“Disease-relevant” to disease model: how FlyBase can help you investigate human disease in Drosophila

Victoria Jenkins
Biocurator, FlyBase

Boston Area Drosophila Meeting
Boston University
June 11, 2020

disease-relevant

l(2)gl and
planar cell polarity

disease model

cancer, epithelial,
LLGL-related

What is a disease model?

variant/allele in defined gene(s)	chemical or anatomical treatment	environmental interaction
kidney disease	Parkinson-like disease, toxin-induced	*P. aeruginosa* infection
Werner syndrome	diabetes mellitus, insulin-dependent, IPC-ablation models	high-sugar diet, obesity

QuickSearch

Human Disease | Protein Domains | Gene Groups | Pathways | GO | Data Class

Search FlyBase | Homologs | GAL4 etc | Expression | Phenotype | References

Search using a disease name/ID/synonym, or a human or fly gene symbol/ID:

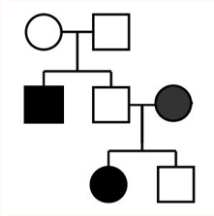
Search

Enter text: heart disease

Alternatively, browse all Human Disease Model reports

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

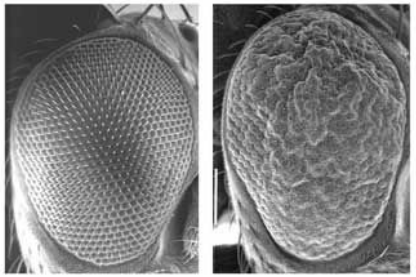
What do papers defining new Drosophila disease models based on genes tend to do?



find human gene(s) and variant(s) associated with patient phenotype

General Information	
Symbol	Dmel\CG4836
Name	
Feature Type	protein_coding_gene
Gene Model Status	Current
Gene Snapshot	Insufficient genetic data

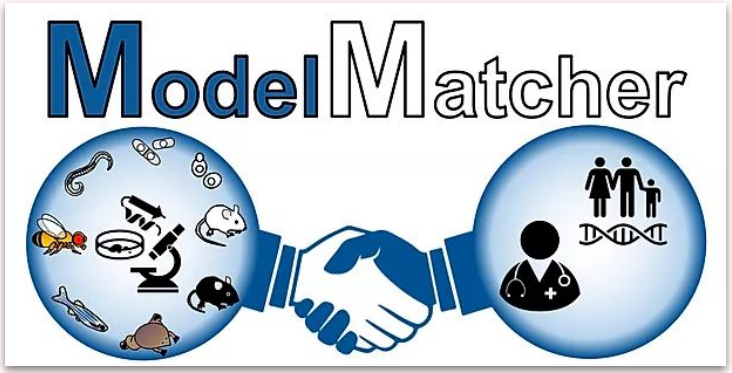
find Drosophila orthologue, select existing alleles or generate novel ones



define relevant phenotype and quantify it

modify phenotype with other genes or treatment

How do model organism researchers pick a disease gene to study?



How do model organism researchers find clinical collaborators for new disease model studies?

Can I develop a novel disease model in Drosophila without a clinical collaborator? Where do I start?

OMIM® omim.org

Online Mendelian Inheritance in Man®

An Online Catalog of Human Genes and Genetic Disorders

NUCLEAR RECEPTOR SUBFAMILY 2, GROUP F, MEMBER 2; NR2F2

HGNC Approved Gene Symbol: NR2F2

CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4; CHTD4

A number sign (#) is used with this entry because of evidence that multiple types of congenital heart defects (CHTD4) are caused by heterozygous mutation in the NR2F2 gene (107773) on chromosome 15q26.

▼ Description

The multiple types of congenital heart defects observed in CHTD4 include atrial, ventricular, and atrioventricular septal defects, double-outlet right ventricle, tetralogy of Fallot, hypoplastic left heart syndrome, aortic stenosis, and coarctation of the aorta. Intrafamilial variability and incomplete penetrance has been reported (Al Turki et al., 2014; Qiao et al., 2018). Some patients exhibit syndromic features such as developmental delay, congenital diaphragmatic hernia, and severe gastroesophageal reflux (High et al., 2016; Upadia et al., 2018).

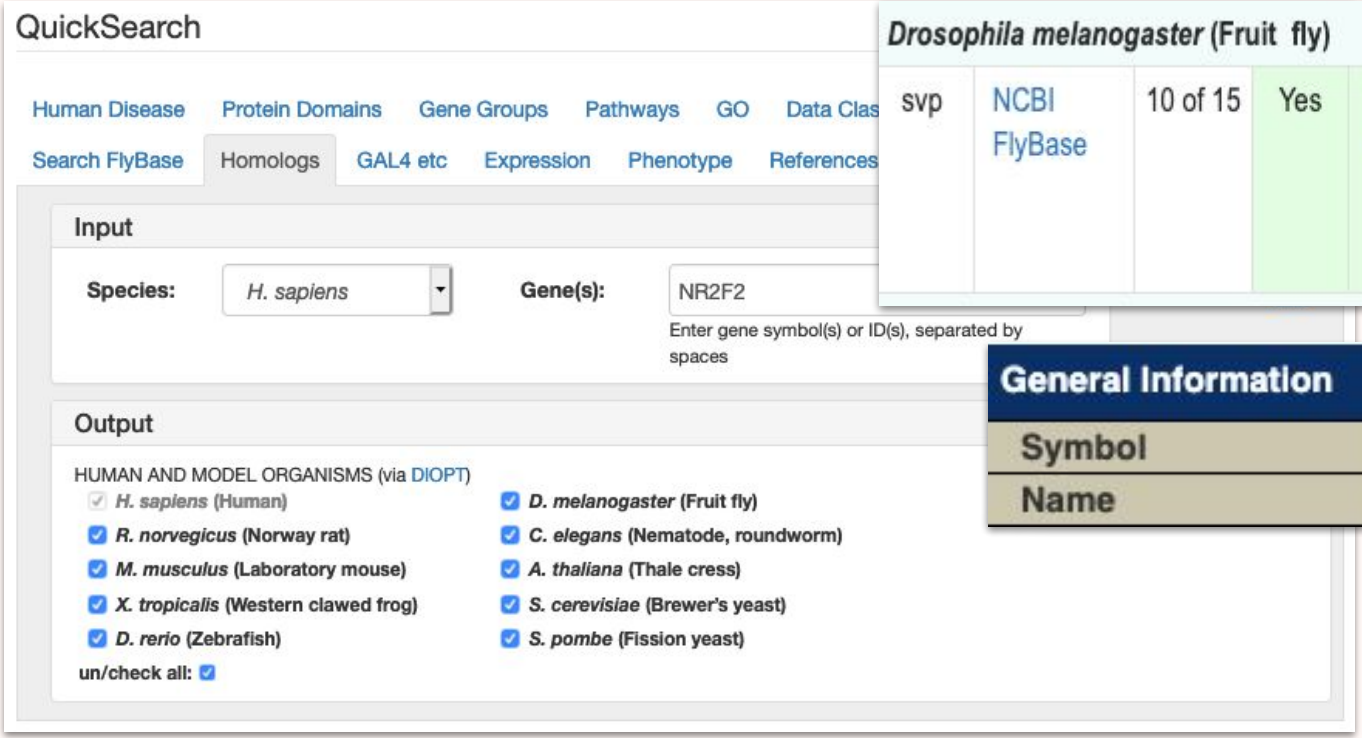
46,XX SEX REVERSAL 5; SRXX5

A number sign (#) is used with this entry because of evidence that 46,XX sex reversal-5 (SRXX5) is caused by heterozygous mutation in the NR2F2 gene (107773) on chromosome 15q26.

▼ Description

SRXX5 is characterized by genital virilization in 46,XX individuals, associated with congenital heart disease and variable somatic anomalies including blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) and congenital diaphragmatic hernia (Bashamboo et al., 2018).

How can I learn about a disease gene's fly homolog(s)?



***Drosophila melanogaster* (Fruit fly)**

svp	NCBI FlyBase	10 of 15	Yes	Yes (+)	eggNOG, Homologene, Isobase, OMA, OrthoFinder, OrthoInspector, orthoMCL, Phylome, RoundUp, TreeFam	(+)

General Information

Symbol	Dmel\svp
Name	seven up

DIOPT
DRSC integrative ortholog prediction tool

General Information

Symbol	Dmel\svp
Name	seven up

Report Sections ?

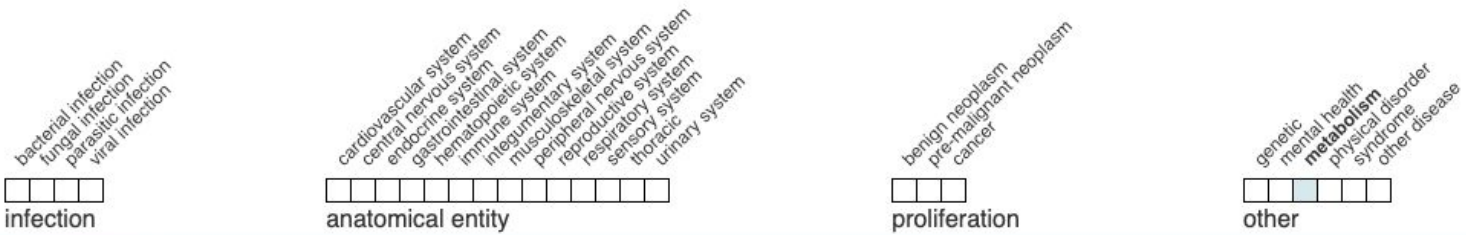
Human Disease Associations

Human Disease Associations

FlyBase Human Disease Model Reports

insulin signaling, regulation of fat storage, Drosophila fat body model

Disease Model Summary Ribbon



Disease Ontology (DO) Annotations

Models Based on Experimental Evidence (1)

Allele	Disease	Evidence	References
svp^{KK108498}	model of type 2 diabetes mellitus	CEA	(*Musselman et al., 2018*)

Potential Models Based on Orthology (0)

Human Ortholog	Disease	Evidence	References

Modifiers Based on Experimental Evidence (1)

Allele	Disease	Interaction	References
svp^{1}	ameliorates central nervous system cancer	modeled by N$^{UAS.icd}$	(*Zacharioudaki et al., 2016*)

General Information	
Symbol	Dmel\svp
Name	seven up

Report Sections ?

Expression Data

GENE

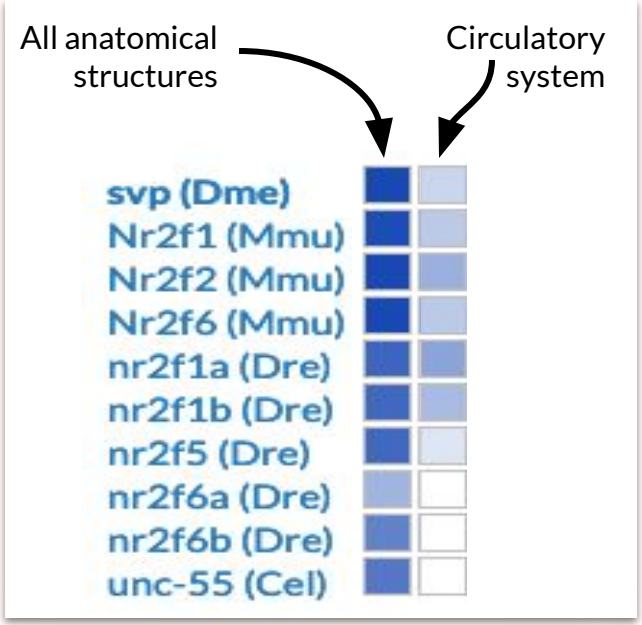
svp

ALLIANCE of GENOME RESOURCES

Expression Compare Ortholog Genes

- Transcript Expression ✓
- Polypeptide Expression ✓
- Expression Deduced from Reporters ✓

embryonic stage 12 -- 15	embryonic heart cardioblast
embryonic stage 11 -- 14	dorsal vessel primordium
embryonic stage 15	embryonic dorsal vessel
	embryonic/larval corpus allatum
embryonic stage	embryonic somatic muscle



General Information	
Symbol	Dmel\svp
Name	seven up

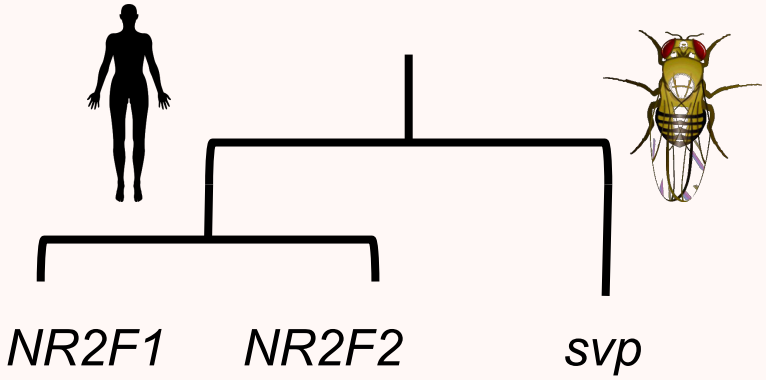
Report Sections ?

Orthologs

Human Orthologs (via DIOPT v7.1)

Homo sapiens (Human) (4)

Species\Gene Symbol	Score	Best Score	Best Reverse Score
Hsap\NR2F2	10 of 15	Yes	Yes
Hsap\NR2F1	9 of 15	No	Yes



NUCLEAR RECEPTOR SUBFAMILY 2, GROUP F, MEMBER 1; NR2F1

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
5q15	Bosch-Boonstra-Schaaf optic atrophy syndrome	615722	AD	3

General Information	
Symbol	Dmel\svp
Name	seven up

Report Sections ?

Orthologs

Human Orthologs (via DIOPT v7.1)

Homo sapiens (Human) (4)

Species\Gene Symbol	Score	Best Score	Best Reverse Score	Source (Compara, eggNOG, Hieranoid, Homologene, Inparanoid, Isobase, OMA, OrthoDB, OrthoFinder, OrthoInspector, orthoMCL, Panther, Phylome, RoundUp, TreeFam, ZFIN)	Alignment	Complementation? Transgene?
Hsap\NR2F2	10 of 15	Yes	Yes	○ ● ○ ● ○ ● ● ○ ● ● ● ○ ● ● ● ×	≡	
Hsap\NR2F1	9 of 15	No	Yes	○ ● ○ ○ ○ ○ ● ○ ● ● ● ● ● ● ● ×	≡	

X

✓

Stocks and Reagents

Stocks (1)

Bloomington	77959	y^1 w^*; PBac{UAS-hNR2F1.B}VK00037/SM6a

Celniker and Bellen, 2017-, A comprehensive human cDNA library for functional gene replacement in flies. A comprehensive human cDNA library for functional gene replacement in flies. [FBrf0237477]

What disease-associated variants have been found in human patients? How do they translate to flies?

OMIM®

- Title
- Gene-Phenotype Relationships
- Text
  - Cloning and Expression
  - Mapping
  - Gene Function
  - Cytogenetics
  - Molecular Genetics
  - Animal Model
- Allelic Variants
  - Table View
- References
- Contributors
- Creation Date
- Edit History

NUCLEAR RECEPTOR SUBFAMILY 2, GROUP F, MEMBER 2; NR2F2

Allelic Variants (9 Selected Examples) :

All ClinVar Variants

Number	Phenotype	Mutation	SNP	gnomAD	ClinVar
.0001	CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4	NR2F2, SER341TYR	rs587777371	-	RCV000116199...
.0002	CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4	NR2F2, ASN205ILE	rs587777372	-	RCV000116200
.0003	CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4	NR2F2, 3-BP DUP, GLN75	rs780808943	-	RCV000116201
.0004	CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4	NR2F2, IVS2, G-A, +1	rs587777374	-	RCV000116202
.0005	CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4	NR2F2, 7-BP DEL, NT92	-	-	-
.0006	CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4	NR2F2, 1-BP DUP, 856G	-	-	-
.0007	CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4	NR2F2, GLY83TER	-	-	-
.0008	46,XX SEX REVERSAL 5	NR2F2, 7-BP DEL, NT97	-	-	-
.0009	46,XX SEX REVERSAL 5	NR2F2, 7-BP DEL, NT103	-	-	-

ClinVar
Clinically relevant variation

UniProt

NM_021005.4(NR2F2):c.1022C>A (p.Ser341Tyr)

Cite this record

Interpretation: Pathogenic

Review status: ★☆☆☆ criteria provided, single submitter

Submissions:

Last evaluated:

Accession:

Variation ID:

Description: single nucleotide variant

341

```
P24468 COT2_HUMAN      290   DHIRIFQEQVEKLKALHVDSAEYSCLKAIVLFTSDACGLSDVAHVESLQEKSQCALEEYV   349
P16375 7UP1_DROME      419   DHIRIFQEQVEKLKALHVDSAEYSCLKAIVLFTTDACGLSDVTHIESLQEKSQCALEEYC   478
                             ************************************:********:*:***************
```

- Variant details
- Conditions
- Gene(s)

NM_021005.4(NR2F2):c.1022C>A (p.Ser341Tyr)

Allele ID: 133687

Variant type: single nucleotide variant

Variant length: 1 bp

Cytogenetic location: 15q26.2

Genomic location: 15: 96337399 (GRCh38) GRCh38 UCSC

15: 96880628 (GRCh37) GRCh37 UCSC

HGVS:

Nucleotide	Protein	Molecular consequence
NC_000015.10:g.96337399C>A		
NC_000015.9:g.96880628C>A		
NM_001145155.2:c.623C>A	NP_001138627.1:p.Ser208Tyr	missense

How do I alert FlyBase to my new model while completing Fast-Track Your Paper (FTYP)?

Human Disease

☑ Description or use of Drosophila model of human disease

Please enter the name(s) of the relevant disease(s) in the text area.
Separate multiple diseases by placing each on a different line; i.e.:

```
heart disease
Parkinson's disease
```

congenital heart defects 4;
OMIM # 615779

Drosophila Reagents

☐ New allele (non-transgenic) or aberration (*e.g.* a deletion)

☐ New transgene

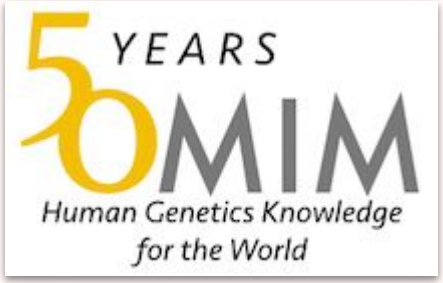
Gene Characterization

☐ Initial or novel characterization

☐ Gene rename

A few relevant resources

flybase.org



omim.org

DRSC/TRiP Functional Genomics Resources

fgr.hms.harvard.edu

alliancegenome.org

uniprot.org

www.ncbi.nlm.nih.gov/clinvar

Thank you!

The FlyBase Consortium:

Norbert Perrimon (PI, Harvard Univ.)

Susan Russo Gelbart (PD, Harvard Univ.)

Thomas Kaufman (co-PI, Indiana Univ.)
Brian Calvi (co-PI, Indiana Univ.)
Richard Cripps (co-PI, Univ. of NM)
Nick Brown (co-PI, Univ. of Cambridge)

Julie Agapite
Giulia Antonazzo
Helen Attrill
Kris Broll
Lynn Crosby
Gil Dos Santos
Kathleen Falls

Phani Garapati
Josh Goodman
Sian Gramates
Victoria Jenkins
Aoife Larkin
Ian Longden
TyAnna Lovato

Steven Marygold
Bev Matthews
Alex McLachlan
Gillian Millburn
Arzu Ozturk-Colak
Clare Pilgrim
Victor Strelets

Carol Sutherland
Chris Tabone
Jim Thurmond
Vitor Trovisco
Pinglei Zhou
Mark Zytkovicz

FlyBase is supported by a grant from the NHGRI (NIH #U41 HG000739), the British Medical Research Council (#MR/N030117/1), and FlyBase Users all over the world.

Extra thanks to Hugo Bellen, Shinya Yamamoto, and everyone at the UDN for their trailblazing work in this field.