

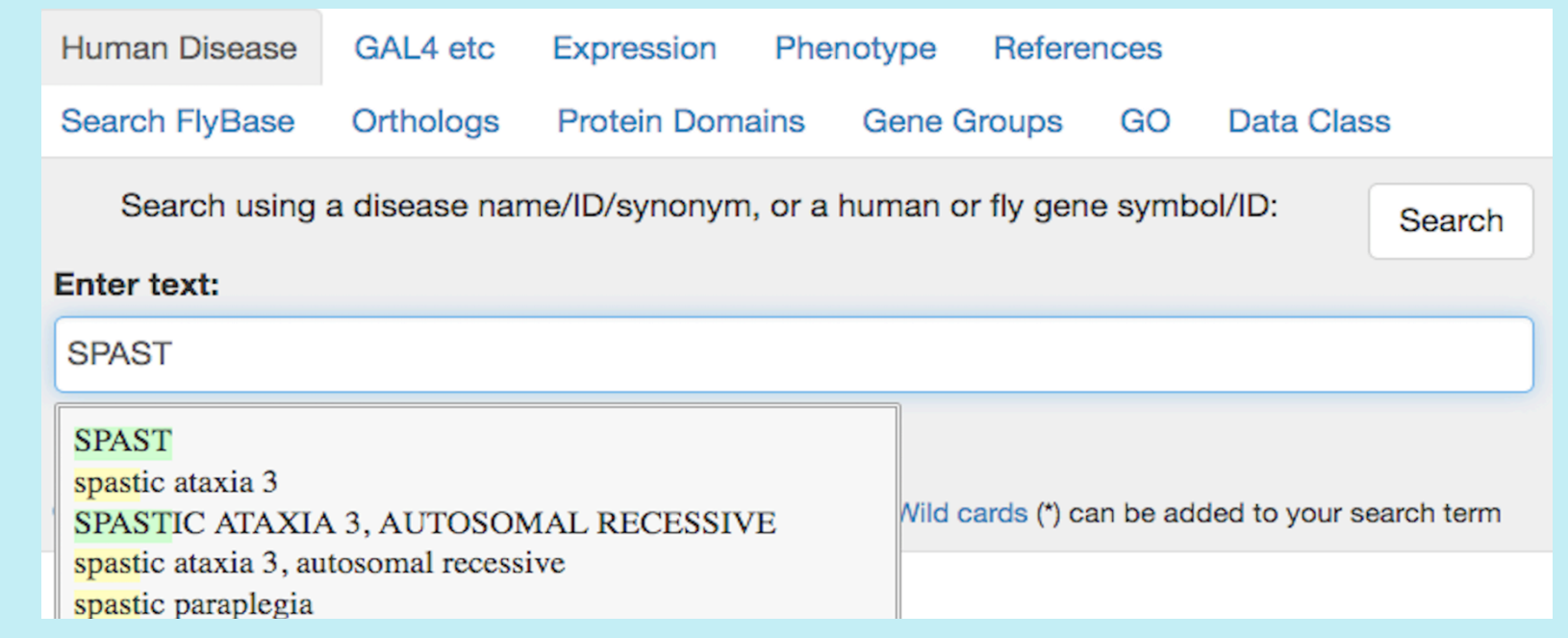


Finding human disease models in FlyBase: You can get there from here

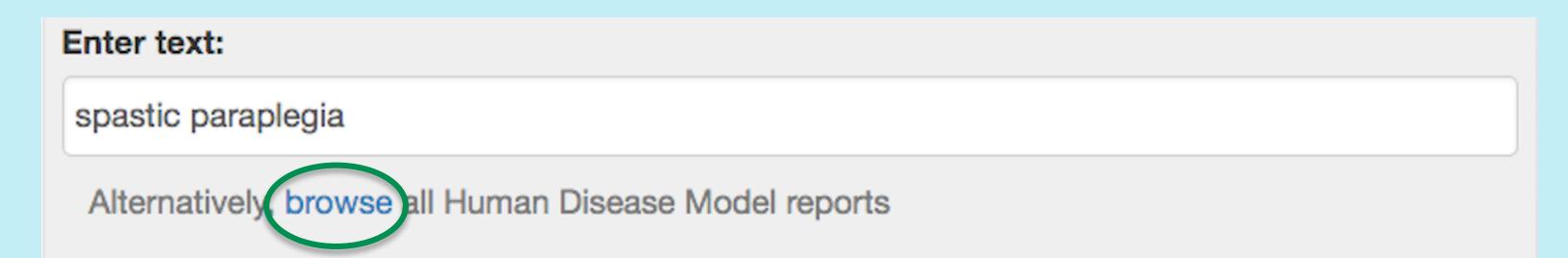
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Many human diseases have been modeled in *Drosophila*, and a large body of literature has accumulated in recent years. FlyBase has been curating disease models using Disease Ontology (DO) annotation and Human Disease Model reports. We provide multiple methods to access disease model data in FlyBase, including a dedicated 'Human Disease' QuickSearch tab, DO term reports, and disease model information embedded in gene and allele reports. We have organized disease model information in a highly interconnected way, so that a user who has landed on any such information can easily navigate to other related information.

The Human Disease QuickSearch Tab



By using the **Human Disease** tab, it is possible to search all FlyBase human disease model data using almost any disease-related search term, including DO terms, Human Disease Models, OMIM phenotypes or genotypes, HGNC symbols, FlyBase genes or alleles, or ID numbers for any of these terms. Autocomplete is enabled for all of these search options; as shown in the example above, the string "SPAST" simultaneously triggers auto-completion of gene symbols, allele symbols, OMIM diseases terms, DO terms, and Human Disease Model names.

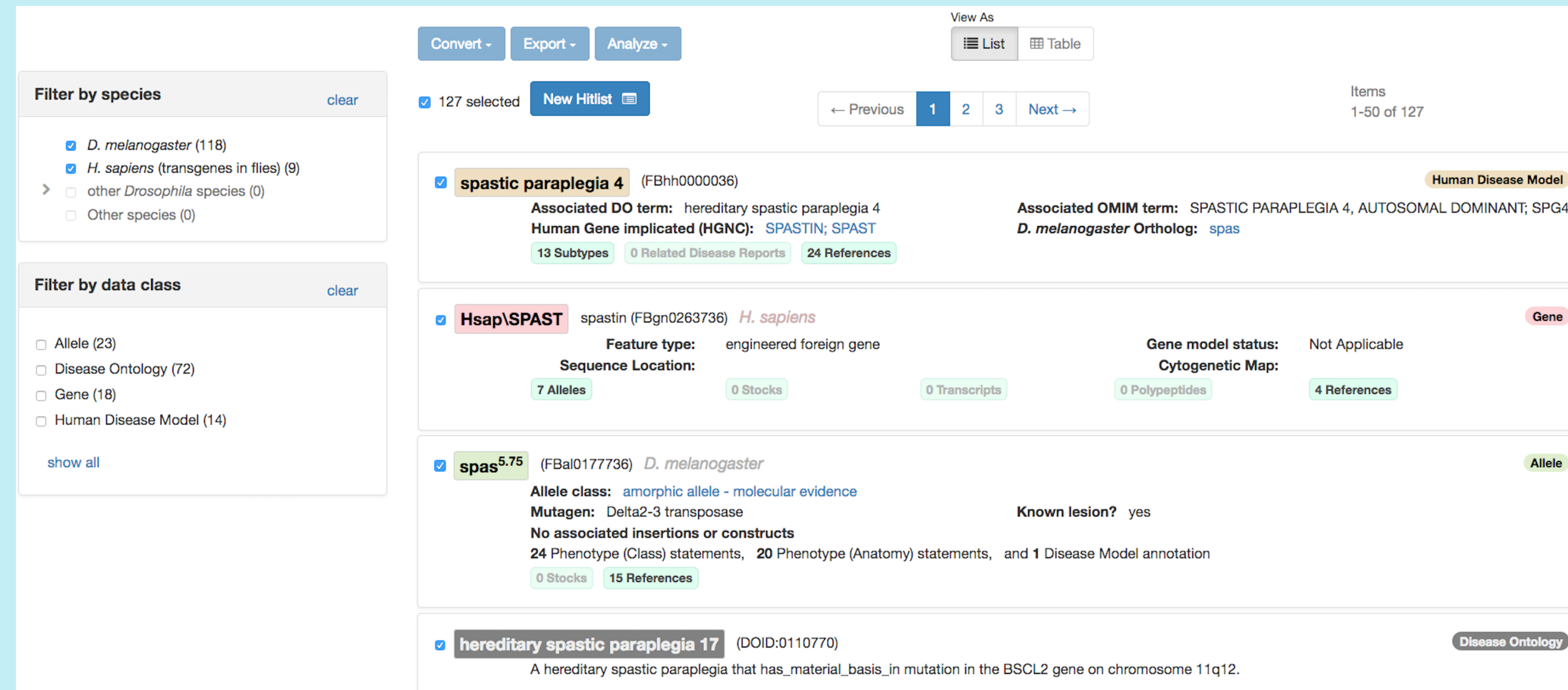


The **Human Disease** tab also includes a link to a browsable index of all Human Disease Model reports; many disease model reports are listed redundantly in the index, allowing a user to browse to a disease from multiple points. Diseases may be listed as a specific subtype of a disease, by mechanistic cause, by symptomatic group, or as part of a major disease classification.

FlyBase Human Disease Model Report Index

- 3-methylglutaconic aciduria
- acute myeloid leukemia
 - acute myeloid leukemia, MLL-AF fusions
 - acute myeloid leukemia, NUP98-HOX9A fusion
 - acute myeloid leukemia, RUNX1-RUNX1T1 fusion
- acyl-CoA dehydrogenase, medium chain, deficiency of
- adrenoleukodystrophy (peroxylated), ACSBG-related
- advanced sleep phase syndrome
 - familial advanced sleep phase syndrome 2
- age-dependent ectopic fat accumulation, HDAC6-related
- Alexander disease

Human Disease Hit-lists



The Human Disease hit-list features four classes of data: Human Disease Models, Disease Ontology terms, genes, and alleles. This hit-list resulted from the search "spastic paraplegia", which includes the hits the Human Disease Model *spastic paraplegia 4*, the gene *Hsap/SPAST* associated with that model, the allele *spas^{5,7}*, and the DO term *hereditary spastic paraplegia 17*.

Like all FlyBase faceted hit-lists, a user can choose to display a subset of data classes. Filtering the hit-list to a single data class allows you to either convert the results to another data class, export to a file or to another FlyBase tool, analyze the results in a data class specific manner, or display the hit-list as a table.

Name	DO Term	OMIM ID	<i>D. melanoga...</i> gene	Human Genes Implicated (HGNC)	# Subtypes	# of Related Disease Terms	# Refs
spastic paraplegia 4	hereditary spastic paraplegia 4	182601	spas	SPASTIN; SPAST	13	0	24
spastic paraplegia 7	hereditary spastic paraplegia 7	607259	Spg7	SPG7 GENE; SPG7	13	0	4
spastic paraplegia 10	hereditary spastic paraplegia 10	604187	Khc	KINESIN FAMILY MEMBER 5A; KIF5A	13	1	9
spastic paraplegia 12	hereditary spastic paraplegia 12	604805	Rtnl2 Rtnl1	RETICULON 2; RTN2	13	0	9
spastic paraplegia 20	Troyer syndrome	275900	spartin	SPARTIN; SPART	13	0	8

This hit-list, resulting from the search "spastic paraplegia", has been filtered to display only Human Disease Models. The table view for this data class highlights the relationships between Human Disease Models, DO terms, and OMIM phenotypes, and displays the associated human disease gene and its orthologous *Drosophila melanogaster* gene.

Disease Information in Allele and Gene Reports

General Information			
Symbol	Dme\spas ¹⁰⁻¹²	Species	<i>D. melanogaster</i>
Human Disease Model Data			
Disease Ontology			
Models (1)			
Disease	Evidence	References	
model of hereditary spastic paraplegia	inferred from mutant phenotype	(Sherwood et al., 2004)	

Alleles associated with disease models are annotated with Disease Ontology terms. **Allele reports** link to Disease Ontology term reports.

Human Disease Model Data			
FlyBase Human Disease Model Reports			
spastic paraplegia 4			
Alleles Reported to Model Human Disease (Disease Ontology)			
Download	Models Data	Interaction Data	
Models (6)			
Allele	Disease	Evidence	References
spas ¹⁰⁻¹²	model of hereditary spastic paraplegia	inferred from mutant phenotype	(Sherwood et al., 2004)
Interactions (1)			
Allele	Disease	Interaction	References
spas ^{5,7}	model of hereditary spastic paraplegia	is ameliorated by Hsap/SPAST ^{14A} .Venus	(Du et al., 2016)

Gene Reports include a Human Disease Model Data section, which displays Human Disease Model Reports associated with the gene and alleles of the gene annotated with DO terms. From here, a user can navigate to DO term and Human Disease Model reports, and to disease-associated alleles.

Human Orthologs (via DIOPT v7.1)				
Gene name	Score	OMIM	OMIM Phenotype	
SPAST1; spastin	15 of 15	604277	SPASTIC PARAPLEGIA 4, AUTOSOMAL DOMINANT; SPG4	↔
FIGLN1; fidgetin like 1	3 of 15	615383		

This section also includes DIOPT-identified human orthologous genes. A user can navigate from here to HGNC gene reports, and to OMIM genotype and phenotype reports. The icons in the right column indicate whether the human gene has been expressed in flies, and whether it functionally complements mutations in the *Drosophila* gene.

Functional Complementation Data		
Dmel gene	Ortholog showing functional complementation	Supporting References
spas	Hsap/SPAST	(Du et al., 2016)

The Integrated Human Disease Model Report

General Information			
Name	spastic paraplegia 4	FlyBase ID	FBhh0000306
Disease Ontology Term	hereditary spastic paraplegia 4	Parent Disease Ontology Term	hereditary spastic paraplegia
OMIM	SPASTIC PARAPLEGIA 4, AUTOSOMAL DOMINANT; SPG4	Parent Disease Ontology Term	hereditary spastic paraplegia
Overview			
This report describes spastic paraplegia 4 (SPG4), which is a subtype of spastic paraplegia; SPG4 exhibits autosomal dominant inheritance. The human gene implicated in this disease is SPAST (spastin), which encodes an ATP-dependent microtubule severing protein and shares sequence similarity with the N-terminal MT1 (microtubule interacting and trafficking) domain of the protein associated with SPG20. There is a single fly ortholog, spas, for which classical amorphic and loss-of-function alleles, RNAi-targeting constructs, and alleles caused by insertional mutagenesis have been generated.			
Multiple different UAS constructs of the human Hsap/SPAST gene have been introduced into flies, including wild-type and genes carrying mutational lesions implicated in SPG4. Heterologous rescue (functional complementation) of some aspects of the phenotype of a Dme\spas null mutation has been demonstrated, including an increase in survival to adulthood. Variant(s) implicated in human disease tested (as transgenic human gene, SPAST); the C448Y, S44L, P45G, and R431 (term) variant forms of the human gene have been introduced into flies.			

Human Disease Model Reports integrate disease information from many parts of FlyBase. Some, like this one, focus on a single disease, while others are parent reports, describing the general characteristics of groups of related but genetically distinct diseases. We've recently added fly model overview reports that collect methods, fly biology, and reviews pertaining to research in broad classes of diseases, such as hematologic cancer or kidney disease.

Specific Disease Summary: spastic paraplegia 4	
OMIM report	SPASTIC PARAPLEGIA 4, AUTOSOMAL DOMINANT; SPG4
Human gene(s) implicated	SPASTIN; SPAST
Symptoms and phenotypes	See general description of spastic paraplegia above. The age of onset and the severity of symptoms both vary widely in cases of SPG4. (EMM, 2013) 15.08.20
Genetics	SPG4 is the most common form of autosomal dominant HSP accounting for approximately 45% of cases. Affected individuals have slowly progressive muscle weakness and spasticity. In rare cases, some individuals may have a complete form associated with seizures, ataxia, memory impairment, cognitive decline and dementia. Hand tremor and upper limb spasticity have also been reported. Great care must be taken when referring to other publications. (from NCBI, Hereditary Spastic Paraplegia, 2014.09.20)
	SPG4 is inherited as an autosomal dominant. It is caused by mutations in the SPAST (spastin) gene. SPG4 is the most common form of autosomal dominant hereditary SPG, comprising up to 60% of cases. (Beverer et al., 2001; Johnson 1130617); Chape et al., 2006; Johnson 1685548; (from OMIM: 182601; 15.08.20)

The Disease Summary includes background information, drawn primarily from OMIM (Online Mendelian Inheritance in Man) and research papers. This section includes links to OMIM genotype and phenotype reports, as well as to references.

- External links
- Genetics Home Reference (condition): spastic-paraplegia-type-4
 - GeneReviews, NCBI Bookshelf: Spastic Paraplegia 4
 - Genetics Home Reference (gene): SPAST
 - Gene Cards: SPAST
 - NCBI Human-Mouse Disease Connection: SPG4
 - National Organization for Rare Disorders: Hereditary Spastic Paraplegia
 - NCBI MedGen: Spastic paraplegia 4, autosomal dominant (SPG4)
 - NCBI Entrez gene: SPAST; spastin
 - GeneDiff: human gene: SPAST
 - MARRVEL (gene): SPASTIN; SPAST

The Disease Summary also includes a collection of external links to other information resources relevant to the disease or its causative gene.

Related Diseases and Orthology

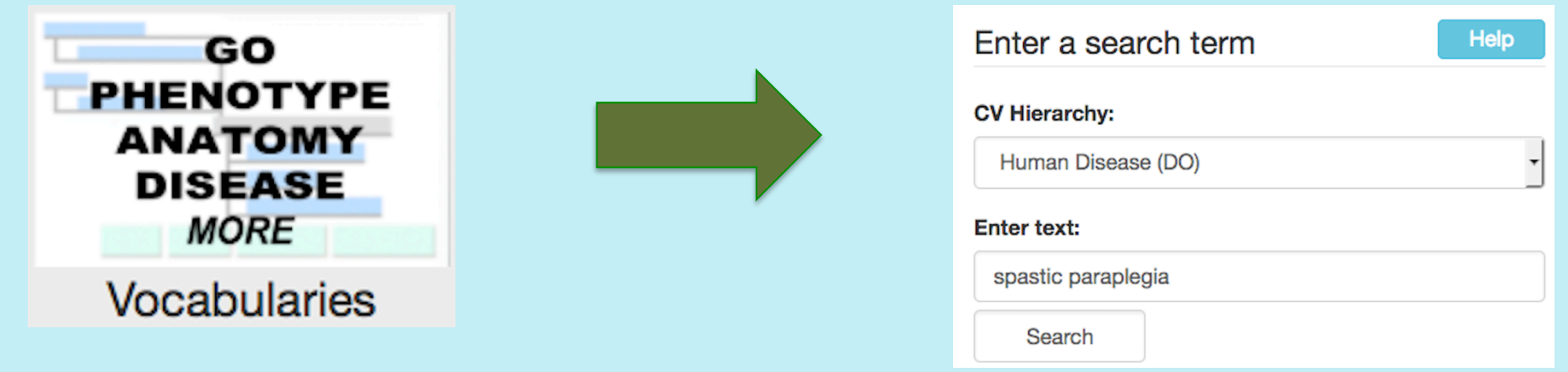
Related Diseases			
Related human health report(s)			
Related Specific Diseases			
OMIM phenotypic series			
Disease	Associated Human gene(s)	Drosophila model	Human transgene in Drosophila
SPG3A	ATL1	spastic paraplegia 3A	
SPG4	SPAST	spastic paraplegia 4	y
SPG7	SPG7	spastic paraplegia 7	
SPG10	KIF5A	spastic paraplegia 10	

The Related Diseases section allows for easy navigation to Disease Model reports for disease subtypes or related diseases, as well as to OMIM phenotype, genotype, and phenotypic series reports.

Ortholog Information	
Human gene(s) in FlyBase	
Hsap/SPAST	
Human gene (HGNC)	
Symbol / Name	
SPAST; spastin	
D. melanogaster ortholog (based on DIOPT)	
Dme\spas (DIOPT, 2013-)	
Comments on ortholog(s)	
One to one; 1 human to 1 Drosophila; additional more distantly related gene(s) in both species.	
Other mammalian ortholog(s) used	
D. melanogaster Gene Information (1)	
Gene Snapshot	
spastin (spas) encodes a member of the AAA ATPase family that assembles into hexamers and severs microtubules along their lengths. The microtubule binding and severing activities of the product of spas are dependent upon tubulin glutamylation levels. Its proposed roles include mitosis, axon transport, synapse formation, dendrite arborization, organelle tubulation, and lipid droplet metabolism. (Date last reviewed: 2018-11-09)	
Comments on ortholog(s)	
Ortholog of human SPAST (1 Drosophila to 1 human); additional more distantly related gene(s) in both species. Dme\spas shares 44% identity and 55% similarity with human SPAST.	

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 include data from elsewhere in FlyBase to compute other parts of the report. Links in this section allow the user to navigate to FlyBase and HGNC (HUGO Gene Nomenclature Committee) gene reports.

Vocabularies: Another Path to Disease Models



The **Vocabularies** tool can be accessed using the button on the FlyBase home page, or from the Tools drop-down menu in the FlyBase toolbar. Select the **Human Disease (DO)** CV Hierarchy and enter a search term; autocomplete is enabled for DO terms.

General Information			
Term	hereditary spastic paraplegia	ID (Ontology)	DOID:2476 (Human Disease)
Definition	"A paraplegia that is characterized by progressive stiffness and contraction (spasticity) in the lower limbs.		
Also Known As	"familial spastic paraplegia"; "French settlement disease"; "hereditary spastic paraparesis" (for all, see Synonyms field below)		
Comment			
Annotations			
Records annotated with this term OR any of its CHILDREN TERMS			
Genes	Human Diseases	Alleles	
22	14	36	
Results list data from multiple species. Please use QueryBuilder to retrieve species-specific data.			
Exact full annotation statements including this term, and relevant records			
Spanning Tree (Parents/Children)			
<ul style="list-style-type: none"> hereditary spastic paraplegia 72 rec. <ul style="list-style-type: none"> hereditary spastic paraplegia 5 hereditary spastic paraplegia 3A 2 rec. hereditary spastic paraplegia 4 2 rec. hereditary spastic paraplegia 3A hereditary spastic paraplegia 3A 2 rec. hereditary spastic paraplegia 4 4 rec. hereditary spastic paraplegia 5A 			

The Disease Ontology term report provides further access to disease model data. The spanning tree allows the user to browse the DO hierarchy, which displays both less specific parental disease categories, and more specific child disease terms. The buttons above the spanning tree lead to hit-lists of genes associated with, Human Disease Model Reports linked to, and alleles annotated with the DO term or its children. The hit-list below includes alleles annotated with the DO term "hereditary spastic paraplegia", or one of its children.

Allele Results					
Symbol	Class	Inserted Elements	# Stocks	Mutagens	Known Lesion?
AriBIP ^{1K109154}			1	in vitro construct	yes
spas ^{5,7} RNA.UAS			0	in vitro construct	yes
futsch ^{EP1419}		P[EP]futsch ^{EP1419}	1	P-element activity	yes

Alleles and Reagents

Alleles Reported to Model Human Disease (Disease Ontology) (13 alleles)			
spas			
Models (6)			
Allele	Disease	Evidence	References
spas ¹⁰⁻¹²	model of hereditary spastic paraplegia	inferred from mutant phenotype	(Sherwood et al., 2004)
spas ¹⁷⁻⁷	model of hereditary spastic paraplegia	inferred from mutant phenotype	(Sherwood et al., 2004)
Interactions (1)			
Hsap/SPAST			
Models (5)			
Allele	Disease	Evidence	References
Hsap/SPAST ¹³⁸⁸ .UAS.Venus	model of hereditary spastic paraplegia	in combination with spas ¹⁰⁻¹²	(Du et al., 2016)
Hsap/SPAST ¹³⁸⁸ .UAS.Venus	model of hereditary spastic paraplegia	in combination with Hsap/SPAST ^{14A} .UAS.Tamoxifen-GFP, spas ^{5,7}	(Baxter et al., 2014)
Hsap/SPAST ^{14C} .UAS.Tamoxifen-GFP	model of hereditary spastic paraplegia	in combination with Hsap/SPAST ¹³⁸⁸ .UAS.Venus, spas ^{5,7}	(Baxter et al., 2014)

The Human Disease Model Report displays DO annotations of alleles of both the transgenically expressed human gene, and orthologous *Drosophila* genes. Links allow the user to navigate to allele reports and DO term reports.

Genetic Tools, Stocks and Reagents			
Sources of Stocks			
Contact lab of origin for a reagent not available from a public stock center.			
Bloomington Stock Center			
Disease Page			
Selected mammalian transgenes			
Allele	Transgene	Publicly Available Stocks	
Hsap/SPAST ¹³⁸⁸ .UAS.Venus	P[UAS-spas ^{5,7} YFP]		
Hsap/SPAST ¹³⁸⁸ .UAS.Venus	P[UAS-SPAST ^{R388} .YFP]		
Selected Drosophila transgenes			
Allele	Transgene	Publicly Available Stocks	
spas ¹⁰⁻¹² .UAS	P[UAS-spas ^{5,7} YFP]		
spas ⁴ RTR.UAS.tgMVC	P[UAS-spas-tync ^{K467R}]		
RNAi constructs available			
Allele	Transgene	Publicly Available Stocks	
spas ^{5,7} RNA.UAS	P[UAS-spas RNAi]		
spas ^{5,7} RNA	P[G0263]	w ¹¹¹⁸ ; P[G0263];v31110	
Selected Drosophila classical alleles			
Allele	Allele class	Mutagen	Publicly Available Stocks
spas ¹⁷⁻⁷		Delta2-3 transposase	
Selected Drosophila classical alleles			
Allele	Allele class	Mutagen	Publicly Available Stocks
spas ^{5,7}		Delta2-3 transposase	

The Genetic Tools, Stocks and Reagents section includes links to allele and transgenic construct reports, to the relevant BDC disease page, and to stock reports for those available from a public stock repository.

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