FSHD model organisms: *Drosophila melanogaster* (fruit flies)

Drosophila are one of the classic genetic model systems used for fundamental biological discoveries. They are also a powerful system for performing genetic screens in a complex living organism.

The Fly

Little fly
Thy summers play,
My thoughtless hand
Has brush'd away

Am not I
A fly like thee?
Or art not thou
A man like me?

For I dance
And drink & sing;
Till some blind hand
Shal brush my wing

If thought is life
And strength & breath;
And the want
Of thought is death;

Then am I
A happy fly,
If I live,
Or if I die

"Songs of Innocence and of Experience" by William Blake 1794

Drosophila sp. have been used in genetic studies since 1906, and the first gene and mutation, the *white* gene, was discovered in 1909 by Thomas Hunt Morgan. His work with *Drosophila* led to the 1933 Nobel Prize in Physiology or Medicine "for his discoveries concerning the role played by the chromosome in heredity."

Flies, like mice, do not have the *DUX4* gene or a Dux family gene.

However, many genes and developmental systems are in fact conserved between humans and flies. Thus, transgenic flies were generated in which the human *DUX4* gene was inserted into the fly genome under regulation of the GAL4/UAS system.

The GAL4/UAS system will allow expression of the human *DUX4* gene in any tissue desired simply by mating the *UAS-DUX4* flies with GAL4 driver lines in which the GAL4 activator is expressed in a tissue-specific manner.

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RESEARCH ARTICLE

Transgenic *Drosophila* for Investigating *DUX4* and *FRG1*, Two Genes Associated with Facioscapulohumeral Muscular Dystrophy (FSHD)

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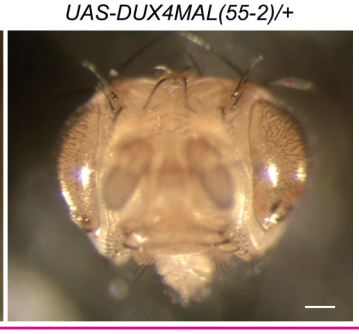
Note: The *gmr-GAL4* line was chosen for two reasons: 1) its eyes typically produce an easily screenable phenotype, and 2) expression of DUX4 in other tissues is lethal.

The *gmr-GAL4* line only expresses in the eyes.

gmr-GAL4/+

gmr-GAL4/+; UAS-DUX4MAL(55-2)/+



Crossing *UAS-DUX4* with *gmr-GAL4* results in a severe eye phenotype, loss of the ommatidia. Ommatidia are independent photoreceptor units in the compound eye. Thus, this shows an adverse effect of DUX4 expression in a living system. One can now perform a mutagenesis screen to identify genes that are involved in the DUX4 affected pathway(s), and then move to the human system for validation.