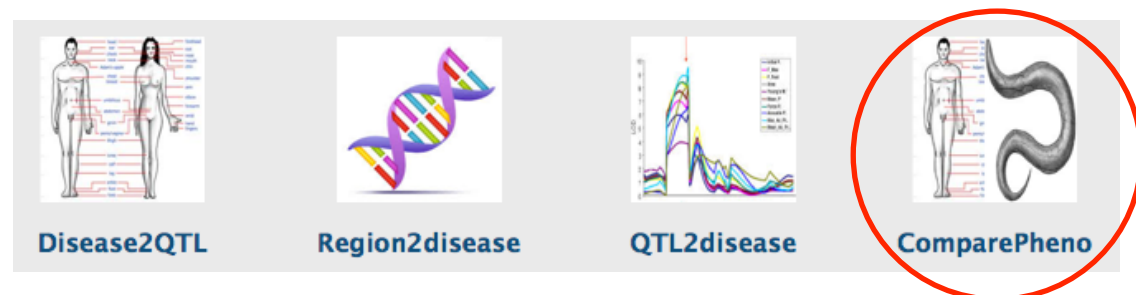


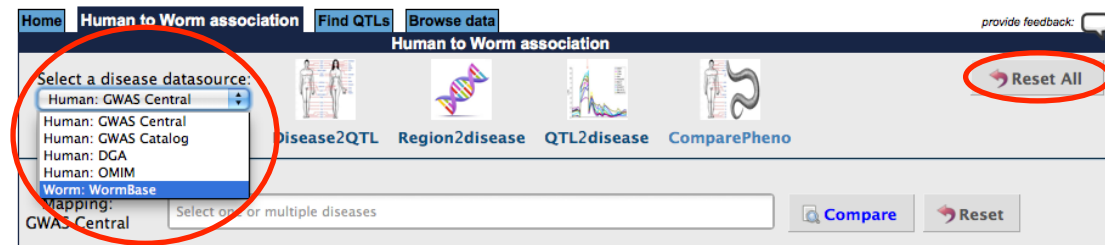
## Supplementary Tutorial S1. Linking disease to worm phenotype from McGary et al. (1)

Go to <http://www.wormqtl-hd.org> to follow this tutorial.

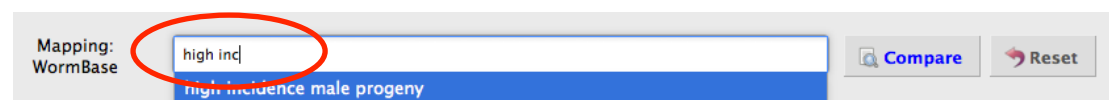
On the home page, select the **ComparePheno** tool.



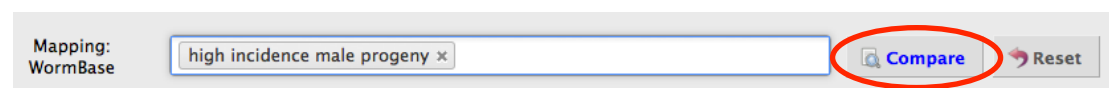
Use **Reset All** for a fresh start. Then select **WormBase** as the data source.



Type in the **search box** to find diseases, for example, “high incidence male progeny”. Click on terms to select them, or press Enter to select the currently highlighted option.



You may continue to add more phenotypes/diseases. This is useful when annotations are fragmented. For example, there are 10 terms for diseases related to breast- and ovarian cancer in OMIM. When you are done, click **Compare** to start the analysis.



After the analysis is completed, you are presented with the results. Here you can explore and interpret all matches. You can sort, filter, and view details about overlap and orthology.

Overlap test for **high incidence male progeny [WormBase]** [Click for details](#)

Show 10 entries

Vs. phenotype	From source	overlap	details	P-value	Single test thres.	Filter: <input type="text"/>
high incidence male progeny	WormBase	63	<a href="#">63 vs 63</a>	1.43E-140	0.05	Single
meiosis var					3.32E-5	YES YES
null X game					3.32E-5	YES YES
organism X ray response variant	WormBase	6	<a href="#">63 vs 8</a>	2.99E-10	0.05	3.32E-5 YES YES
DNA recombination variant	WormBase	5	<a href="#">63 vs 5</a>	7.65E-10	0.05	3.32E-5 YES YES
intestinal fluorescence increased	WormBase	5	<a href="#">63 vs 7</a>		3.32E-5	YES YES
male fertility variant	WormBase	5	<a href="#">63 vs 7</a>	1.57E-8	0.05	3.32E-5 YES YES
G tract instability	WormBase	6	<a href="#">63 vs 13</a>	1.72E-8	0.05	3.32E-5 YES YES
organism UV hypersensitive			<a href="#">63 vs 50</a>	4.39E-8	0.05	3.32E-5 YES YES
organism hypersensitive X ray irradiation	WormBase	4	<a href="#">63 vs 5</a>	2.6E-7	0.05	3.32E-5 YES YES

Showing 1 to 10 of 455 entries [Previous](#) [Next](#)

You can filter on hits related to breast cancer. Type any part of a term in the **Filter box**, e.g. 'breast'.

Show 10 entries

Filter:

Vs. phenotype	From source	Genes overlap	Overlap details	P-value	Single test thres.	Bonferroni thres.	Single test signif.?	Bonferroni signif.?
{Breast cancer, susceptibility to}, 114480 (3)	OMIM	2	<a href="#">63 vs 4</a>	1.39E-3	0.05	5.29E-5	YES	NO
{Breast and colorectal cancer, susceptibility to} (3)	OMIM	1	<a href="#">63 vs 2</a>	3.08E-2	0.05	5.29E-5	YES	NO
malignant neoplasm of breast	DGA	2	<a href="#">63 vs 23</a>	4.86E-2	0.05	2.48E-4	YES	NO
hereditary breast ovarian cancer	DGA	1	<a href="#">63 vs 6</a>	8.96E-2	0.05	2.48E-4	NO	NO
Breast cancer	GWAS Catalog	1	<a href="#">63 vs 9</a>	1.31E-1	0.05	1.02E-4	NO	NO
Breast size	GWAS Catalog	1	<a href="#">63 vs 14</a>	1.97E-1	0.05	1.02E-4	NO	NO

You can look in detail at the overlap by clicking on the **Overlap details** for this phenotype.

{Breast cancer, susceptibility to}, 114480 (3)	OMIM	2	<a href="#">63 vs 4</a>	1.39E-3	0.05	5.29E-5	YES	NO
--	------	---	-------------------------	---------	------	---------	-----	----

This shows the genes associated with your input diseases or phenotypes, the genes associated with the disease or phenotype it is tested against, and any genes shared between the two groups. When matching human to worm (or *vice versa*), the corresponding orthologs are shown.

Input genes: WBGene00016151, WBGene00013143, WBGene00008921, WBGene00008878, WBGene00012370, WBGene00001863, WBGene00006963, WBGene00001865, WBGene00000537, WBGene00011142, WBGene00000591, WBGene00006406, WBGene00019004, WBGene00004296, WBGene00004297, WBGene00000862, WBGene00003405, WBGene00006976, WBGene00012209, WBGene00002219, WBGene00018357, WBGene00015915, WBGene00000499, WBGene00000939, WBGene00006414, 38 more...

(Breast cancer, susceptibility to), 114480 (3) genes: PHB, CHEK2, CDS1, BARD1

Overlapping genes: WBGene00000499 (ortholog: CHEK2), WBGene00000265 (ortholog: BARD1)

OK

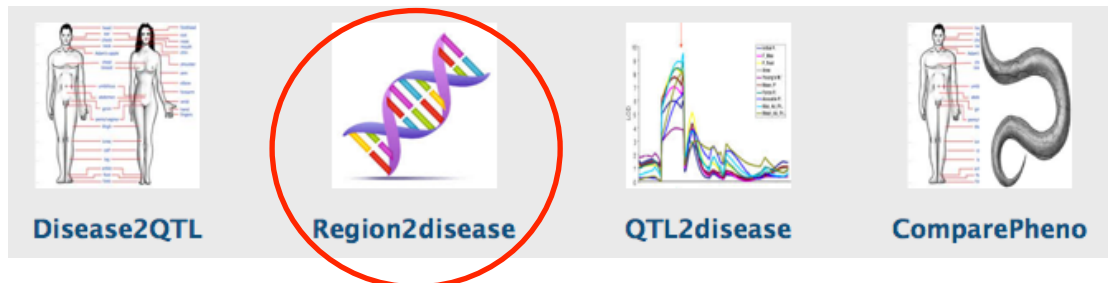
## REFERENCES

1. McGary, K.L., Park, T.J., Woods, J.O., Cha, H.J., Wallingford, J.B. and Marcotte, E.M. (2010) Systematic discovery of nonobvious human disease models through orthologous phenotypes. *Proc Natl Acad Sci U S A*, 107, 6544-6549.

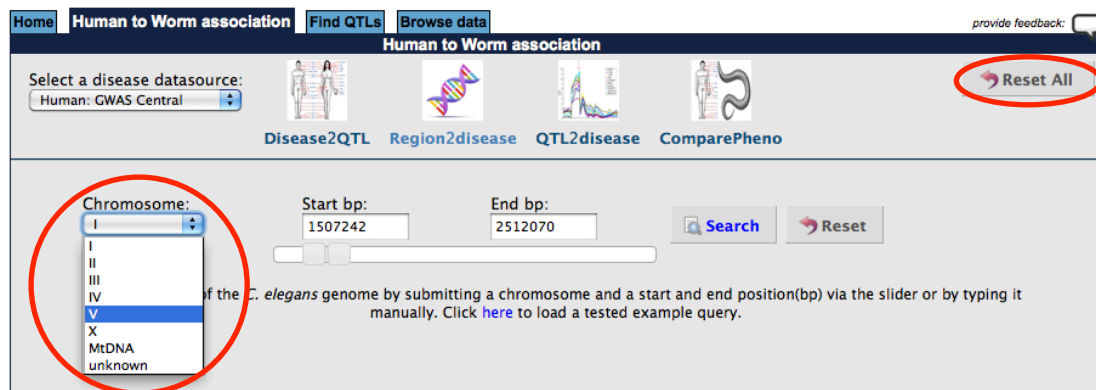
## Supplementary Tutorial S2. Worm eQTL hotspot from two temperature expression data from Li et al. (1)

Go to <http://www.wormqtl-hd.org> to follow this tutorial.

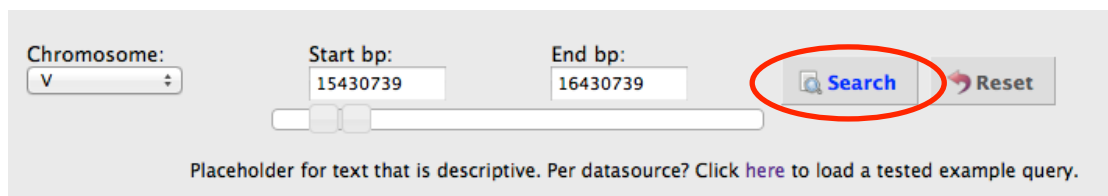
On the home page, select the **Region2disease** tool.



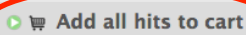
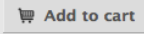
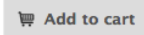
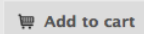
Use **Reset All** for a fresh start. Then select **Chromosome V** as the starting point.



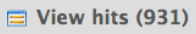

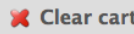
By using the sliders or typing manually, you can select a region on this chromosome. Fill in **15430739** as start bp, and **16430739** as end bp. Click **Search** to query this region.



There are apparently 931 probes located in this region. You can add individual probes to the Shopping Cart, or all at once. Click **Add all hits to cart** to add them all.

Found 931 hits.			
			
Show <input type="text" value="10"/> entries		Filter: <input type="text"/>	
Probe name	Orthology	Disease associations	
 <b>WSU12232</b>	Ce: <a href="#">W8Gene00001054</a> Hs: <a href="#">DPP10</a>	GWAS Catalog: Obesity-related traits	
 <b>AGIUSA13391</b>	Ce: <a href="#">W8Gene00001054</a> Hs: <a href="#">DPP10</a>	GWAS Catalog: Obesity-related traits	
 <b>WSU18477</b>	Ce: <a href="#">W8Gene00001054</a> Hs: <a href="#">DPP10</a>	GWAS Catalog: Obesity-related traits	

You can find phenologs for this group of probes (actually: the genes for which these probes are reporting) by clicking on **Disease enrichment**.

 View hits (931)  View cart (931)  Plot QTLs  **Disease enrichment**  Clear cart

Found 931 hits.

All 931 hits are currently in your cart.

After the analysis is completed, you are presented with the results. Here you can explore and interpret all matches. You can sort, filter, and view details about overlap and orthology.

Overlap test for [chrV:15430739-16430739 \[Region search\]](#) [Click for details](#)

Show 10 entries Filter:

Vs. phenotype	From source	overlap	Overlap details	P-value	Single test thres.	E	Filter on keywords
Response to antineoplastic agents	CWAS Catalog	1	<a href="#">10 vs 2</a>	4.92E-3	0.05	1	
sister chromatid segregation defective early emb	WormBase	2	<a href="#">10 vs 50</a>	6.27E-3	0.05	3.32E-5	YES NO
Palmitic acid (16:0) plasma levels	CWAS Catalog	1	<a href="#">10 vs 5</a>	1.23E-2	0.05	1.02E-4	YES NO
thermotolerance increased	WormBase	1	<a href="#">10 vs 6</a>			3.32E-5	YES NO
RAB-11 recycling endosome localization variant	WormBase	2	<a href="#">10 vs 112</a>	2.93E-2	0.05	3.32E-5	YES NO
transposon silencing variant	WormBase	1	<a href="#">10 vs 19</a>	4.59E-2	0.05	3.32E-5	YES NO
lysosome-related organelle morphology variant	WormBase	2	<a href="#">10 vs 176</a>	6.68E-2	0.05	3.32E-5	NO NO
RAB-11 recycling endosome morphology variant	WormBase	2	<a href="#">10 vs 189</a>	7.58E-2	0.05	3.32E-5	NO NO
passage through meiosis defective early emb	WormBase	1	<a href="#">10 vs 38</a>	8.98E-2	0.05	3.32E-5	NO NO
transgene expression reduced	WormBase	2	<a href="#">10 vs 212</a>	9.26E-2	0.05	3.32E-5	NO NO

Showing 1 to 10 of 54 entries Previous Next

To view details for the match with “Response to antineoplastic agents”, click on the **10 vs 2** link in the **Overlap details** column.

Input genes: WBGene00003079, WBGene00012348, WBGene00010214, WBGene00004452, WBGene00001792, WBGene00001054, WBGene00001876, WBGene00001875, WBGene00001813, WBGene00008996

Response to antineoplastic agents genes: PPP2R5E, ACOX3

Overlapping genes: WBGene00012348 (ortholog: PPP2R5E)

Gene	Overlap details	P-value	Single test thres.	Filter
Response to antineoplastic agents	1	4.92E-3	0.05	1.02E-4 YES NO

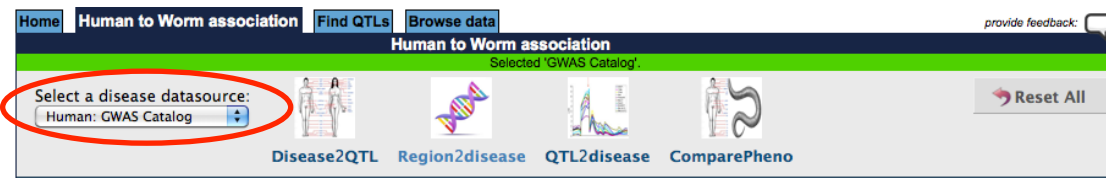
OK

To see what QTLs are related to “Response to antineoplastic agents” from GWAS Catalog, click the **Disease2QTL** tool in the top menu.

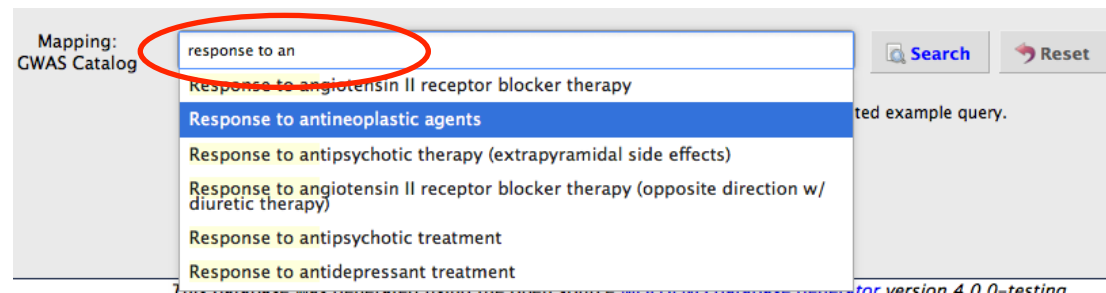
Select a disease datasource Worm: WormBase

[Disease2QTL](#) [Region2disease](#) [QTL2disease](#) [ComparePheno](#) [Reset All](#)

Select **GWAS Catalog** as the data source.



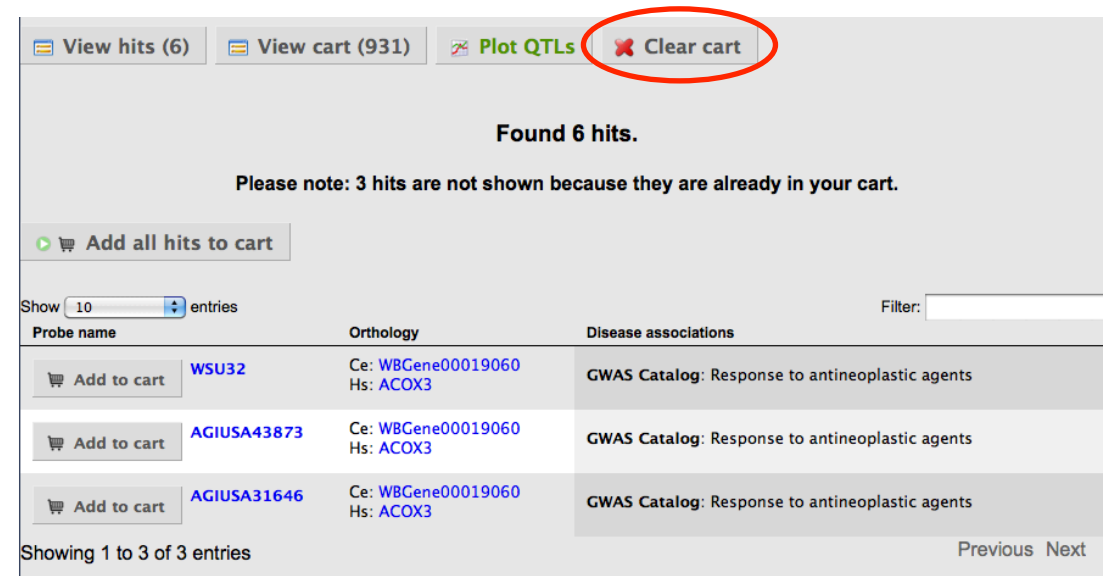
Find and select **"Response to antineoplastic agents"**.



Click **Search**.

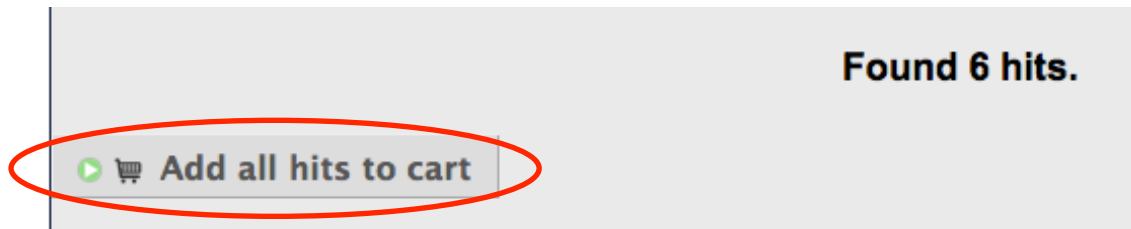


Notice that there are 6 hits, but 3 were already in your Shopping Cart from using the Region2disease tool earlier. You are not allowed to plot QTLs for as many as 900+ probes currently in your cart. Click on **Clear cart**.



Probe name	Orthology	Disease associations
<a href="#">WSU32</a>	Ce: <a href="#">WBGene00019060</a> Hs: <a href="#">ACOX3</a>	GWAS Catalog: Response to antineoplastic agents
<a href="#">AGIUSA43873</a>	Ce: <a href="#">WBGene00019060</a> Hs: <a href="#">ACOX3</a>	GWAS Catalog: Response to antineoplastic agents
<a href="#">AGIUSA31646</a>	Ce: <a href="#">WBGene00019060</a> Hs: <a href="#">ACOX3</a>	GWAS Catalog: Response to antineoplastic agents

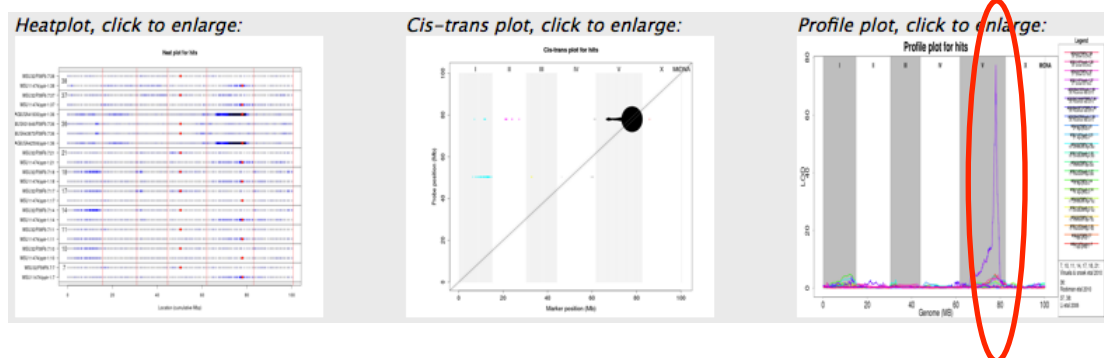
Click on **Add all hits to cart**. The 6 probes reporting for the worm orthologs of *PPP2R5E* (WBGene00012348) and *ACOX3* (WBGene00019060) are added to the cart.



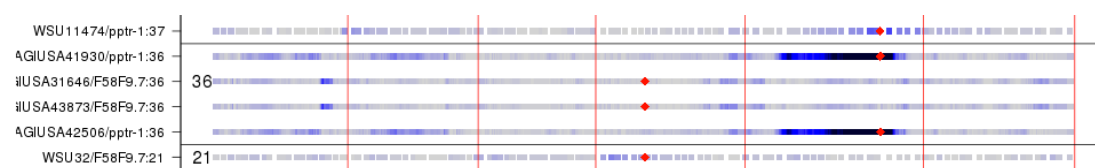
Now you can visualize any QTL data for these probes in the database by clicking on **Plot QTLs**.



You will notice a highly significant *cis*-eQTL that can be investigated further.



For example, open a detailed view of this eQTL by clicking the **Heatplot**.



## REFERENCES

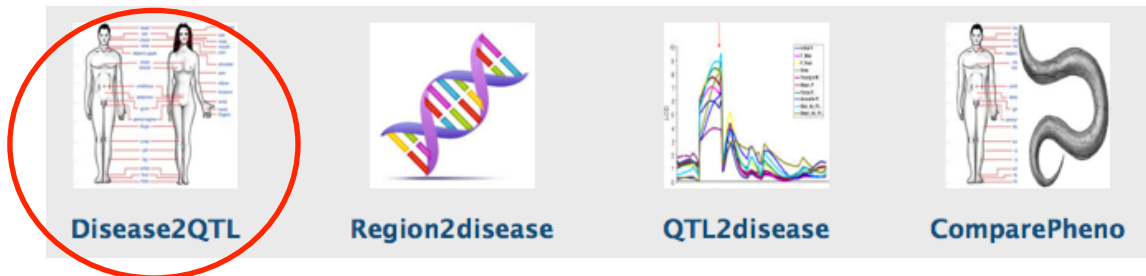
1. Li, Y., Alvarez, O.A., Gutteling, E.W., Tijsterman, M., Fu, J., Riksen, J.A.G., Hazendonk, E., Prins, P., Plasterk, R.H.A., Jansen, R.C. *et al.* (2006) Mapping Determinants of Gene Expression Plasticity by Genetical Genomics in *C. elegans*. *PLoS Genet*, **2**.



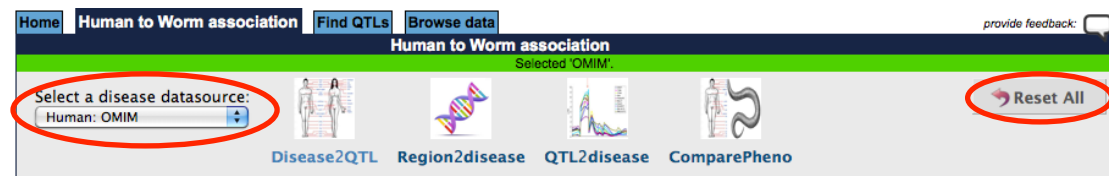
### Supplementary Tutorial S3. Osmotic stress as a model for Bardet-Biedl syndrome from Rodriguez et al. (1)

Go to <http://www.wormqtl-hd.org> to follow this tutorial.

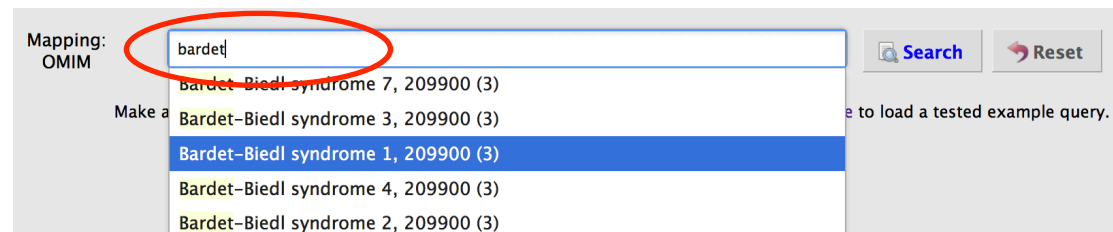
On the home page, select the **Disease2QTL** tool.



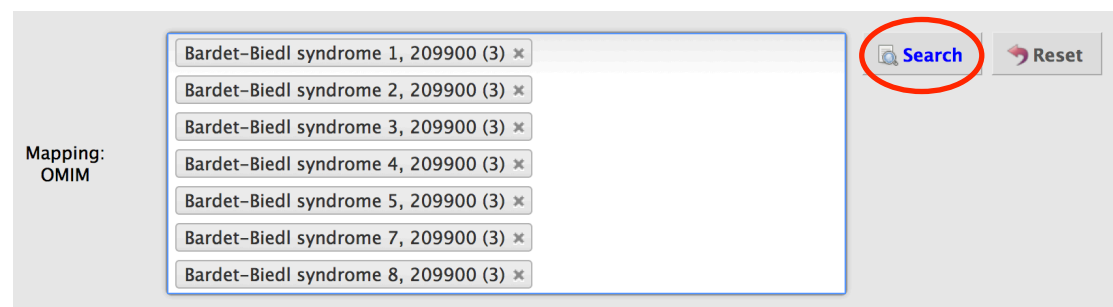
Use **Reset All** for a fresh start. Then select **OMIM** as the data source.



Type in the **search** box to find diseases, for example, “Bardet-Biedl syndrome”. Click on terms to select them, or press Enter to select the currently highlighted option.



Select all terms related to “Bardet-Biedl syndrome”, and click **Search**.



There are 18 probes related to this disease. You can add individual probes to the Shopping Cart, or all at once. Click **Add all hits to cart** to add them all.

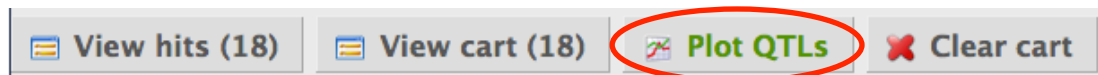
**Found 18 hits.**

**Add all hits to cart**

Show  entries
Filter:

Probe name	Orthology	Disease associations
<div style="display: flex; align-items: center; margin-bottom: 5px;"> <div style="border: 1px solid gray; padding: 2px 5px; margin-right: 5px;">  Add to cart         </div> <div> <b>AGIUSA29166</b> </div> </div>	Ce: <a href="#">WBGene00000241</a> Hs: <a href="#">BBS1</a>	<b>GWAS Catalog:</b> Bipolar disorder <b>WormBase:</b> associative learning variant, amphid phasmid morphology variant, cilia morphology variant, Variant, lethal, postembryonic development variant, organism morphology variant, embryonic lethal, maternal sterile <b>OMIM:</b> Bardet-Biedl syndrome 1, 209900 (3)
<div style="display: flex; align-items: center; margin-bottom: 5px;"> <div style="border: 1px solid gray; padding: 2px 5px; margin-right: 5px;">  Add to cart         </div> <div> <b>AGIUSA36441</b> </div> </div>	Ce: <a href="#">WBGene00000241</a> Hs: <a href="#">BBS1</a>	<b>GWAS Catalog:</b> Bipolar disorder <b>WormBase:</b> associative learning variant, amphid phasmid morphology variant, cilia morphology variant, Variant, lethal, postembryonic development variant, organism morphology variant, embryonic lethal, maternal sterile <b>OMIM:</b> Bardet-Biedl syndrome 1, 209900 (3)

To visualize the QTLs for these probes across all datasets, click on **Plot QTLs**.



You will notice two locations where significant QTLs seem to be located.

**Results for my selected hits:**

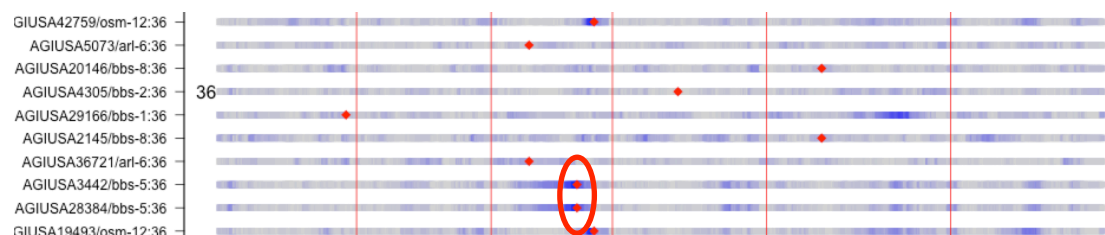
(get a [permanent link to these results](#))

*Heatplot, click to enlarge:*

*Cis-trans plot, click to enlarge:*

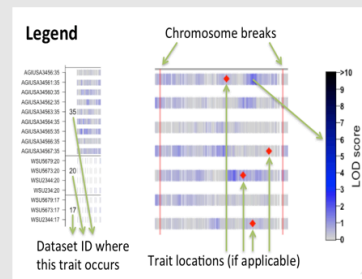
*Profile plot, click to enlarge:*

Click the **Heatplot** to get a more detailed view. Here you see the probe names and dataset identifiers. Notice the cis-eQTL for *bbs-5* on chromosome III.



You can even download the **source data** used to create these plots if you wish to know every exact LOD score, marker- and probe locations down to the basepair.

**Legend, click to enlarge:**

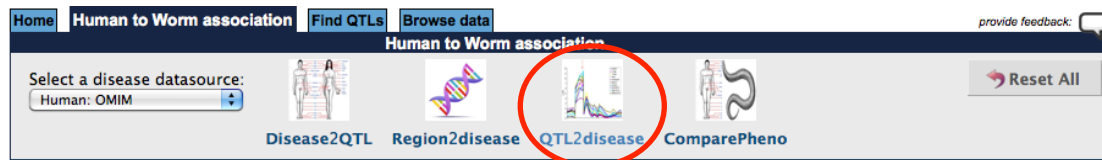


**More downloads:**

Get the [Cytoscape network](#) for this plot. ([how-to import](#))  
 Get the [Cytoscape nodes](#) for this plot. ([how-to import](#))  
 Note: includes **significant results only**. (LOD > 3.5)  
 Save both files. Import network (has LOD scores), then node attributes (chrom, bploc, dataset). [Example visualization](#)

Get the generated [source data](#) for these plots.  
 Get the generated [multiplot plot R script](#).  
 Get the generated [cistrans R plot script](#).  
 Get the generated [profile R plot script](#).

The *cis*-eQTL is reported by probe AGIUSA3442 in the rock\_qtl (Rockman et al.) dataset. You can investigate this QTL region further by using the **QTL2disease** tool, selected from the top menu.



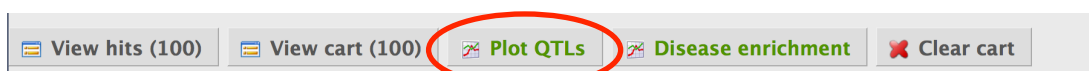
Here, choose dataset **rock\_qtl**, probe **AGIUSA3442**, and threshold **5**. Click on **Search**.

The screenshot shows the search form in the QTL2disease tool. The 'Dataset' dropdown is set to 'rock\_qtl', the 'Probe/trait' dropdown is set to 'AGIUSA3442', and the 'LOD threshold' is set to '5'. The 'Search' button is highlighted with a red circle. A 'Reset' button is also visible.

Around the peak marker of the detected QTL, the 50 closest probes on each side are selected, resulting in a total of 100 probes. Click **Add all hits to cart** to select them all.

<a href="#">Add all hits to cart</a>		
Show 10 entries	Filter:	
Probe name	Orthology	Disease associations
<a href="#">Add to cart</a> AGIUSA25481	Ce: <a href="#">WBGene00011563</a> Hs: <a href="#">JMJD4</a>	<b>GWAS Catalog:</b> Height <b>WormBase:</b> sterile, lethal, growth variant, life span variant, vulva development variant, embryonic lethal, general pace of development defective early emb
<a href="#">Add to cart</a> AGIUSA33092	Ce: <a href="#">WBGene00011563</a> Hs: <a href="#">JMJD4</a>	<b>GWAS Catalog:</b> Height <b>WormBase:</b> sterile, lethal, growth variant, life span variant, vulva development variant, embryonic lethal, general pace of development defective early emb

With all probes now in the shopping cart, you can visualize their QTLs by clicking **Plot QTLs**.

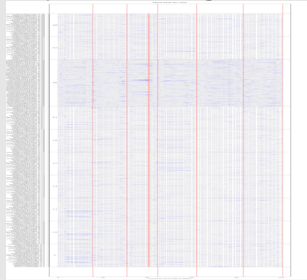


You will find back the original QTL for *bbs-5* on chromosome III, and also discover other QTLs reported by probes located underneath the QTL peak. In this case, there seem to be QTLs at the selected region on chromosome III, but also at the end of chromosome II.

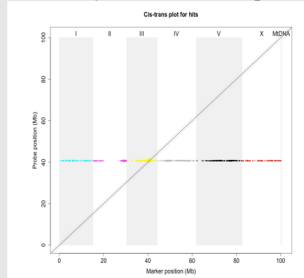
## Results for my selected hits:

(get a [permanent link to these results](#))

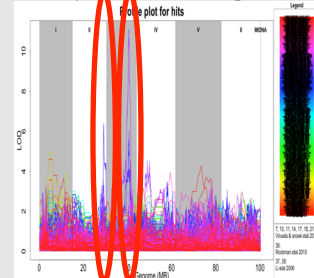
Heatplot, click to enlarge:



Cis-trans plot, click to enlarge:



Profile plot, click to enlarge:



When clicking the **Heatplot** for these QTLs, you will find them back in greater detail. It turns out there is, amongst others, a *cis*-eQTL reported for a gene named *T07C4.10* that can be investigated further.



## REFERENCES

1. Rodriguez, M., Snoek, L.B., De Bono, M. and Kammenga, J.E. (2013) Worms under stress: *C. elegans* stress response and its relevance to complex human disease and aging. *Trends in genetics : TIG*, **29**, 367-374.