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

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Biocurator, FlyBase

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Boston University
June 11, 2020
disease-relevant

\textit{l}(2)\textit{g}l \text{ and planar cell polarity}

disease model

cancer, epithelial, LLGL-related
### What is a disease model?

<table>
<thead>
<tr>
<th>Variant/allele in defined gene(s)</th>
<th>Chemical or anatomical treatment</th>
<th>Environmental interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>kidney disease</td>
<td>Parkinson-like disease, toxin-induced</td>
<td><em>P. aeruginosa</em> infection</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>diabetes mellitus, insulin-dependent, IPC-ablation models</td>
<td>high-sugar diet, obesity</td>
</tr>
</tbody>
</table>
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:

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
- find Drosophila orthologue, select existing alleles or generate novel ones
- define relevant phenotype and quantify it
- modify phenotype with other genes or treatment

**General Information**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>DmelCG4836</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td></td>
</tr>
<tr>
<td>Feature Type</td>
<td>protein_coding_gene</td>
</tr>
<tr>
<td>Gene Model Status</td>
<td>Current</td>
</tr>
<tr>
<td>Gene Snapshot</td>
<td>Insufficient genetic data</td>
</tr>
</tbody>
</table>
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?
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-p toesis-epicanthus inversus syndrome (BPES) and congenital diaphragmatic hernia (Bashamboo et al., 2018).
How can I learn about a disease gene's fly homolog(s)?
### Human Disease Associations

**FlyBase Human Disease Model Reports**

- **Insulin signaling, regulation of fat storage, Drosophila fat body model**

**Disease Model Summary Ribbon**

- **Anatomical entity**
- **Proliferation**
- **Other**

**Disease Ontology (DO) Annotations**

#### Models Based on Experimental Evidence (1)

<table>
<thead>
<tr>
<th>Allele</th>
<th>Disease</th>
<th>Evidence</th>
<th>References</th>
</tr>
</thead>
</table>
| svp
| model of type 2 diabetes mellitus | CEA | (Musselman et al., 2018) |

#### Potential Models Based on Orthology (0)

<table>
<thead>
<tr>
<th>Human Ortholog</th>
<th>Disease</th>
<th>Evidence</th>
<th>References</th>
</tr>
</thead>
</table>

#### Modifiers Based on Experimental Evidence (1)

<table>
<thead>
<tr>
<th>Allele</th>
<th>Disease</th>
<th>Interaction</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>svp1</td>
<td>ameliorates central nervous system cancer</td>
<td>modeled by N\text{UAS}.tcd</td>
<td>(Zacharioudaki et al., 2016)</td>
</tr>
</tbody>
</table>
### General Information

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Dme\svp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>seven up</td>
</tr>
</tbody>
</table>

### Transcript Expression
- embryonic stage 12 -- 15: embryonic heart cardioblast
- embryonic stage 11 -- 14: dorsal vessel primordium
- embryonic stage 15: embryonic dorsal vessel
- embryonic stage: embryonic/larval corpus allatum

### Polypeptide Expression
- nr2f1 (Dre)
- nr2f1b (Dre)
- nr2f5 (Dre)
- nr2f6a (Dre)
- nr2f6b (Dre)
- unc-55 (Cel)

### Expression Deduced from Reporters
- All anatomical structures
- Circulatory system

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**Expression**

- Check to compare ortholog genes

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</tr>
</tbody>
</table>

**Human Orthologs (via DIOPT v7.1)**

<table>
<thead>
<tr>
<th>Species\Gene Symbol</th>
<th>Score</th>
<th>Best Score</th>
<th>Best Reverse Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsap\NR2F2</td>
<td>10 of 15</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hsap\NR2F1</td>
<td>9 of 15</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Location</th>
<th>Phenotype</th>
<th>Phenotype MIM number</th>
<th>Inheritance</th>
<th>Phenotype mapping key</th>
</tr>
</thead>
<tbody>
<tr>
<td>5q15</td>
<td>Bosch-Boonstra-Schaaf optic atrophy syndrome</td>
<td>615722</td>
<td>AD</td>
<td>3</td>
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</tbody>
</table>
### General Information

<table>
<thead>
<tr>
<th>Symbol</th>
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</thead>
<tbody>
<tr>
<td>Name</td>
<td>seven up</td>
</tr>
</tbody>
</table>

### Human Orthologs (via DIOPT v7.1)

<table>
<thead>
<tr>
<th>Homo sapiens (Human) (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Species\Gene Symbol</strong></td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>HsapNR2F2</td>
</tr>
<tr>
<td>HsapNR2F1</td>
</tr>
</tbody>
</table>

### Stocks and Reagents

<table>
<thead>
<tr>
<th>Stocks (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloomington</td>
</tr>
</tbody>
</table>

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

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

Allelic Variants (9 Selected Examples):

<table>
<thead>
<tr>
<th>Number</th>
<th>Phenotype</th>
<th>Mutation</th>
<th>SNP</th>
<th>gnomAD</th>
<th>ClinVar</th>
</tr>
</thead>
<tbody>
<tr>
<td>.0001</td>
<td>CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4</td>
<td>NR2F2, SER341TYR</td>
<td>rs587777371</td>
<td>-</td>
<td>RCV00116199...</td>
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<tr>
<td>.0002</td>
<td>CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4</td>
<td>NR2F2, ASN205ILE</td>
<td>rs587777372</td>
<td>-</td>
<td>RCV00116200</td>
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<tr>
<td>.0003</td>
<td>CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4</td>
<td>NR2F2, 3-BP DUP, GLN75</td>
<td>rs780808943</td>
<td>-</td>
<td>RCV00116201</td>
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<tr>
<td>.0004</td>
<td>CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4</td>
<td>NR2F2, IVS2, G-A, +1</td>
<td>rs587777374</td>
<td>-</td>
<td>RCV00116202</td>
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<tr>
<td>.0005</td>
<td>CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 4</td>
<td>NR2F2, 7-BP DEL, NT92</td>
<td>-</td>
<td>-</td>
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<td>.0006</td>
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<td>NR2F2, 1-BP DUP, 856G</td>
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<td>NR2F2, GLY83TER</td>
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<td>-</td>
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<tr>
<td>.0008</td>
<td>46,XX SEX REVERSAL 5</td>
<td>NR2F2, 7-BP DEL, NT97</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>.0009</td>
<td>46,XX SEX REVERSAL 5</td>
<td>NR2F2, 7-BP DEL, NT103</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
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

**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: flybase.org
- OMIM: omim.org
- Alliance of Genome Resources: alliancegenome.org
- UniProt: uniprot.org
- DRSC/TRiP Functional Genomics Resources: fgr.hms.harvard.edu
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.)
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Phani Garapati
Josh Goodman
Sian Gramates
Victoria Jenkins
Aoife Larkin
Ian Longden
TyAnna Lovato
Steven Marygold
Bev Matthews
Alex McLachlan
Gillian Millburn
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Victor Strelets
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Chris Tabone
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Vitor Trovisco
Pinglei Zhou
Mark Zytkovicz

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