeletal muscle.

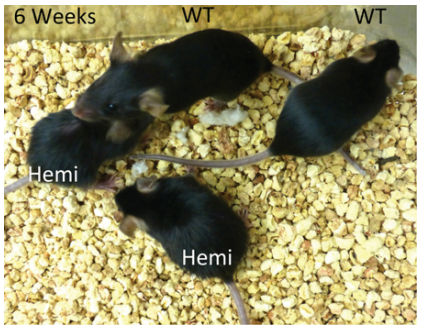
The Jackson Laboratory

B6(Cg)-*Gt(ROSA)26Sor*$^{tm1.1(DUX4*)Plj}$/J

Stock No: **028710** | FLExDUX4

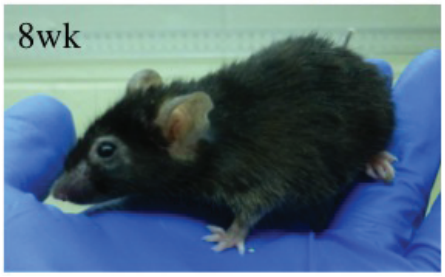
Targeted Mutation

FLExDUX4 mice are available for purchase from the Jackson Laboratory. They are easy to breed and maintain in the lab.



FLExDUX4 mice, in the absence of cre, are healthy and only show a minor alopecia phenotype.

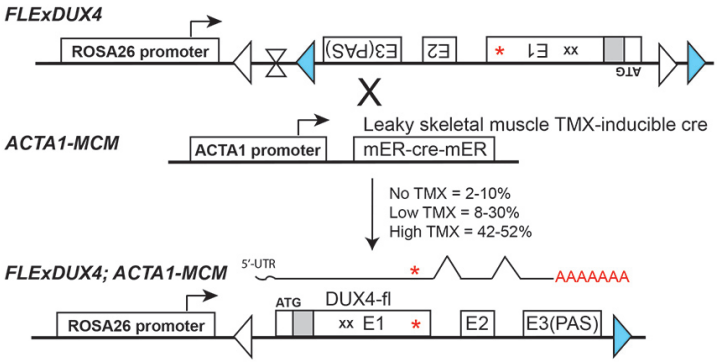
WT = Wild Type (normal, nontransgenic)
Hemi = Hemizygous (one copy of the transgene)



Homozygous (two copies of the transgene) FLExDUX4/FLExDUX4

FSHD model organisms: FLExDUX4 FSHD-like mouse (Pt 2)

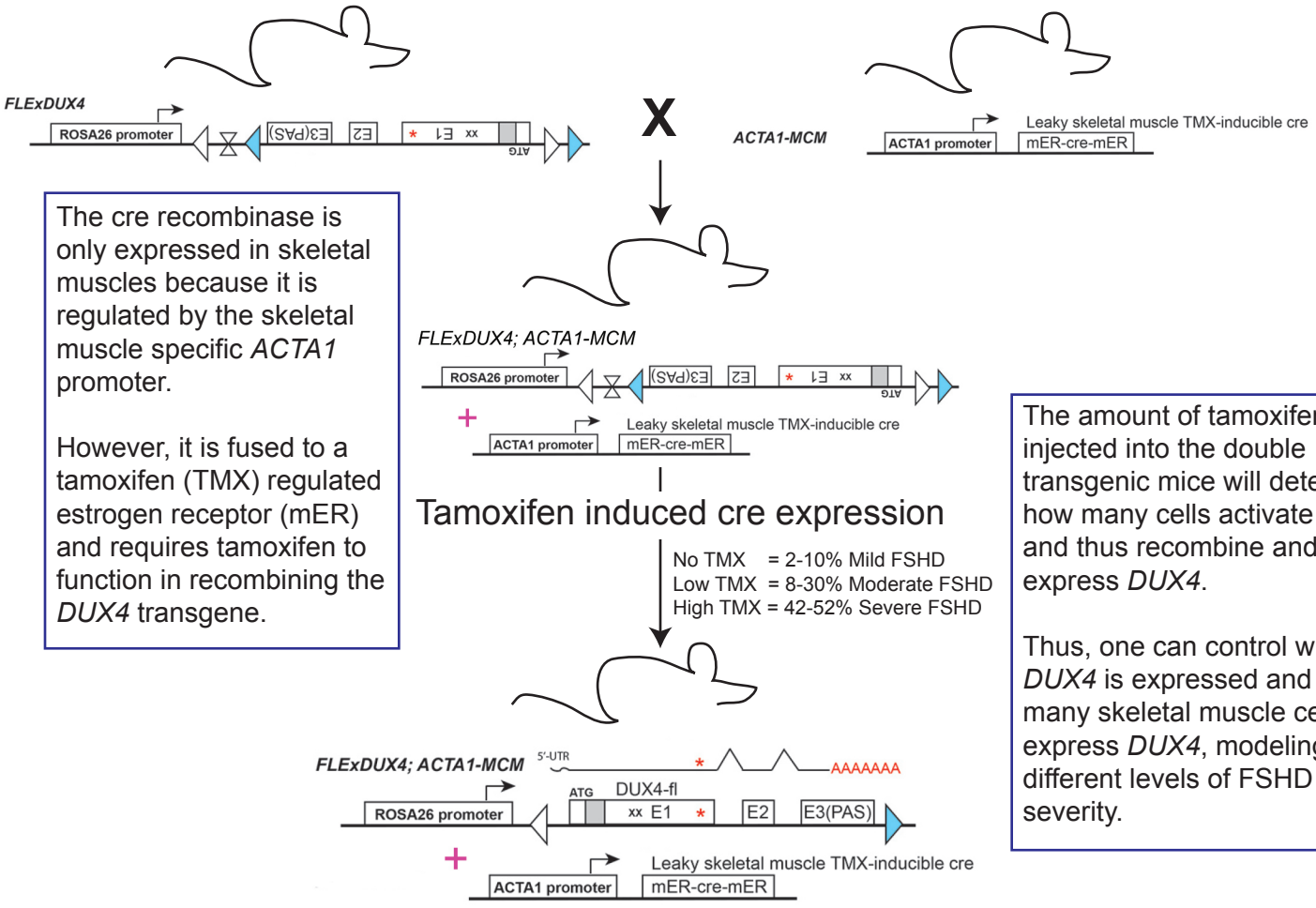
The FLExDUX4 mouse can be used to create FSHD-like pathology varying in age of onset and degree of severity making it a highly versatile model for therapeutic development and preclinical testing.



The FLExDUX4 mice need to be mated with a line of mice that express the cre recombinase in order to activate expression of the *DUX4* gene.

The *DUX4* transgene is flanked by loxP sites, which are DNA sequences recognized by cre. Cre activates DNA recombination between loxP sites.

The design of this particular system, whereby the two white loxP sites recombine and the two blue loxP sites recombine, results in permanent recombination and flipping of the *DUX4* transgene orientation.



The cre recombinase is only expressed in skeletal muscles because it is regulated by the skeletal muscle specific *ACTA1* promoter.

However, it is fused to a tamoxifen (TMX) regulated estrogen receptor (mER) and requires tamoxifen to function in recombining the *DUX4* transgene.

The amount of tamoxifen injected into the double transgenic mice will determine how many cells activate cre and thus recombine and express *DUX4*.

Thus, one can control when *DUX4* is expressed and how many skeletal muscle cells express *DUX4*, modeling different levels of FSHD severity.

DUX4 gene expression in skeletal muscles.

FSHD model organisms: FLExDUX4 FSHD-like mouse (Pt 3)

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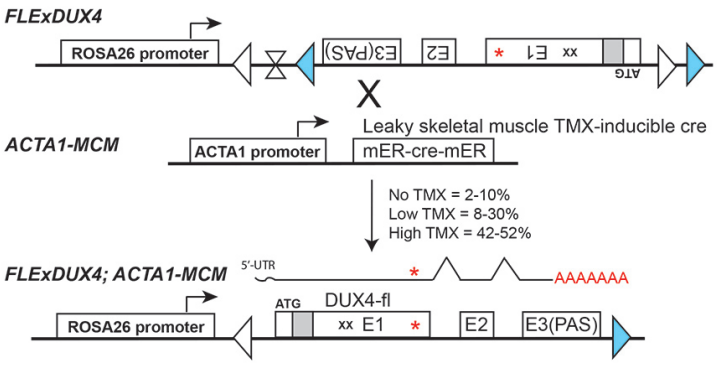

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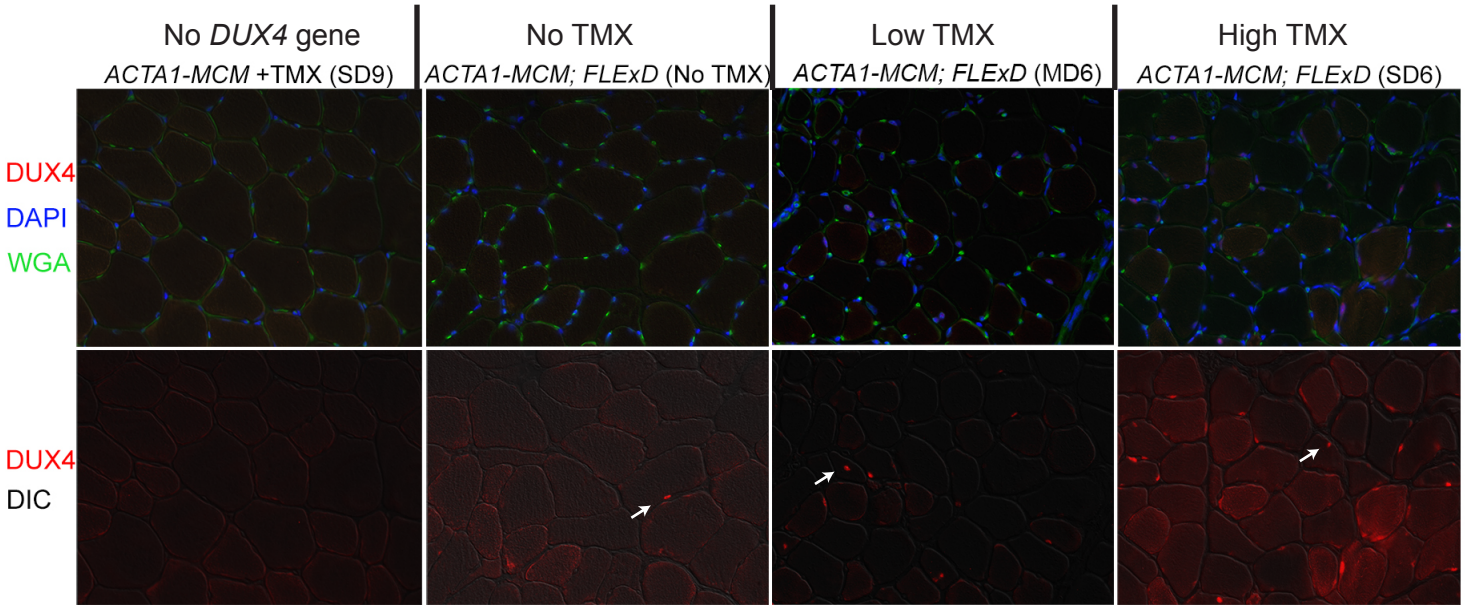
The muscles of FLExDUX4; ACTA1-MCM double transgenic mice express increasing levels of DUX4 protein in repsonse to increased tamoxifen (TMX) induction of gene recombination. Increased DUX4 protein correlates with more severe disease.



Histology of cross-sections of skeletal muscles from FSHD-like mouse models with different severity of FSHD-like pathology.

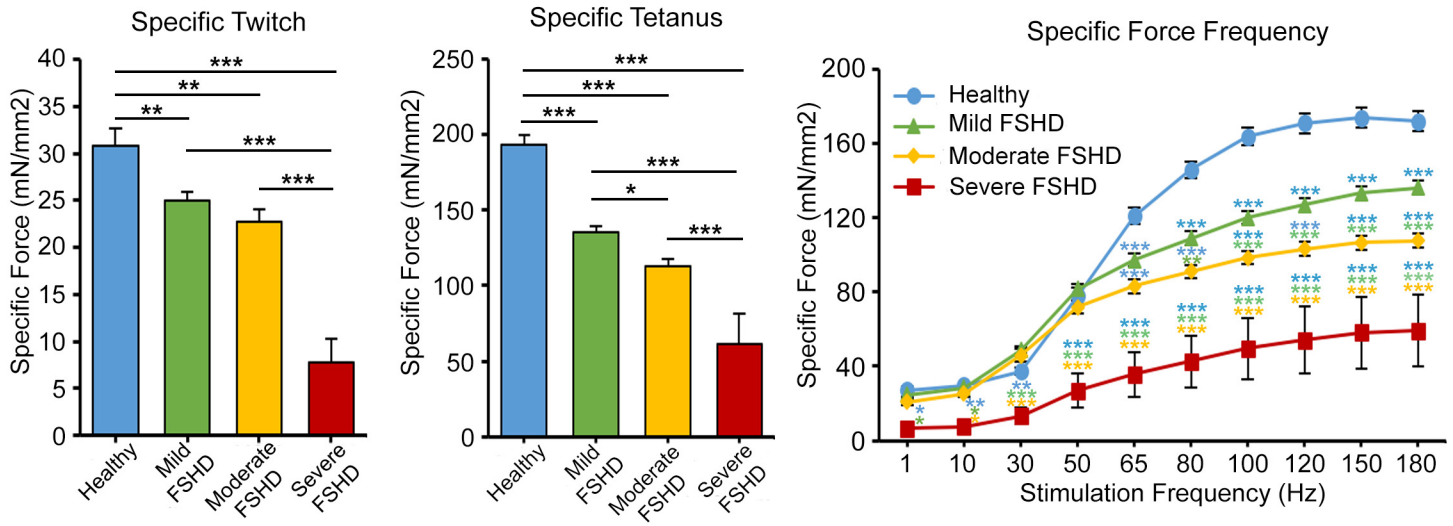
Upper: Muscle cells are outlined in green and all the muscle cell nuclei are in blue.
Lower: DUX4 protein appears red (fluorescently labeled); white arrows point to examples of DUX4 positive muscle cell nuclei.

FSHD model organisms: FLExDUX4 FSHD-like mouse (Pt 4)

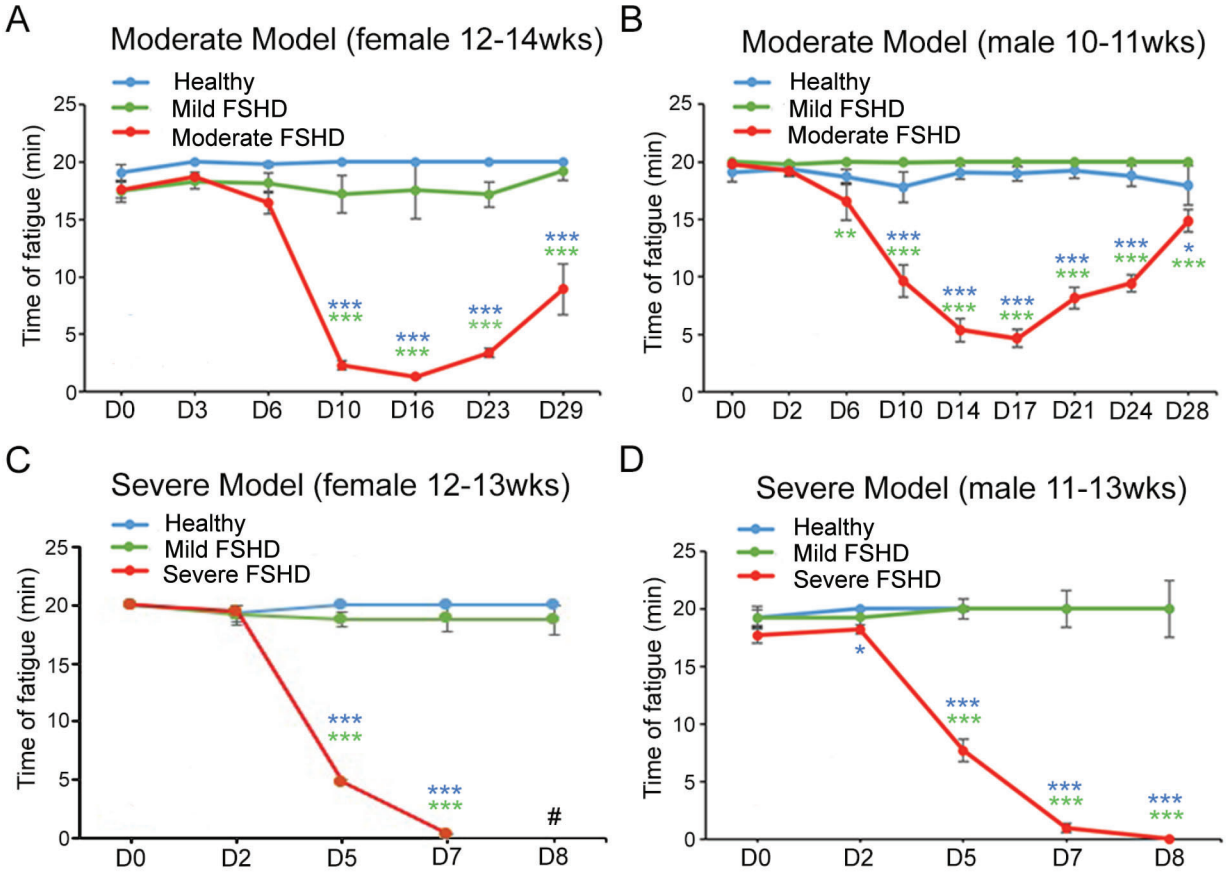
The FLExDUX4 mouse can be used to create FSHD-like pathology varying in age of onset and degree of severity making it a highly versatile model for therapeutic development and preclinical testing.

DUX4-expressing FLExD mice are excellent models to test therapeutics targeting DUX4

Increasing levels of DUX4 in skeletal muscles leads to decreased strength and function.



Increasing levels of DUX4 in skeletal muscles leads to decreased treadmill running.



DUX4 is induced on Day 0 (D0) and mice are run on a treadmill till exhaused.