D1389

Human Disease Model Reports in FlyBase

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ABSTRACT The use of Drosophila melanogaster as a model for studying human disease is well established, reflected by the steady increase in both the number and proportion of fly papers describing human disease models in recent years. In order to improve both the visibility and accessibility of human disease model research, FlyBase has recently begun producing Human Disease Model Reports. These reports provide an integrated informational resource regarding specific diseases and fly disease models and their potential impacts on translational research.

The Integrated Human Disease Model Report

General Information

Name	amyotrophic lateral sclerosis 8	FlyBase ID	FBhh0000020
Disease Ontology ID	DOID:0050752	Parent Disease	amyotrophic lateral sclerosis
OMIM	AMYOTROPHIC LATERAL SCLEROSIS 8; ALS8	Parent Disease DOID	DOID:332

Overview

This report describes amyotrophic lateral sclerosis 8 (ALS8), which is a subtype of amyotrophic lateral sclerosis. The human gene implicated in this disease is VAPB, which is a member of the vesicle-associated membrane protein (VAMP)-associated protein (VAP) family. This gene is also associated with the disease spinal muscular atrophy, late-onset, Finkel type (OMIM:182980, FBhh0000254). There is a single fly ortholog, Vap-33A, for which classical amorphic and hypomorphic alleles, RNAi-targeting constructs, and alleles caused by insertional mutagenesis have been generated.

- Disease Summary Information
- Related Diseases
- Ortholog Information
- D. melanogaster Gene Informati
- Synthetic Gene(s) Used (0)
- Experimental Findings
- Summary of Physical Interactior
- Alleles Reported to Model Huma
- Genetic Tools, Stocks and Reag
- References (16)

Disease Summary Information

Specific Disease Summary: amyotrophic lateral sclerosis 8

OMIM report	AMYOTROPHIC LATERAL SCLEROSIS 8; ALS8
Human gene(s) implicated	VESICLE-ASSOCIATED MEMBRANE PROTEIN-ASSOCIATED PROTEIN B; VAPB
Symptoms and phenotype	ALS8 is an autosomal dominant slowly progressive disorder characterized by fasciculations, cramps, and postural tremor (Nishimura, et al., 2004, pubmed:15060112; Nishimura, et al., 2004, pubmed:15372378). [From OMIM:608627, 2015.12.16]
Genetics	ALS8 is caused by heterozygous mutation in the VAPB gene. [from OMIM:608627, 2015.02.12]

Each Human Disease Model Report integrates information about a specific disease from many parts of FlyBase. The Disease Summary includes background information, primarily from OMIM (Online Mendelian Inheritance in Man).

Related Diseases

Related Diseases

Related human health report(s)	spinal muscular atrophy, late onset, Finkel type
Related Specific Diseases	
OMIM phenotypic series	Amyotrophic lateral sclerosis Frontotemporal dementia and/or Amyotrophic Lateral Sclerosis

Disease	Associated Human gene(s)	Drosophila model	Human transgene in Drosophila
ALS1	SOD1	amyotrophic lateral sclerosis 1	y
ALS4	SETX		
ALS5	SPG11		
ALS6	FUS	amyotrophic lateral sclerosis 6	y

The Related Diseases section allows for easy navigation to disease subtypes, or to diseases caused by the same gene or mechanism.

Experimental Findings

Experimental Findings

Summary

Dmel\caz is similar in structure to the human gene FUS (FBrf0217025, FBrf0218546). Dmel\caz protein is expressed in the central nervous system of larval and adult flies, and has a nuclear localization (FBrf0218682). Dmel\caz mutants exhibit decrease in longevity, locomotor defects, disorganization of motor neurons in the ventral nerve cord, and defects in synaptic transmission and presynaptic efficacy at the larval neuromuscular junction (FBrf0214276, FBrf0216240,

Description of Experiments

- Mammalian transgenics: heterologous resc
- Mammalian transgenics: transgenic pheno
- Mammalian transgenics: interactions
- Mammalian transgenics: pertubations and
- Drosophila genes: relevant phenotypes
- Drosophila recombinant constructs: pheno
- Drosophila genes: interactions
- Drosophila genes: pertubations and treatm
- Additional information
- Proposed mechanisms

Pan-neuronal expression of wild-type or ALS-associated mutant Hsap\FUS protein restores adult viability to Dmel\caz mutants. Pan-neuronal expression of wild-type, but not mutant, Hsap\FUS protein rescues locomotive and longevity phenotypes of Dmel\caz mutants. (These experiments used GAL4 allele Scer\GAL4$^{elav\text{-}C155}$ (pan-neuronal); UAS alleles Hsap\FUS$^{Scer\UAS.10x.T:Zzzz\FLAG}$, Hsap\FUS$^{P525L.10x.Scer\UAS.T:Zzzz\FLAG}$, and Hsap\FUS$^{R522G.10x.Scer\UAS.T:Zzzz\FLAG}$; and mutant allele caz^{383} in a CG32576$^{+t5.0}$ genetic background). (*Wang et al., 2011*)

A subset of Disease Reports include data curated from papers. Statements are written in a clear accessible style, and end with a listing of genetic reagents. The Summary is a curated synthesis of the experimental data.

Orthologs and Promoted Data

Ortholog Information

Human gene(s) in FlyBase	Hsap\LRRK2
Human gene (HGNC)	
Symbol / Name	LRRK2: leucine-rich repeat kinase 2
D. melanogaster ortholog	Dmel\Lrrk

In the Ortholog Information section we associate the human gene identified as the cause of the disease, whether it has been transgenically expressed in flies, and its orthologous fly gene. These gene associations allow us to promote data from elsewhere in FlyBase.

Disease Ontology Allele Annotation

Lrrk

Models

Allele	Disease	Evidence	References
Lrrk^{e03680}	model of Parkinson's disease	inferred from mutant phenotype	(*Lin et al., 2015*)
Lrrk$^{RC.Scer\UAS.T:Zzzz\FLAG}$	model of Parkinson's disease	inferred from mutant phenotype	(*Godena et al., 2014*)

Interactions

Hsap\LRRK2

Models

Interactions

Allele	Disease	Interaction	References
Hsap\LRRK2$^{Scer\UAS.cVa}$	model of Parkinson's disease	is ameliorated by Hsap\PARK7$^{Scer\UAS.cYa}$	(*Venderova et al., 2009*)

Thus, we can display Disease Ontology annotations of alleles of both the fly and human genes. Other promoted data types include physical interactions, and genetic tools, stocks and reagents.

Genetic Tools, Stocks and Reagents

Sources of Stocks

Bloomington Stock Center Disease Page	Parkinson disease

Selected mammalian transgenes

Allele	Transgene	Publicly Available Stocks
Hsap\LRRK2$^{Scer\UAS.cVa}$	P{UAS-hLRRK2.WT}	
Hsap\LRRK2$^{I1122V.Scer\UAS}$	P{UAS-hLRRK2.I1122V}	

RNAi constructs available

Allele	Transgene	Publicly Available Stocks
Lrrk^{GD11670}	P{GD11670}	w^{1118}; P{GD11670}v22139
Lrrk$^{dsRNA.Scer\UAS.cla}$	P{UAS-Lrrk.RNAi}	
Lrrk^{KK100916}	P{KK100916}	P{KK100916}VIE-260B

In the Genetic Tools, Stocks and Reagents section we include a link to the relevant BDSC disease page, and indicate whether a stock is available from a public stock repository.

Searching for Disease Model Information

The QuickSearch tool on the FlyBase front page offers three options to search for human disease information:

① The Simple tab searches exact text strings.
② The dedicated Human Disease tab searches the Disease Ontology (DO).
③ The Human Disease tab also includes a link to a browseable list of Human Disease Model Reports.

Disease model information in FlyBase is organized using a "you can get there from here" philosophy. A user may locate a bit of disease model information in a disease model report, a gene report, or a DO term report. Each of these reports includes links to the other reports.

1. Simple Search

QuickSearch — Human Disease | Expression | GO | Phenotype | References — Simple | Orthologs NEW | Protein Domains | Gene Groups | Data Class

Species: include non-Dmel species — Search

Enter text: TDP-43

Note: Wild cards (*) can be added to your search term

- Finds all instances of "TDP-43"
- Does not search DO

Your query phrase "TDP-43" returned 144 matches

Hits	Data Class
2	Genes
0	Stocks
77	References
1	Human Disease

Gene Report

Intermediate hitlist includes multiple data types

Name	amyotrophic lateral sclerosis 10
Disease Ontology ID	DOID:0060201
OMIM	AMYOTROPHIC LATERAL SCLEROSIS 10 WITH OR WITHOUT FRONTOTEMPORAL DEMENTIA; ALS10

- Disease Summary Information
- Related Diseases
- Ortholog Information

Human gene(s) in FlyBase: Hsap\TARDBP

Human gene (HGNC): Symbol / Name: TARDBP: TAR DNA binding protein; D. melanogaster ortholog: Dmel\TBPH

- Alleles Reported to Model Human Disease
- Genetic Tools, Stocks and Reagents

DO Term Report

Gene Reports

Allele Reports

The Human Disease Model Report links to DO, Gene and Allele Reports

2. Human Disease Tab

QuickSearch — Human Disease | Expression | GO | Phenotype | References — Simple | Orthologs NEW | Protein Domains | Gene Groups | Data Class

Disease term: amyotrophic lateral sclerosis — Search

Alternatively, browse Human Disease reports

Note: Wild cards (*) can be added to your search term

Finds only Disease Ontology terms.

Annotations

Records which annotation includes this term *OR* any of its *CHILDREN TERMS*

Genes 53 | Human Diseases 11 | Alleles 130

Spanning Tree (Parents/Children) — Only view relationship: is_a

```
neurodegenerative disease
  motor neuron disease
    amyotrophic lateral sclerosis 194 rec.
      amyotrophic lateral sclerosis type 8 4 rec.
      amyotrophic lateral sclerosis type 9
      amyotrophic lateral sclerosis type 10 1 rec.
      amyotrophic lateral sclerosis type 11
```

- Spanning tree allows browsing of DO hierarchy.
- Aqua buttons correspond to Genes, Alleles or Disease Reports to which a DO term or one of its children is attached.

20	Hsap\TAF15	1	amyotrophic lateral sclerosis	98	TBPH$^{Scer\UAS.cDa}$
21	Hsap\TARDBP	2	amyotrophic lateral sclerosis 10	99	TBPH$^{Scer\UAS.cLa}$
42	Syx1A	3	amyotrophic lateral sclerosis 6	100	TBPH$^{Scer\UAS.T:Avic\GFP}$
43	TBPH	4	amyotrophic lateral sclerosis 1	101	TBPH$^{Scer\UAS.T:Disc\RFP}$
44	TER94	5	amyotrophic lateral sclerosis 8	102	TBPH$^{\Delta 23}$
49	Zzzz\GGGGCC	6	amyotrophic lateral sclerosis 14	103	TBPH$^{\Delta 142}$
50	Zzzz\poly-GA	7	amyotrophic lateral sclerosis 17	104	TER94^{03775}
		8	amyotrophic lateral sclerosis 18	105	TER94^{k15502}

Buttons lead to hit lists of Genes, Disease Reports, and Alleles. Genes may include fly genes, human transgenes (Hsap), or artificial genes (Zzzz).

Symbol	Dmel\TBPH
Name	TAR DNA-binding protein-43 homolog
Feature type	protein_coding_gene

Human Disease Model Data

FlyBase Human Disease Model Reports: amyotrophic lateral sclerosis 10

Models

Allele	Disease
TBPH$^{Scer\UAS.cLa}$	model of amyotrophic lateral sclerosis model of frontotemporal dementia

Disease Report

DO Term Report

Allele Report

The Disease Ontology Term Report allows navigation to Gene, Disease, and Allele Reports. Gene Reports link to Disease, DO and Allele reports.

3. Browseable List

QuickSearch — Human Disease | Expression | GO | Phenotype | References — Simple | Orthologs NEW | Protein Domains | Gene Groups | Data Class

Disease term: amyotrophic lateral sclerosis — Search

Alternatively, browse Human Disease reports

Note: Wild cards (*) can be added to your search term

FlyBase Human Disease Model Report List

- 3-Methylglutaconic aciduria
- acute myeloid leukemia
  - acute myeloid leukemia, RUNX1-RUNX1T1 fusion
- Alexander disease
- alpha-1-antitrypsin deficiency
- Alzheimer disease
  - Alzheimer disease 1
  - Alzheimer disease 3
  - Alzheimer disease 4
- amyotrophic lateral sclerosis
  - amyotrophic lateral sclerosis 1
  - amyotrophic lateral sclerosis 2
  - amyotrophic lateral sclerosis 6
  - amyotrophic lateral sclerosis 8
  - amyotrophic lateral sclerosis 10
  - spinocerebellar ataxia 2
  - amyotrophic lateral sclerosis 14

Disease Report

The Human Disease Model Report List consists of links to those reports. Some reports are redundantly listed; in the example below, dentatorubro-pallidoluysian atrophy is both a subtype of spinocerebellar ataxia, and is a disease caused by polyglutamine repeat expansion.

- spinocerebellar ataxia
  - dentatorubro-pallidoluysian atrophy
  - spinocerebellar ataxia 1
  - spinocerebellar ataxia 2
- polyglutamine diseases
  - dentatorubro-pallidoluysian atrophy
  - Huntington disease
  - Machado-Joseph disease

Coming Soon

QuickSearch — Human Disease | Expression | GO | Phenotype | References — Simple | Orthologs NEW | Protein Domains | Gene Groups | Data Class

Search Human Disease Model Reports — e.g. Alzheimer's, thyroid carcinoma — Search

OR

DISEASE (Disease name or synonym, Disease Ontology (DO) term, or OMIM ID)
HUMAN GENE (HGNC symbol/ID)
DROSOPHILA GENE (symbol or FBgn)

Search Disease Ontology — e.g. Alzheimer's, thyroid carcinoma

This option searches only Disease Ontology terms and synonyms; does not search by gene

Alternatively, browse Human Disease reports

Note: Wild cards (*) can be added to your search term

An integrated Human Disease tab will allow searching by disease, human gene, or Drosophila gene.

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