FSHD model organisms: Mice

FSHD-like model mice are critical tools for FSHD research.

Mice do not have a version of the human *DUX4* gene (no true ortholog - derived from same ancestral gene). However, mice do contain a Dux family gene (*Dux*) that performs the same biological function as *DUX4*. Thus, there is some debate in the field of using *Dux* overexpression in mice as a model of FSHD. However, while this may provide important data on the biology of *Dux/DUX4*, it would not be a useful model for preclinical testing of potential FSHD therapeutics *in vivo*.

There are several ways to express human *DUX4* in mice:

- Inject mice with a virus or plasmid expressing DUX4 mRNA.

DUX4, a Candidate Gene for Facioscapulohumeral Muscular Dystrophy, Causes p53-Dependent Myopathy In Vivo

Lindsay M. Wallace, BA,[1,2] Sara E. Garwick, BS,[2] Wenyan Mei, PhD,[3,4] Alexandra Belayew, PhD,[5] Frederique Coppee, PhD,[5] Katherine J. Ladner, PhD,[6,7] Denis Guttridge, PhD,[1,6,7] Jing Yang, PhD,[3,4] and Scott Q. Harper, PhD[1,2,3]

Annals of Neurology (2011) 69:540-52

In this study, the Harper lab created an AAV (adeno-associated virus) that expressed the human DUX4. When injected into mouse muscle, DUX4 expression caused massive pathology. This model can be used to test therapeutic approaches that target the DUX4 mRNA.

- Engineer transgenic *DUX4* mice.
  Transgenic mice have a foreign piece of DNA (transgene) inserted into their genome.

Intrinsic Epigenetic Regulation of the D4Z4 Macrosatellite Repeat in a Transgenic Mouse Model for FSHD

PLoS Genetics (2013) 9:e1003415

Yvonne D. Krom[1☯], Peter E. Thijssen[1☯], Janet M. Young[2], Bianca den Hamer[1], Judit Balog[1], Zizhen Yao[2], Lisa Maves[2], Lauren Snider[2], Paul Knopp[3], Peter S. Zammit[3], Tonnie Rijkers[1], Baziel G. M. van Engelen[4], George W. Padberg[4], Rune R. Frants[1], Rabi Tawil[5], Stephen J. Tapscott[2]*, Silvère M. van der Maarel[1]*

The first transgenic FSHD mouse models, termed D4Z4-2.5 and D4Z4-12.5 mice, contained the human 4q35.2 region with either 2 or 12 D4Z4 RUs. These did not show an FSHD phenotype but did show FSHD-like epigenetics.

Subsequently, three conditional (the *DUX4* gene is induced by the investigator) transgenic *DUX4* model mouse lines did show strong FSHD-like pathology and characteristics.

Muscle pathology from stochastic low level DUX4 expression in an FSHD mouse model

Darko Bosnakovski[1,2,3], Sunny S.K. Chan[1,2], Olivia O. Recht[1,2], Lynn M. Hartweck[1,2], Collin J. Gustafson[1,2], Laura L. Athman[1,2], Dawn A. Lowe[4] & Michael Kyba[1,2]

Nature Communications (2017) 8:550

AAV-mediated follistatin gene therapy improves functional outcomes in the TIC-DUX4 mouse model of FSHD

Carlee R. Giesige,[1,2] Lindsay M. Wallace,[2] Kristin N. Heller,[2] Jocelyn O. Eidahl,[2] Nizar Y. Saad,[2] Allison M. Fowler,[2] Nettie K. Pyne,[2] Mustafa Al-Kharsan,[2] Afrooz Rashnonejad,[2] Gholamhossein Amini Chermahini,[2] Jacqueline S. Domire,[2] Diana Mukweyi,[2] Sara E. Garwick-Coppens,[2] Susan M. Guckes,[2] K. John McLaughlin,[2,3] Kathrin Meyer,[2] Louise R. Rodino-Klapac,[2,3] and Scott Q. Harper[1,2,3]

JCI Insight (2018) 3(22):e123538

RESEARCH ARTICLE

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

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

PLoS One (2018) 13:e0192657

- Create human FSHD xenograft mice: Mice that grow human FSHD muscle from transplanted cells.

Research Paper

Muscle xenografts reproduce key molecular features of facioscapulohumeral muscular dystrophy

Experimental Neurology (2019) 320:113011

Amber L. Mueller[a], Andrea O'Neill[a], Takako I. Jones[b], Anna Llach[a,1], Luis Alejandro Rojas[c], Paraskevi Sakellariou[a,d], Guido Stadler[e,2], Woodring E. Wright[e], David Eyerman[c], Peter L. Jones[b], Robert J. Bloch[a,*]

FSHD model organisms: Available FSHD mouse models

FSHD-like model mice are critical tools for FSHD research.

Mice do not have the *DUX4* gene (no true ortholog - derived from same ancestral gene).

Thus, the human *DUX4* gene and FSHD region have been put into the mouse genome in several different contexts to generate transgenic FSHD-like mouse models.

These FSHD-like model mice are all available to academic and pharmaceutical FSHD labs.

Intrinsic Epigenetic Regulation of the D4Z4 Macrosatellite Repeat in a Transgenic Mouse Model for FSHD

Yvonne D. Krom[1,9], Peter E. Thijssen[1,9], Janet M. Young[2], Bianca den Hamer[1], Judit Balog[1], Zizhen Yao[2], Lisa Maves[2], Lauren Snider[2], Paul Knopp[3], Peter S. Zammit[3], Tonnie Rijkers[1], Baziel G. M. van Engelen[4], George W. Padberg[4], Rune R. Frants[1], Rabi Tawil[5], Stephen J. Tapscott[2]*, Silvère M. van der Maarel[1]*

PLoS Genetics (2013) 9:e1003415

Contain *D4Z4* arrays with either 2.5RUs or 12.5RUs. *DUX4* expression is not inducible. FSHD-like epigenetics, but no FSHD-like phenotypes.

The Jackson Laboratory

B6N.Cg-Tg(DUX4*)1Maar/J
Stock No: **027991** | D4Z4-2.5
Congenic, Transgenic

The Jackson Laboratory

B6N.Cg-Tg(FRG1,FRG2,DUX4*)34Maar/J
Stock No: **028012** | D4Z4-12.5
Congenic, Transgenic

Muscle pathology from stochastic low level DUX4 expression in an FSHD mouse model

Darko Bosnakovski[1,2,3], Sunny S.K. Chan[1,2], Olivia O. Recht[1,2], Lynn M. Hartweck[1,2], Collin J. Gustafson[1,2], Laura L. Athman[1,2], Dawn A. Lowe[4] & Michael Kyba[1,2]

Nature Communications (2017) 8:550

DUX4 expression induced by tetracycline, can turn *DUX4* expression on and off. Develop FSHD-like pathology.

The Jackson Laboratory

STOCK *Hprt*$^{tm1(tetO-DUX4)Kyba}$/J
Stock No: **030749** | iDUX4pA
Targeted Mutation

RESEARCH ARTICLE

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

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

PLoS One (2018) 13:e0192657

DUX4 expression can be induced by cre. Develop FSHD-like pathology when crossed with skeletal muscle-specific cre mouse line in absense of tamoxifen, more severe with tamoxifen.

The Jackson Laboratory

B6(Cg)-*Gt(ROSA)26Sor*$^{tm1.1(DUX4*)Plj}$/J
Stock No: **028710** | FLExDUX4
Targeted Mutation

AAV-mediated follistatin gene therapy improves functional outcomes in the TIC-DUX4 mouse model of FSHD

Carlee R. Giesige,[1,2] Lindsay M. Wallace,[2] Kristin N. Heller,[2] Jocelyn O. Eidahl,[2] Nizar Y. Saad,[2] Allison M. Fowler,[2] Nettie K. Pyne,[2] Mustafa Al-Kharsan,[2] Afrooz Rashnonejad,[2] Gholamhossein Amini Chermahini,[2] Jacqueline S. Domire,[2] Diana Mukweyi,[2] Sara E. Garwick-Coppens,[2] Susan M. Guckes,[2] K. John McLaughlin,[2,3] Kathrin Meyer,[2] Louise R. Rodino-Klapac,[2,3] and Scott Q. Harper[1,2,3]

JCI Insight (2018) 3(22):e123538

DUX4 expression induced by cre. DUX4 protein is epitope-tagged. Develop FSHD-like pathology when crossed with skeletal muscle-specific cre mouse line and induced with tamoxifen.

The Jackson Laboratory

B6.129S6-*Gt(ROSA)26Sor*$^{tm1(DUX4)Sqh}$/J
Stock No: **032779** | Rosa26-DUX4
Congenic, Targeted Mutation