

RGD: A Tutorial for Data, Searches and Tools

<http://rgd.mcw.edu>

RGD: A Tutorial for Data, Searches and Tools

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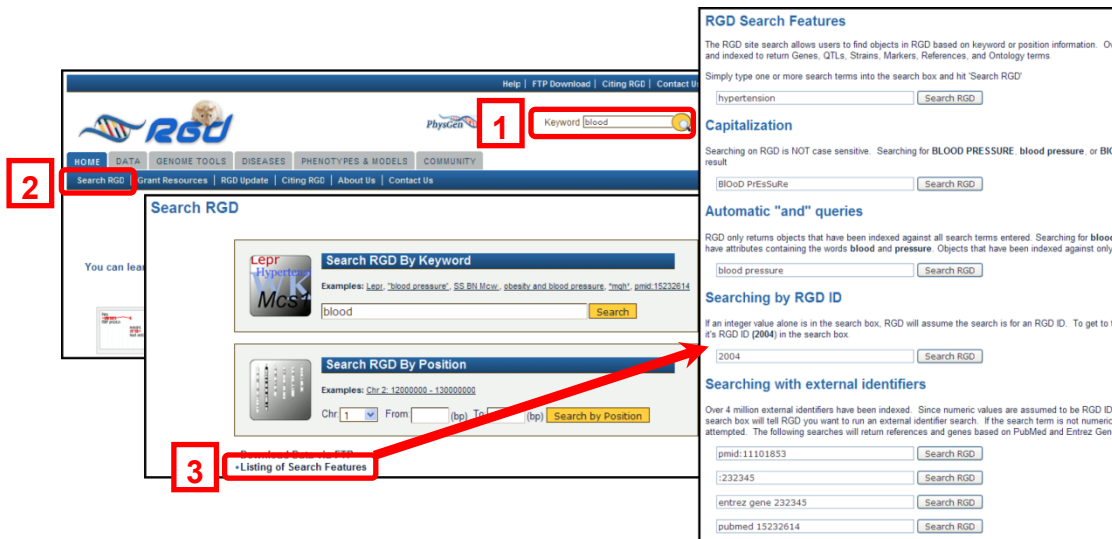
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RGD: A Tutorial for Data, Searches and Tools

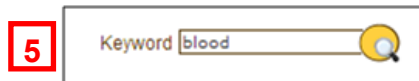
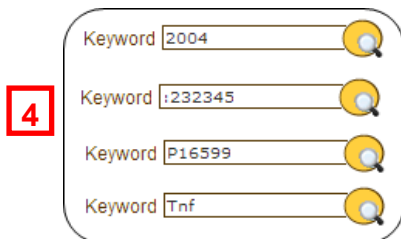
Data and Searches

Search by keyword, external identifier or RGD ID

1. On any RGD web page, e.g. the RGD home page (<http://rgd.mcw.edu>), keyword searches either of the exact term or using a * as a wildcard can be made using the box at the top right corner of the page.



2. RGD's Keyword search can also be accessed by clicking on the "Search RGD" menu item under the "HOME" tab. This will take you to the "Search RGD" page.
3. For detailed information about the RGD Keyword search click the "Listing of Search Features" on the "Search RGD" page.



4. RGD's Keyword search includes searching by RGD ID. Any numeric value entered into these boxes will be searched for as an RGD ID. To search for a numeric external identifier such as an Entrez Gene or PubMed ID, include a colon (:) in front of the ID. If the search term is not numeric, such as a UniProtKB ID, an external identifier search is always attempted.
5. For the purpose of this example, enter the word "blood" in one of the keyword search boxes and click the magnifying glass icon.

RGD Search Result
1425 records found for search term **blood**

GENES
311 Found [View Genes for All Species](#)

Rattus norvegicus	89	View Rat Genes Report
Mus musculus	24	View Mouse Genes Report
Homo sapiens	198	View Human Genes Report

QTLs
478 Found [View QTLs for All Species](#)

Rattus norvegicus	377	View Rat QTLs Report
Mus musculus	24	View Mouse QTLs Report
Homo sapiens	77	View Human QTLs Report

STRAINS
50 Found

Rattus norvegicus	50	View Rat Strains Report
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REFERENCES
586 Found [View References for All Species](#)

Ontologies

Curators at RGD make annotations to genes, QTLs and strains using standardized vocabularies/ontologies. Your search returned annotations to the terms below.

Gene Ontology
vasoconstriction
vasodilation

Result Matrix

	Rat	Mouse	Human
Genes	89	24	198
QTLs	377	24	77
Strains	50	0	0
SSLPs	0	0	0
References	586	0	0

- The Search Result page gives a summary of all of the RGD objects which matched the search term. In addition the search returns all of the ontology terms which matched. To see a list of the genes, QTL and/or strains that are annotated to a particular ontology term, click on the term to go to the Ontology Report page. For more information on the Ontology Report page, see below.
- To see a list of all of the rat genes that matched the search term "blood", click the "View Rat Genes Report" link or the number "89" in the Result Matrix.

Genes search result for *Rattus norvegicus*
[View Results for all Objects and Ontologies](#)

89 records found for search term **blood**

Refine Term:

Assembly: Chr:

Sort By:

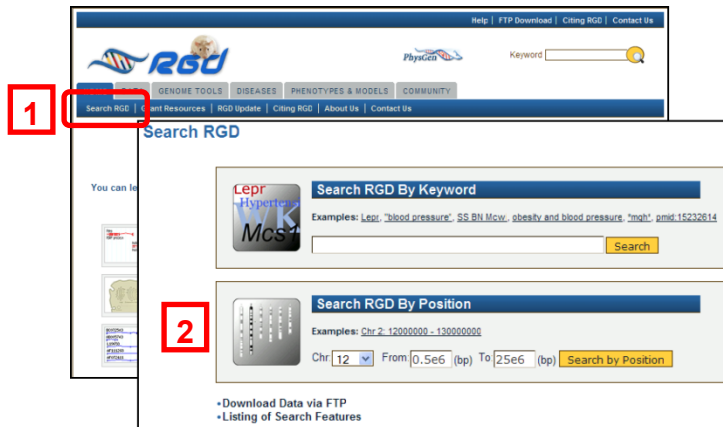
Export This Report To: [CSV](#) [TAB](#) [Printer](#) [Genome Viewer](#)

RGD ID	Symbol	Name	Description	Chr	Start	Stop	Species	Annotations	Match	Type
1359650	Xk	X-linked Kx blood group (McLeod syndrome) homolog	human homolog is a red cell membrane protein whose deficiency causes the McLeod syndrome, a disorder characterized by blood group, neuromuscular and hematopoietic abnormalities	X	25591152	25624913	Rat	10	description, old_gene_name	gene, name
620451	Rhd	Rh blood group, D antigen	blood group gene; produces antigens on the surface of erythrocytes	5	153638642	153672532	Rat	5	description, old_gene_name	gene, name
628609	Abol1	ABO blood group-like 1	histo-blood group protein with A- and B-transferase activities	3	5253078	5270252	Rat	12	description, old_gene_name	gene, name

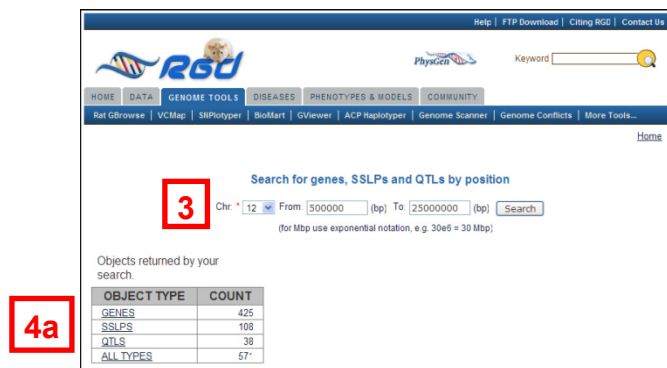
- Information included in the gene result list includes the gene RGD ID, symbol, name, description and chromosomal position as well as the number of ontology annotations associated with that gene.
- The box in the upper right corner of the page shows the current search term and allows the user to refine the search by changing the search term and/or selecting a particular chromosome. The genomic or genetic position information can be changed by using the drop-down box labeled "Assembly" and the results can be sorted by any of the columns simplifying the task of finding the particular result needed.
- Tabs at the top of the results box allow users to easily move between results for rat, mouse, human or all three.
- Results can be exported as CSV or tab-delimited text files, sent to a printer, or viewed in their genomic context using the RGD Genome Viewer. See below for more information on RGD's Genome Viewer.

Search by Position

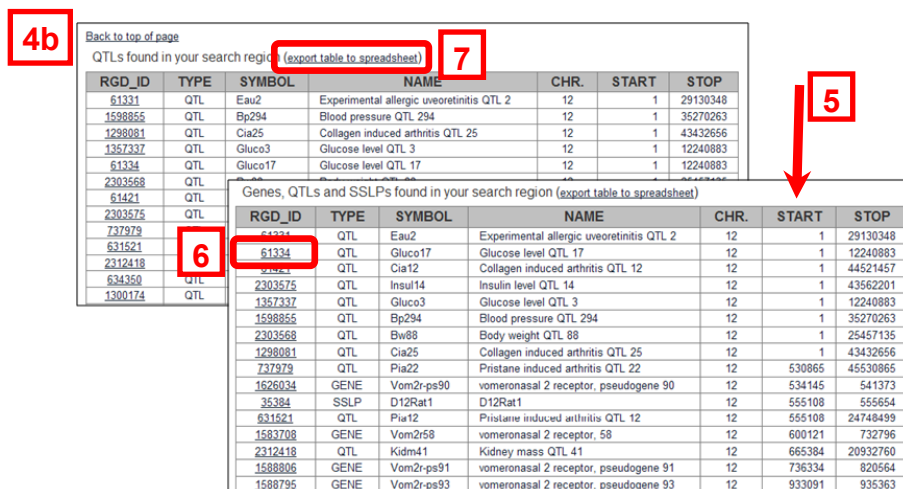
1. On the RGD home page (<http://rgd.mcw.edu/>), under the tab which reads "HOME" click the menu item "Search RGD". This will take you to the "Search RGD" page.



2. In the "Search RGD By Position" box, select chromosome 12 and enter 500000 into the "From:" box and 25000000 into the "To:" box. Note that for simplicity mega base pair positions can be entered using exponential notation making these positions 0.5e6 and 25e6, as shown. Click the "Search by Position" button.



3. On the resulting page, notice that the search criteria are displayed at the top of the page. The search can be refined or expanded using these boxes.
4. Also notice that a summary table of the objects returned by the search is shown. Click on "QTLs" to navigate down to the table displaying all QTLs located within the search region. You can return to the top of the page using either your browser's "back" button, or the "Back to top of page" link located below each table.



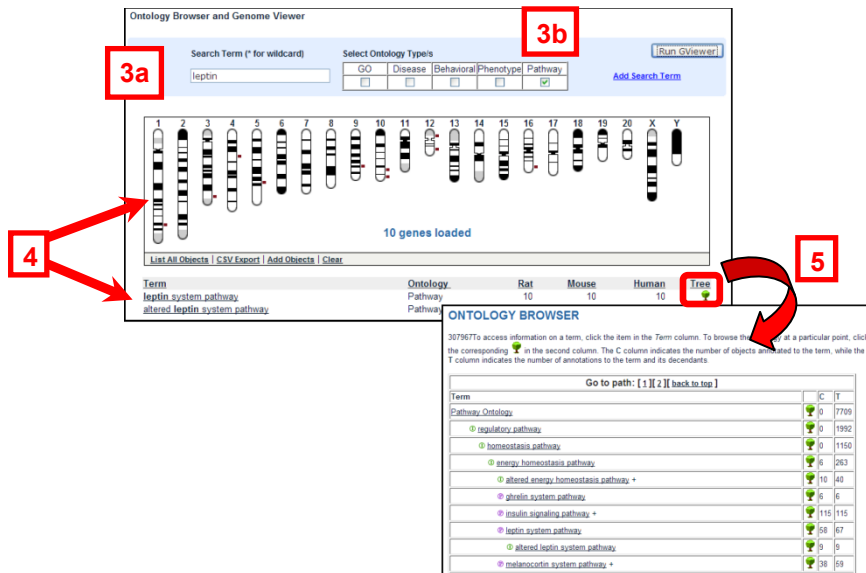
- From the QTLS table, scroll down to the table which displays all of the objects located within the search region. Notice that the results are ordered by base pair position.
- Click one of the RGD ID links to navigate to the report page for that gene, QTL or SSLP.
- Returning to the results page, click the “export table to spreadsheet” link to download the results as a comma-separated text file which can then be opened in Excel for ease of analysis.

Ontology Search and RGD’s Gene Pages

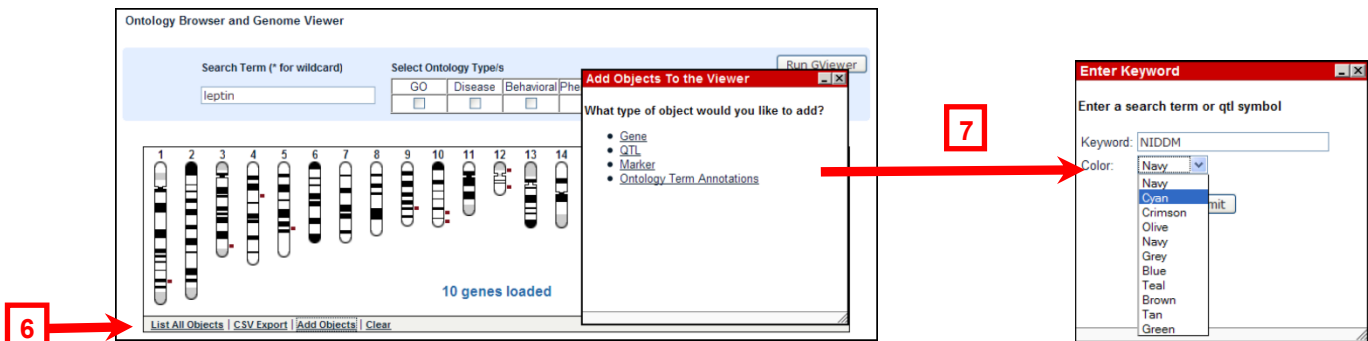
RGD is using several controlled vocabularies for the annotation of genes, QTL and strains. These include the three vocabularies of the Gene Ontology (GO function, process and component) along with Disease (DO), Phenotype (MP) and Pathway (PW) Ontologies. For rat genes all these vocabularies are used, for human genes DO, MP and PW and for mouse genes DO and PW are being used, respectively. DO and MP are also used for the annotations of rat and human QTL and of rat strains.

The image contains two screenshots of the RGD website. The left screenshot shows the 'RGD Data' page. In the top navigation bar, the 'Ontologies' link is highlighted with a red box. In the main content area, the 'ONTOLOGIES' link is highlighted with a red box labeled '1'. The right screenshot shows the 'Genome Tools' page. In the top navigation bar, the 'GViewer' link is highlighted with a red box. In the main content area, the 'Genome Viewer' link is highlighted with a red box labeled '2'.

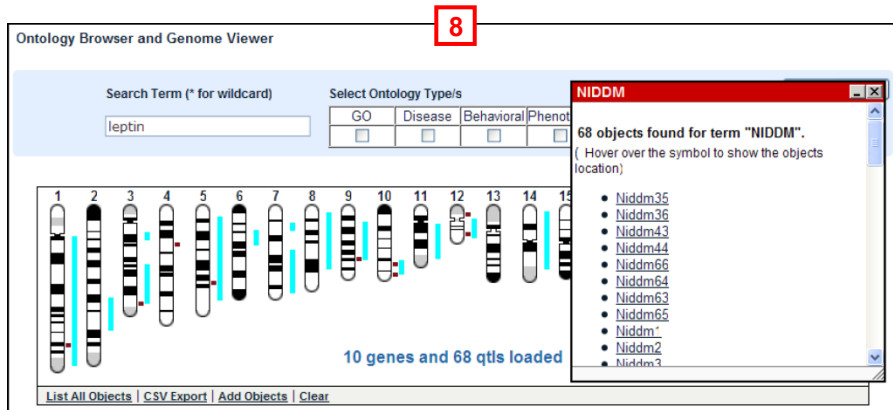
- The **Ontology Browser** and **GViewer** can be used to search one or several vocabularies for terms of interest and to find what objects have been annotated to them. Click the “DATA” tab to access a page listing all of the data types in RGD. Click “Ontologies” in the list of data types or in the menu at the top to access a simple Ontology Browser.
- Click the “GENOME TOOLS” tab to access a page listing all RGD’s tools. Click “GViewer” in the menu at the top or “Genome Viewer” in the list of tools to access the Ontology Search/GViewer.



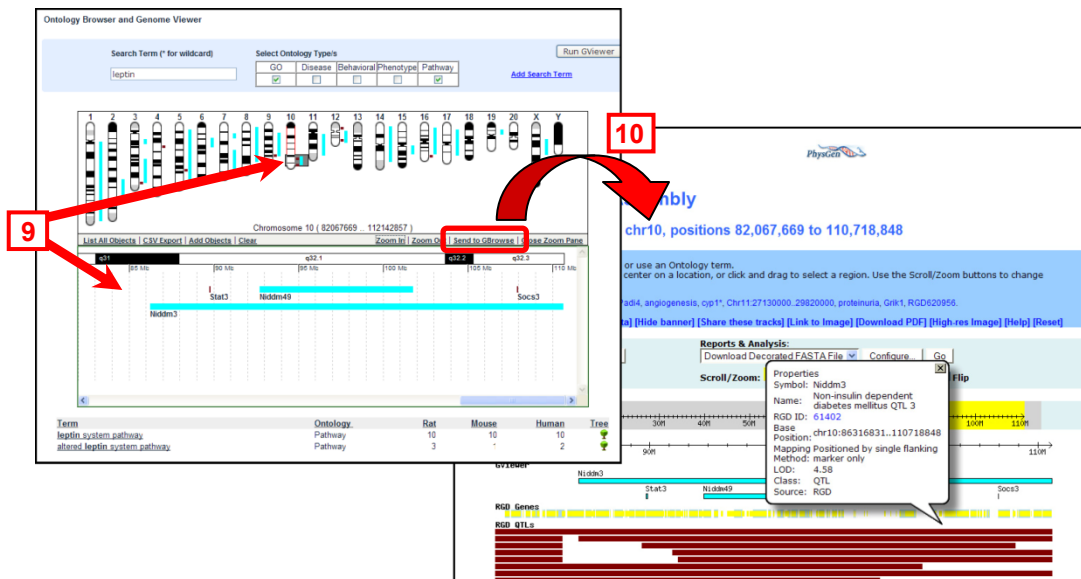
- As an example, enter “leptin” into the search box. The default is for all of the ontologies to be selected. Click all of the check boxes except “pathway” to search only RGD’s Pathway Ontology. Click “Run GViewer”.
- The search returns a screen with a GViewer image of all of the genes annotated to PW terms that include the word “leptin”. In addition a box contains a list of all of the ontology terms which match the search criteria with counts of the number of annotations to each term for rat, mouse and human.
- Note that clicking on the tree icon in the entry for the ontology term will bring up a diagram of the placement of that term in the ontology.



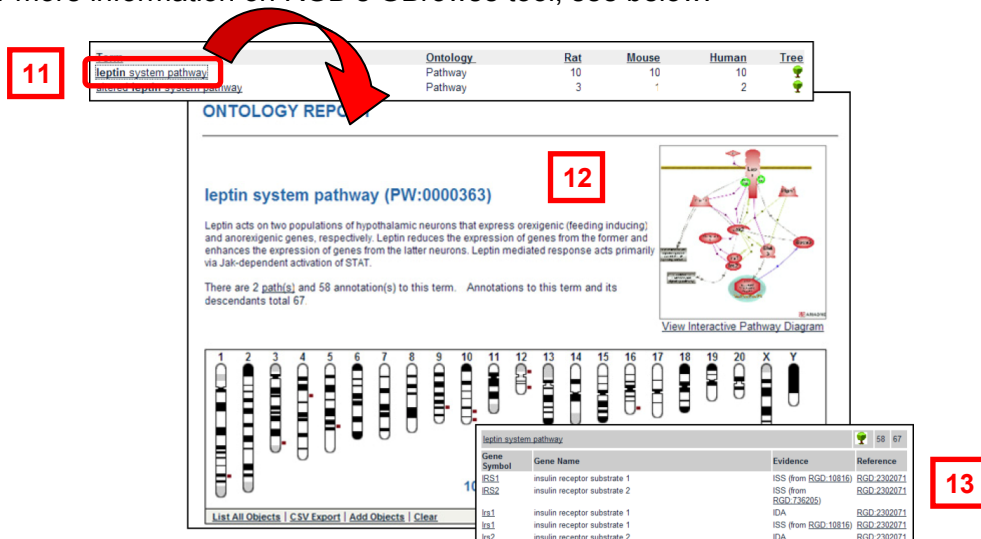
- Looking at the GViewer tool, you can see a line of options along the bottom of the image which allow you to view or download a list of all of the objects displayed, add more objects to the display or clear the display and start over.
- If you click the “Add Objects” link a box will open giving you the option of searching for objects such as genes, QTL or SSLP Markers, or for another ontology term to view where objects annotated to that term overlap with the results you are already viewing. For this example, click the link for “QTL” and enter “NIDDM” in the search box. Select “Cyan” from the drop down list of colors and click “Submit”.



8. All of RGD's rat Niddm QTL are now displayed as cyan bars and a list of the QTL is displayed.



9. To zoom into an area of a chromosome, click on the chromosome at the position you would like to see more closely. A zoom pane showing the selected area with its genes and QTL appears below the main display pane. The area can be moved by sliding the selected area along the chromosome in the main display. You can double click the slider to lock it into place.
10. To see the area you have zoomed into in its broader genomic context, click the "Send to GBrowse" button. RGD's rat Genome Browser will open up with the GViewer results displayed as a separate track. For more information on RGD's GBrowse tool, see below.



the whole protein, while links such as those for InterPro, Pfam and SMART give information on domains, families and protein structure.

QTL Search and QTL Reports

- From the RGD home page (<http://rgd.mcw.edu>), or any internal page, click on the Data tab at the top of the page. The submenu in the blue bar lists the various types of biological data stored in RGD (A). Click on “QTLs” to open the QTL query page.

The image consists of two screenshots of the RGD website. The left screenshot shows the 'QTL Search' page. A red box labeled '1' highlights the 'DATA' tab in the top navigation bar. Another red box labeled '2' highlights the 'QTLs' link in the submenu. A red box labeled '3' highlights the search box containing the text 'blood pressure'. A red box labeled '4' highlights the 'Search QTLs' button. A red box labeled '5' highlights the 'Search QTLs' button in the 'Limit Results (optional)' section. The right screenshot shows the search results for 'blood pressure' in *Rattus norvegicus*. A red box labeled '6' points to the 'Export This Report To' options (CSV, TAB, Printer, Genome Views). A red box labeled '7' highlights the 'Refine Term' box. A red box labeled '8' highlights the 'Export This Report To' options. A red box labeled '9' highlights the 'Bp7' symbol link in the first row of the results table.

RGD ID	Symbol	Name	LOD	p-value	Trait	Sub-Trait	Chr	Start	Stop	Species	Annotations	Match	Type
6255131	Bp7	blood pressure QTL	7.4	.0001	Blood pressure	self-loaded systolic	5	6255131	168174140	Rat	2	trait_name	qtl
6255131	Bp49	Blood pressure QTL	4.9	.001	Blood pressure		5	6255131	103059258	Rat	4	trait_name	qtl
165063650	Bp100	Blood pressure QTL	4.9	.001	Blood pressure	systolic	5	165063650	165074526	Rat	2	trait_name	qtl
133969001	Bp103	Blood pressure QTL	3.2		Blood pressure	systolic	5	133969001	171001807	Rat	2	trait_name	qtl
165074526	Bp121	Blood pressure QTL	4.2	.0005	Blood pressure		5	165074526	173096209	Rat	2	trait_name	qtl
40017184	Bp116	Blood pressure QTL	3.8		Blood pressure	systolic	5	1	40017184	Rat	2	trait_name	qtl
133295069	Bp132	Blood pressure QTL	3.8		Blood pressure	systolic	5	133295069	173096209	Rat	2	trait_name	qtl
121964552	Bp147	Blood pressure QTL	4.3	.0001	Blood pressure	systolic	5	121964552	126386030	Rat	3	trait_name	qtl
80918908	Bp156	Blood pressure QTL	1.6		Blood pressure	self-loaded systolic	5	80918908	135818908	Rat	2	trait_name	qtl

- In the keyword search box, enter “blood pressure”.
- The QTL search gives you several additional options that you can use to narrow your search. These include chromosomal position and species. For the genomic position you can select a chromosome number or both a chromosome and base pair position. You also have the option to change the genomic assembly that the position information refers to and/or choose to include or exclude objects that do not map to the selected genome assembly. For this example, select chromosome 5.
- You can also select a species. Notice that RGD also stores information on mouse and human quantitative trait loci and you can search for QTLs from any or all of these species. For this example, leave the default selection, Rat.
- Click on the “Search QTLs” button to run the search.
- Examine the QTL results page. The QTL search result page contains a list of all rat QTLs in RGD which match the search criteria. For each QTL, in addition to the RGD ID, symbol and name, the list gives the LOD score, the p value if available, trait and subtrait, and the base pair position on the chromosome.
- Options in the box at the top of the form allow you to refine your search term, change the genome assembly which positions are given for and sort the results by any of the available columns.
- Search results can be exported as a CSV or tab-delimited text file, sent to a printer, or viewed in the Genome Viewer by clicking on the appropriate link.
- Click on the symbol for Bp7 to go to the RGD report page for that QTL.

The screenshot shows the RGD QTL Report for Rat: Bp7. The page is annotated with red boxes and arrows labeled 9 through 16. Box 9 points to the Trait description. Box 10 points to the Strains section. Box 11 points to the Map Summary section. Box 12 points to the 'Select a browser to view' dropdown. Box 13 points to the Annotations section. Box 14 points to the Candidate Genes section. Box 15 points to the Other database links section. Box 16 points to the References section. A red arrow points from box 11 to the Map Data table.

Map Data:	Marker	Symbol	Map Name	Chr.	Position
Flank 1		D5Mit9	Other Maps	5	
			RH 3.4	5	384.6
			genome_assembly 3.1	5	
			RGSC genome assembly v3.4	5	
Peak		Edn2	genome_assembly 3.1	5	
			Other Maps	5	q36
			RGSC genome assembly v3.4	5	
Flank 2		D5Mco10	Rat Celera Assembly	5	
			Other Maps	5	
			genome_assembly 3.1	5	
			RGSC genome assembly v3.4	5	

10. RGD QTL Report pages supply manually curated, detailed information about quantitative trait loci. In the Description section of the page, notice the trait and subtrait which are linked to this chromosomal locus. The “Method” line gives detailed information on the experimental methods used to measure the trait. Ontology annotations for associated disease and phenotype terms are shown. Click on “hypertension” or on “increased blood pressure” to go to the Disease or Mammalian Phenotype ontology report pages for the respective terms. RGD curates statistical measurements from QTL papers and supplies them in a searchable format. Notice that for this QTL both LOD score and P value are given.
11. RGD links QTL reports to the reports for the strains that were used to generate each QTL. Click on “SS/Jr” to navigate to the Strain Report page for that rat strain.
12. QTLs are defined by corresponding marker positions used to establish linkage. Notice that on the Map Summary line both peak and flanking marker positions are given. Scroll down to the Map Data section to view the map positions of the three markers. RGD uses genomic, genetic and RH maps to localize markers for QTLs.
13. Just above the Map Data section is a view of the Bp7 QTL on chromosome 5. Use the dropdown list labeled “Select a browser to view” to choose one of the genome browsers within RGD or on other websites such as UCSC or NCBI to view the Bp7 QTL in its genomic context.
14. Scroll down to the “Annotations” section. This section of the page gives free text notes which supply extra information about the QTL. Each note is linked to the reference from which that information was curated. Click on “61059” to read the abstract for the paper from which the note “SS allele associated with increased blood pressure” was derived.
15. The Related Objects section of the page lists any related QTLs and/or candidate genes. Click on “Edn2” to view the gene report page for the candidate gene “endothelin 2”. Note that the gene report page also supplies the information that Edn2 is a candidate gene for Bp7 and contains a link to the QTL.
16. “Other database links” provides links to information on Bp7 in external databases. Click “RatMap” to view the RatMap report or “Entrez Gene” to view the information from NCBI’s Entrez Gene database. The data at Entrez Gene is derived from RGD’s QTL data.
17. The References section links to a page which lists all of the references associated with Bp7. Click “Article(s) about Bp7 (3 curated references)” to view the citations for the three papers associated with Bp7. Links are provided to the abstracts at RGD and at PubMed.

Strain Search and Strain Reports

1. From the RGD home page (<http://rgd.mcg.edu>), or any internal page, click on the Data tab at the top of the page. The submenu in the blue bar lists the various types of biological data stored in RGD (A). Click on “Strains” to open the Strain query page.

- The RGD Strain Search works in the same way as the general Keyword search at the top of the page except that it only searches for strains. For this example, enter “cop” in the “Keyword” search box under “Strain Search”.
- Click the “Search Strains” button to navigate to the Strains Search results page.
- Notice that the search returns the list of all strains where “COP” occurs anywhere in the indexed fields of the strain record. In addition to the obvious options of symbol and name, these include previous nomenclature and origin. Note in the results list you will see substrains and congenic strains in addition to the parental COP strain.
- Click the link for “COP” to go to the Strain Report page for the parental strain.

- RGD’s Strain Report pages display a wealth of valuable information on individual rat strains. In the “Basic Details” section, notice the information on Genetic markers, Coat Color and number of inbred Generations. In the Origin section, parent strain pages give information on the origins of not only the parental strain, but also all of the corresponding substrains.
- In the section above “Basic Details” click the link for “COP/CrI” to go to the page for this substrain. Notice that this Strain Report only gives information for the substrain, but includes a link to both the parent strain and the COP/OlaHsd substrain.
- Scroll down to the “Annotations” section.
- Detailed notes on topics such as “Lifespan and Spontaneous Disease” and “Drugs and Chemicals” have been written by RGD curators. Click the “1334449” link in the “Reference” column beside the first note under “Drugs and Chemicals” to read the abstract for the paper from which the note “Strain has decreased sensitivity to DES-induced pituitary growth” was curated. Notice that the Reference report page shows a link to the PubMed page which includes a link to the free full text of this article.

- Returning to the Strain Report, scroll down to the Ontology section to view the Disease and Phenotype Ontology annotations that have been assigned to this strain. Click on the link for “mammary alveolar hyperplasia” to review the information for this Mammalian Phenotype term.
- Returning once again to the strain page, scroll down to view the list of RGD QTLs which were generated using this strain. Click on the link for Ept10 to navigate to the QTL report page for Estrogen-induced pituitary tumorigenesis QTL 10. (See information on the QTL report pages elsewhere in this handout for details on using RGD QTL reports.)

The screenshot shows the RGD interface for a strain report. The 'Ontology (2)' section lists terms like 'mammary hyperplasia' and 'mammary resistance'. Below it, the 'Strain SSLP data' section is highlighted with a red box labeled '12'. The 'Strain QTL data' section lists various QTLs such as 'Mammary carcinoma susceptibility QTL 3' and 'Liver neoplastic nodules remodeling frequency'. The 'Associated References' section is highlighted with a red box labeled '13', listing references for COP and COP/Cl strains.

- Returning to the COP/Cl strain page, either click the link at the top of the page or use your browser’s “Back” button to navigate back to the COP parental strain page. Scroll down to the Strain SSLP data section. Notice that information on the markers typed in the COP/OlaHsd substrain is listed there. Directly beneath this section you will see that QTL data for the parental strain and both substrains is listed in the Strain QTL data segment. The QTLs listed for the COP/Cl substrain here are the same as those listed on that substrain’s strain report.
- Finally, scroll down to the “Associated References” section. This section lists all of the references associated with the COP strain and its substrains. Click on the last link in the list for COP/Cl, “7: Strecker TE et al...” to view the same Reference Report that you accessed from the COP/Cl report page.

Reference/Author Search and Reference Reports

- From the RGD home page (<http://rgd.mcw.edu>), or any internal page, click on the Data tab at the top of the page. The submenu in the blue bar lists the various types of biological data stored in RGD (A). Click on “References” to open the Reference query page.

The screenshot shows the RGD Reference Search interface. At the top, the 'DATA' tab is highlighted with a red box labeled '1'. Below it, the search input field contains the text 'blood pressure rapp 1998' and is highlighted with a red box labeled '2'. The search results are displayed in a table, with the first entry highlighted by a red box labeled '4'. Red arrows point to the 'Refine Term' and 'Sort By' options, which are highlighted with a red box labeled '3'. The table has columns for RGD ID, Title, Citation, Abstract, and PubMed ID. The first entry is titled 'Linkage analysis and construction of a congenic strain for a blood pressure QTL on rat chromosome 9'.

- Multiple search terms can be entered into the strain keyword search box. So for instance, enter “blood pressure rapp 1998” and the tool will automatically search for articles in RGD that meet all of the search criteria. Click “Search References” to locate the relevant references.

- On the results page, note once again that the search can be refined or the results sorted using the options in the box at the top of the form. The search results can be exported as a CSV or tab-delimited text file or sent to a printer. Results include the RGD ID, title and citation of the reference. The full abstract can be viewed directly on the search results page by clicking "...(more)". The result in this list also gives one-click access to the abstract in PubMed via the link in the "PubMed" column.
- Click the link for the article by Rapp et al ("Linkage analysis and construction...") to view the abstract for that article.

Reference Report

Linkage analysis and construction of a congenic strain for a blood pressure QTL on rat chromosome 9.

5 Rapp JP, Garrett MR, Dene H, Meng H, Hoebee B, Lathrop GM.
Citation: Rapp JP, et al., Genomics 1998 Jul 15;51(2):191-6
Status: COMPLETED

Abstract (?)
A blood pressure quantitative trait locus was found (LOD = 5.0) on rat chromosome 9 derived from Dahl salt-sensitive (S) and Dahl salt-resistant (R) rats. The F2 strain introgressing the R low-blood-pressure QTL allele on chromosome 9 designated S.R(chr 9), had a lower blood pressure (19 mm Hg) than 1000 F1 rats (2% NaCl diet for 24 days), proving the existence of a blood pressure QTL on chromosome 9.

Show data curated from this reference **7**

External Database Links

PubMed
6 Rapp JP, et al., Genomics 1998 Jul 15;51(2):191-6 (9722941)

Related Objects Report **8**

There are 7 entries in RGD covered by this reference.

GENES
Symbol Name
Inha inhibin alpha

STRAINS
Symbol Name
SR/Ur Salt Resistant
SS/Ur Salt Sensitive
SS.SR-Inha/Ur -na-

QTLs
Symbol Name
Bp34 Blood pressure QTL 34

SSLPS
Symbol Name
D9Uia6 -na-
D9Uia9 -na-

- On the Reference report page, note that each author's name is a link. Click a name to view all of the articles in RGD by that author.
- The reference report page also includes a link to the abstract record in PubMed. Click the citation under "External Database Links" to view the abstract at PubMed.
- Finally, on the reference report page click the link labeled "Show data..." to view all of the data objects that have been curated from this reference.
- The Related Objects report shows that 7 objects have annotations derived from the Rapp et al reference. These include one gene, three strains, one QTL and two SSLPs. Click on the symbol for any of these objects to view the report page for that object.

Pathway Annotations and Visualization

- Similar to a search for GO, a search using the keyword 'leptin' within the Pathway Ontology brings up "leptin system pathway" and "altered leptin system pathway" – the two terms in the vocabulary that contain the word "leptin".

Term	Ontology	Rat	Mouse	Human	Tree
leptin system pathway	Pathway	10	10	10	
altered leptin system pathway	Pathway	3	1	2	

1

ONTOLGY REPORT

leptin system pathway (PW:0000363)

Leptin acts on two populations of hypothalamic neurons that express orexigenic (feeding inducing) and anorexigenic genes, respectively. Leptin reduces the expression of genes from the former and enhances the expression of genes from the latter neurons. Leptin mediated response acts primarily via Jak-dependent activation of STAT.

2 There are 2 path(s) and 58 annotation(s) to this term. Annotations to this term and its descendants total 67.

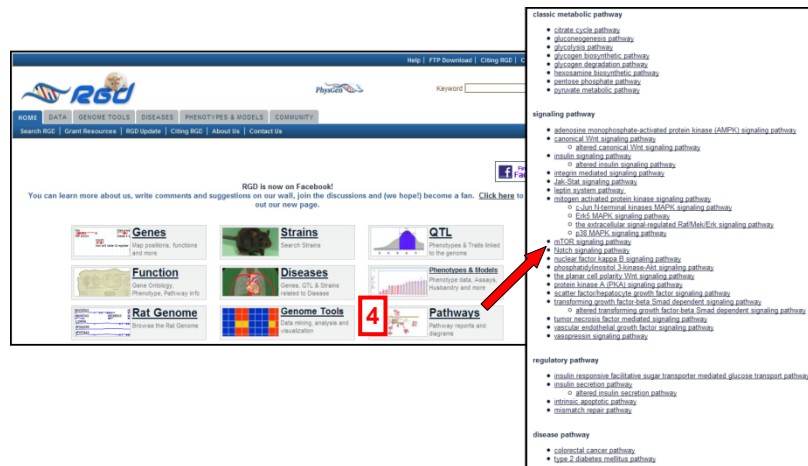
3

View Interactive Pathway Diagram

Gene Symbol	Gene Name	Evidence	Reference
IRS1	insulin receptor substrate 1	ISS (from BGD:10816)	RGD:2392071
IRS2	insulin receptor substrate 2	ISS (from BGD:738205)	RGD:2392071
Irs1	insulin receptor substrate 1	IDA	RGD:2392071
Irs1	insulin receptor substrate 1	ISS (from BGD:10816)	RGD:2392071
IRS2	insulin receptor substrate 2	IDA	RGD:2392071

List All Objects | CSV Export | Add Objects | Clear

- Click on the term “leptin system pathway” to view all the objects annotated to that term. The ontology report shows a GViewer image of the rat genes annotated to that term, as well as a list of rat, human and mouse genes annotated to the term and the paths to the term. Unlike GO annotations which are done on a gene-by-gene basis, annotations to pathway terms aim at capturing the network information, i.e., the identification of all genes which according to published reviews are components of a particular pathway and the subsequent annotation of these genes to the term.
- In addition to the annotation of genes to pathway terms, RGD builds interactive pathway diagrams using the Pathway Studio 5.0 from Ariadne Genomics. A growing list of classic metabolic, signaling, regulatory and disease pathway diagrams have already been incorporated into RGD. These diagrams are accessible from the Ontology report page by clicking on the pathway diagram icon at the top right side of the page.



- Alternatively, the entire list of pathway diagrams can be viewed by clicking on the “Pathways” button on the RGD home page. From the list, click on the name of a pathway to explore its diagram.

leptin system pathway

6a **Entities**

- Protein
- Small Molecule
- Treatment
- Cell Process
- Disease
- Cell Object
- Pathway
- Complex
- Functional Class

Relationships

- Binding
- Unknown/Relation
- Regulation
- Expression
- MutSynthesis
- PromoterBinding

Description **7**

The leptin system plays an essential role in energy homeostasis - the balance of energy expenditure. Leptin acts on two classes of neurons, those expressing CART and those expressing the appetite stimulating peptides NPY and AgRP, and those expressing the latter. The products of the *Pomc* and *AgRP* are agonists and antagonists, respectively and the leptin melanocortin 4 receptor (MCH4R) is a G-protein coupled receptor (GPCR) that is a member of the class I cytokine receptor family. Leptin signaling occurs primarily via the Jak2-Stat3 pathway. Leptin binds to and activates of Jak2. Jak2 activation involves oligomerization, binding to and activation of Jak2. Jak2 activation involves phosphorylation of tyrosine residues on the cytoplasmic domain of leptin to the LepR-Jak2 complex followed by Stat3 phosphorylation. P-Stat3 dimerizes and regulates the transcription of target genes, including *Socs3*. *Socs3* and other sites within the LepR-Jak2 complex provides a negative regulation also imparted by Ptpn1. In vitro, Ptpn1 dephosphorylates both Jak2 and Irs1/2. In vivo, Ptpn1 dephosphorylates both Jak2 and Irs1/2 and include PI3K via Jak2 activation of Irs (insulin receptor substrates) and which acts upstream of the pathway. It has been shown that Sh2bpm1 (plekstrin and src homology 2 domains) - can recruit Irs1 and Irs2 in response to activated Jak2 to promote tyrosine phosphorylation of Irs1/2 that Stat and Socs proteins as well as Ptpn1 contain SH2 - src homology 2-containing targets. Ptpn1, acting upstream of ERK1/2 pathway can inhibit receptor or Jak2. To see the ontology report for annotations, GViewer and download click to see the ontology report for related GO term - GO:0933210

8

Abbreviations

POBAC - pro-opiomelanocortin
 CART - Cocaine and Amphetamine Related Transcript
 NPY - neuropeptide Y
 AgRP - agouti-related protein
 Jak2 - Janus activated kinase 2
 Stat3 - signal transducers and activators of transcription 3
 Socs3 - suppressors of cytokine signaling
 Ptpn1 - protein tyrosine phosphatase, non-receptor type 1
 Ptpn11 - src homology 2-containing tyrosine phosphatase
 Irs1 - insulin receptor substrate 1
 Irs2 - insulin receptor substrate 2
 Sh2bpm1 - SH2-B PH domain containing signaling mediator

9

References

PMID:12010538 12072865 9070213 9618284 16336196 15316008 15821101 18664086 10794713 17273380 17872473

Import into Pathway Studio

[Leptin_system_pathway.gps](#)

5

6b

6a

6b

Shapes

- Nuclear receptors
- Kinases
- Phosphatases
- Extracellular protein
- Ligands
- Transcription factor
- Receptors

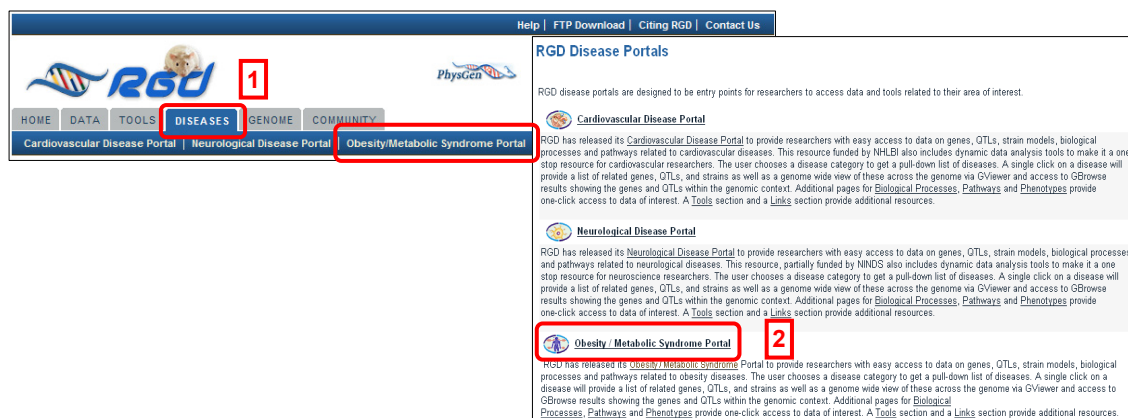
- The leptin system pathway diagram is shown here. Icons for individual genes link to the RGD records for those genes. Those for related pathways link to the diagrams for the respective pathways. Where a single icon represents multiple objects, such as target genes, a link is provided to a separate page with the complete list to simplify the diagram structure.

- Along with the diagram itself, all diagram pages provide a legend for entities, relationships and shapes as designed by Ariadne Genomics.
- Note the detailed description of the pathway
- A list of abbreviations and a list of references that are hyperlinked to PubMed are provided.
- In addition to viewing the diagram, users can import the diagram.gpp file into their own Pathway Studio tool. The Ariadne Genomics logo is displayed on all diagram pages.

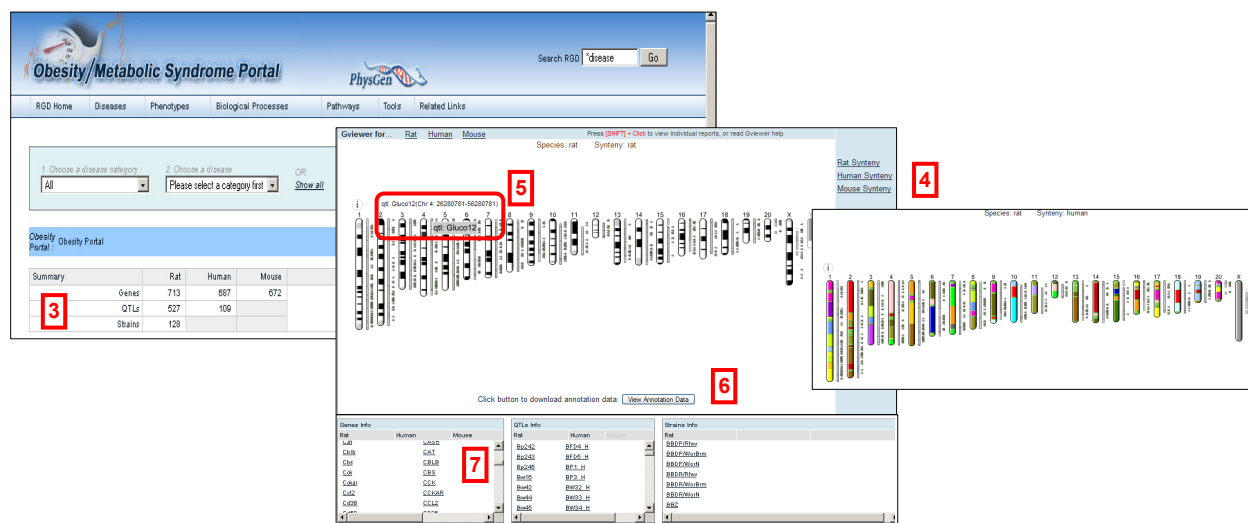
RGD Tools

Disease Portals

RGD is providing disease and disease related information for rat, human and mouse genes, rat and human QTL and rat strains. In an effort to offer better ways for organizing and presenting these data, RGD has begun implementing the Disease Portals project. Portals so far offered are for the cardiovascular, neurological and obesity/metabolic syndrome disorders.

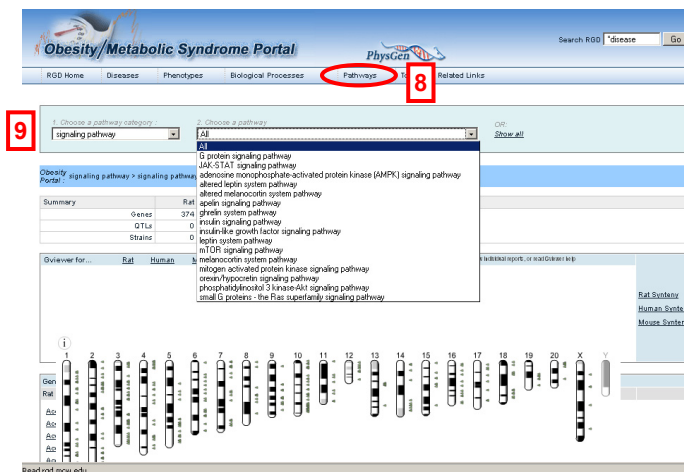


- From the main RGD webpage click on the **DISEASES** tab to access a list of available portals
- Select “Obesity / Metabolic Syndrome Portal” either in the menu bar at the top or in the portals list.



- The default view for all portals is a display of all objects (genes, QTL and strains) annotated to disease terms within the portal. Note that a summary of the number of objects of each species is included at the top of the page.
- A rat GViewer image shows a genome-wide view of annotated genes and QTLs. Click on “Human Synteny” to view an image with the human syntenic regions denoted by color.
- Mouse over one of the objects in the diagram to see the symbol and position information for that object.

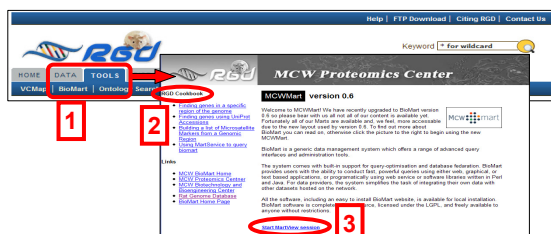
- Click “View annotation Data” to download a list of the annotated objects with their genomic positions.
- Lists of annotated objects are located beneath the GViewer image. You can scroll up and down the list. Also, each object is hyperlinked to its report page, i.e., clicking on it one gets to the gene, QTL or strain report page.



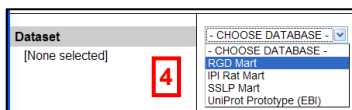
- In addition to this default display, you can choose a disease category and a specific disease within the category or make such selections for phenotypes, biological processes or pathways within the portal to see the annotated objects. All annotations are based on controlled vocabularies: the Disease Ontology (DO), the Mammalian Phenotype Ontology (MP), GO Process Ontology (one of the three vocabularies of GO), and the Pathway Ontology (PW). Click on the “Pathway link” to access this section of the portal.
- In the drop down lists at the top of the page, select “signaling pathway”. Notice that the items in the second list change according to what you choose for the first term. Also note that the lists of objects and the GViewer image change according to the ontology and the terms selected.

BioMart

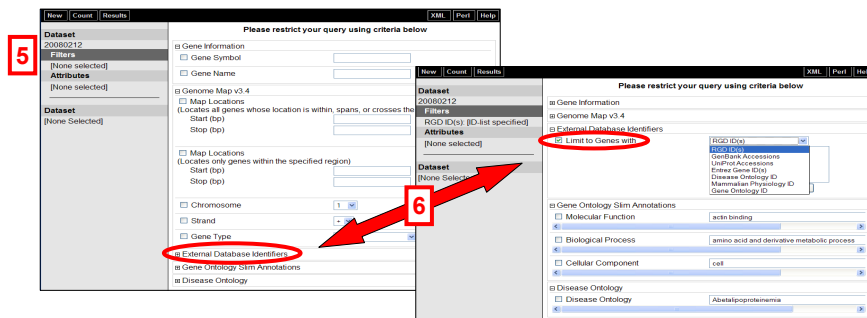
- RGD’s BioMart tool allows the user to query RGD for specific data based on both input and output criteria. Once a dataset is selected, that data is filtered based on the input criteria and the data retrieved is determined by the output criteria. From the RGD home page (<http://rgd.mcw.edu>), or any internal page, click the **TOOLS** tab at the top of the page and select **BioMart** on the menu bar to access the MCWMart home page.



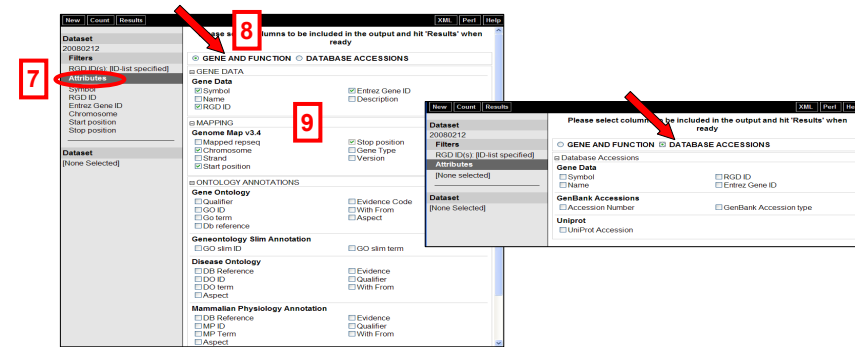
- Notice the **RGD Cookbook** links in the left margin. These pages walk you through some common problems.
- To access the RGD BioMart tool, click **Start MartView session**.



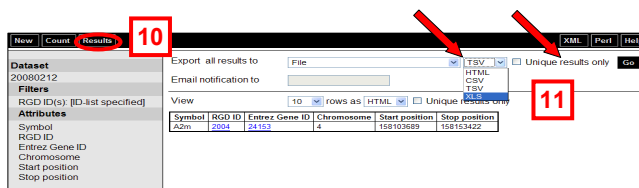
- There are several datasets to choose from. Select **RGD Mart**.



- Click Filters to access a form which will allow you to limit the genes for which you get information. A subset of the RGD genes can be selected based on a single symbol and/or name, map position, a list or file containing gene, sequence or ontology identifiers, and/or a variety of ontology terms.
- For this example, click the plus sign (+) next to “External Database Identifiers”, click the check box for “Limit to Genes with” and type “2004” into the text box under “RGD ID(s)”. If you wanted to upload a file of IDs you would click the “Browse...” button to locate and upload your file.



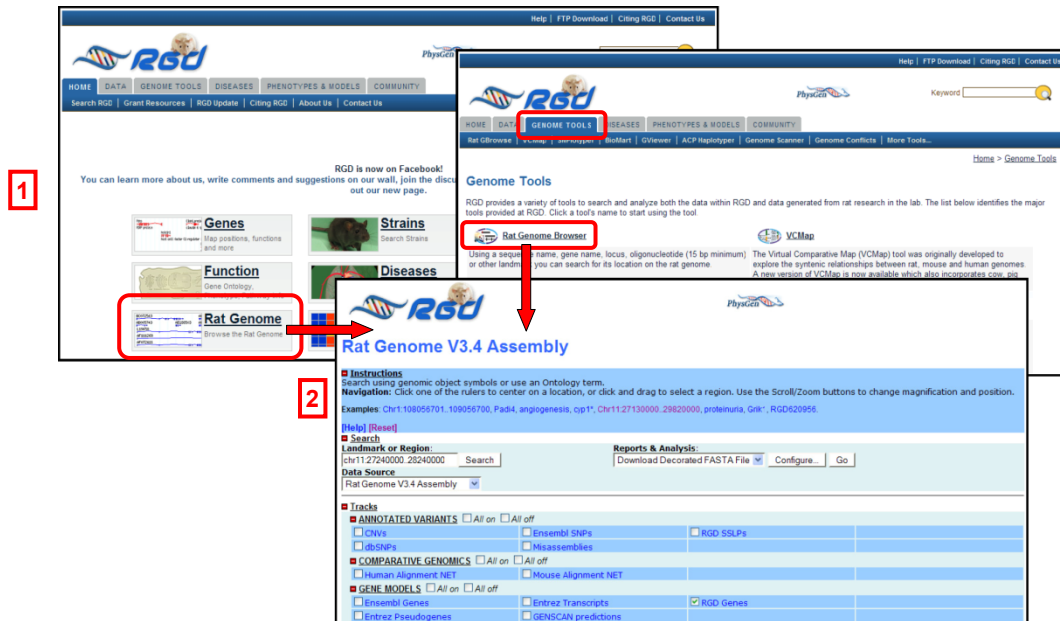
- Select “Attributes” in the menu on the left. Choose the type of data that you wish to obtain for the genes you have selected, either “GENE AND FUNCTION” data or “DATABASE ACCESSIONS”.
- For this example, keep the default selection of gene and function. This includes gene IDs and nomenclature, map data and annotations for any or all of the four ontologies that RGD uses—Gene, Disease, Phenotype and Pathway.
- Click the check boxes for Symbol, RGD ID, Entrez Gene ID, Chromosome and Start and Stop positions.



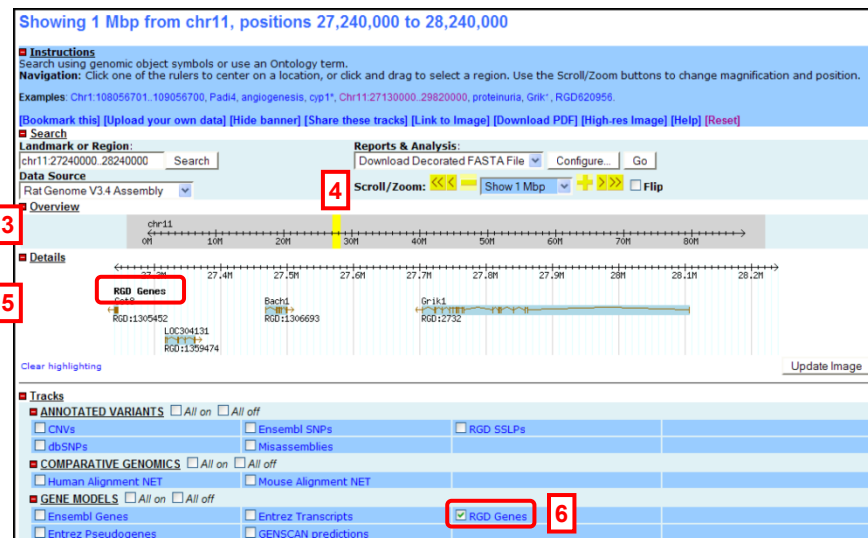
- Click the Results button at the top of the page to view the selected data for RGD ID 2004.
- Results can be viewed on the website or downloaded to a file as HTML, Comma or Tab separated Values or Excel spreadsheet. For both the download function and viewing on the website, you can choose “Unique results only” to avoid redundant annotations.

GBrowse

- You can access the RGD Rat Genome Browser, or GBrowse, from the RGD home page (<http://rgd.mcg.edu>) by clicking on the button labeled “Rat Genome”, or from any RGD page, by clicking on the “GENOME TOOLS” tab at the top of the page. On the Genome Tools page, click the Rat Genome Browser link to access GBrowse.

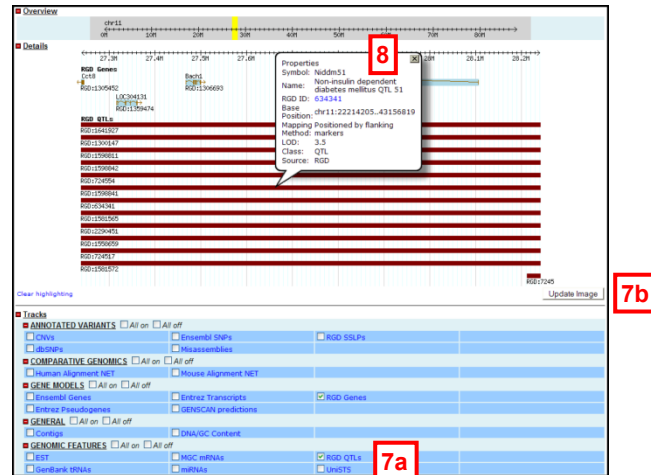


- Notice at the top of the page there is a section with instructions for using GBrowse including examples of possible searches. Below this section, type “chr11:27240000..28240000” into the “Landmark or Region” box under Search. Note that you can also enter symbols or keywords into this box. Directly under this, the default for “Data Source” is Rat Genome V3.4 Assembly. Keep this as the source, but notice that other data sources are available including the Human genome. Click the Search button to display the region entered.

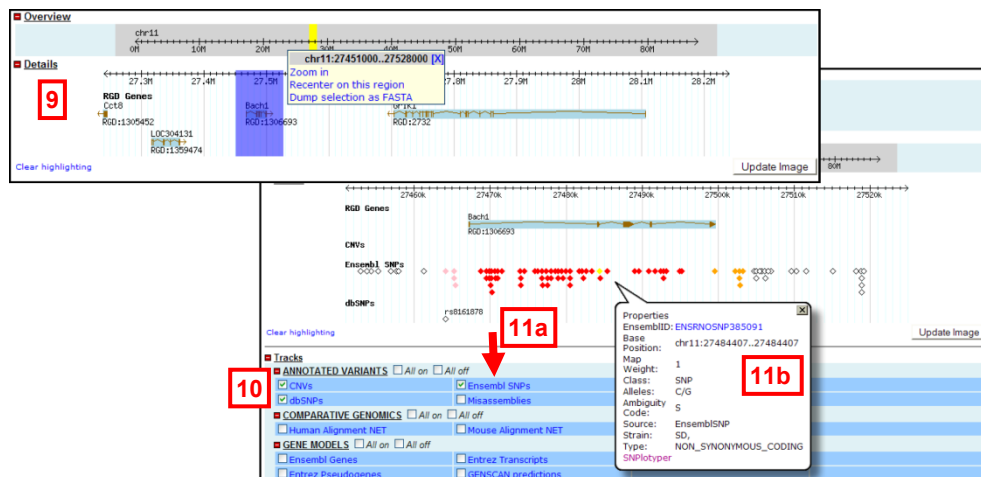


- The Overview section shows a diagram of the entire chromosome 11 with a yellow box/line showing the section which is displayed in the Details section. Clicking on the overview diagram will move the Details display to the location where you clicked. The number of base pairs displayed remains the same. Use your browser’s “Back” button to return to the original position.
- You can also use the arrows to scroll up or down the chromosome, and the dropdown box or plus/minus buttons to increase or decrease the number of base pairs displayed. Use your browser’s “Back” button to return to the original size and/or position.
- In the Details section, if you have used GBrowse before the tool will use your previous settings. To clear these settings, use the “Reset” button at the top of the page. If you have not used the tool before or if you have cleared the settings, the default view is only the RGD Genes track.

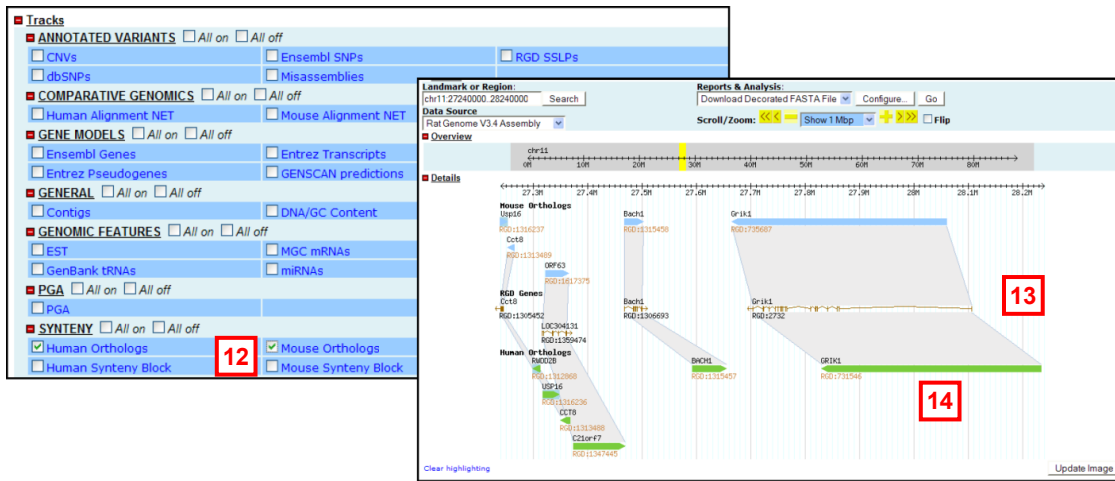
- If you scroll down to the “Tracks” section of the page you can see the variety of different data types that GBrowse can display. Because only RGD genes are presently being displayed, only that box is checked.



- To see all of the QTL that overlap your region, scroll down to the GENOMIC FEATURES segment of the Tracks section. Check the box for RGD QTLs and click the “Update Image” button.
- Note that when you mouse over any object in GBrowse, such as a QTL or gene, a balloon pops up with detailed information about that object. What information is displayed depends on the object. In this case, the QTL nomenclature, RGD ID, base pair position, mapping method and LOD score are shown. Notice that the RGD ID is a link that will take you to the corresponding QTL report.



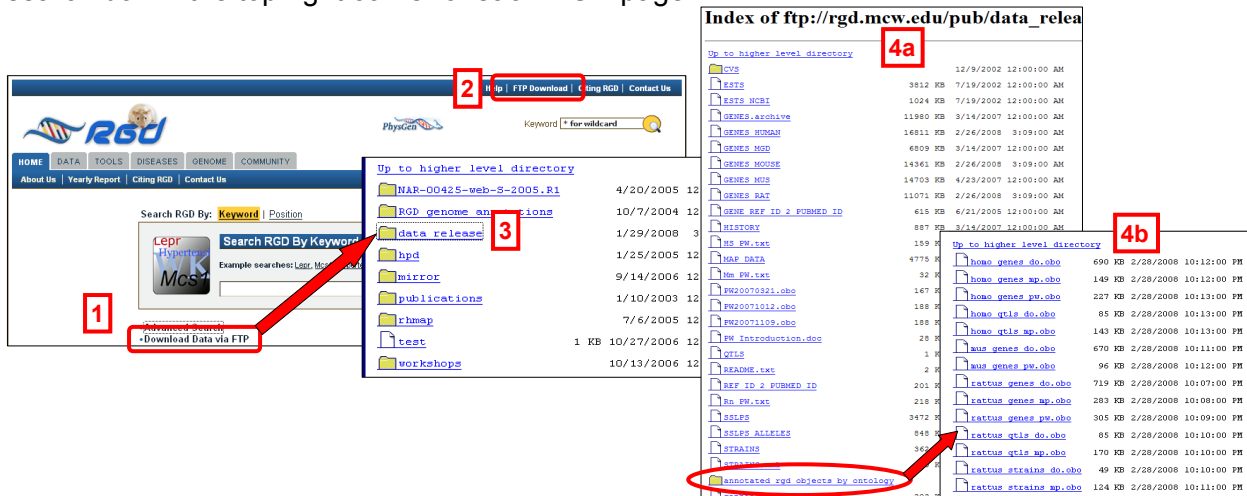
- RGD’s GBrowse has tracks for a number of annotated variants including SSLPs, copy number variants and SNPs from both dbSNP and Ensembl. To see the SNPs for the gene Bach1, click and drag your mouse along the scale line in the Details section to select the portion that contains just that gene. A popup box gives you the option to Zoom in, Recenter the image or download the selection as a FASTA file. Select “Zoom in”. The image is automatically updated.
- Scrolling down to the Tracks section, uncheck the box for RGD QTLs, check the one for Ensembl SNPs and click “Update Image”.
- The diamond shapes that represent SNPs in GBrowse are color coded to show the type of SNP each is. For a list of the colors and their meaning, click the text (not the check box) for “Ensembl SNPs”. A new window will open up which gives more information about the various tracks. Mousing over a SNP will open a popup balloon that displays more information about that SNP, including what type of SNP it is. If you mouse over the yellow SNP in the second exon of the Bach1 gene you will see that it is a “Non-synonymous coding” SNP.



- RGD's rat GBrowse now includes information on rat-mouse-human synten. Using your browser's "Back" button, go back to the original image of the rat genes within chr11:27240000..28240000, or alternatively, click the "Reset" button and re-enter the genomic position of interest. Notice that the rat genes that are displayed have blue shading behind them. This indicates that those genes have mouse and/or human orthologous genes that are currently not being displayed. Scrolling down to the bottom of the Tracks section, select the tracks for "Human Orthologs" and "Mouse Orthologs" and click "Update Image".
- The display now shows a number of orthologous mouse and human genes with grey shaded areas linking the rat genes to their orthologs. Hover over a mouse gene to open a popup balloon that displays more information about that gene including its symbol, name, RGD, MGI and Entrez Gene IDs, and its genomic position in mouse. The RGD, MGI and Entrez Gene IDs are links to that gene's record on the corresponding website.
- Note that the sizes of the genes in the different species have not been adjusted. If the rat gene is longer or shorter than the orthologous mouse or human gene, this is reflected in the sizes of the bars representing those genes.

FTP Downloads

- Data can be downloaded in bulk from our ftp site. Click "Download Data via FTP" above the Keyword search box in the top right corner of each RGD page.



- Another link to "FTP Download" appears in the menu bar at the very top of each RGD page.
- On the FTP site, select the "data release" directory.
- The data release directory contains a variety of files containing data compiled from the RGD database for rat, mouse and human genes, rat and human QTLs and rat strains. In addition, a subdirectory holds individual files with annotations of various objects to particular ontologies.