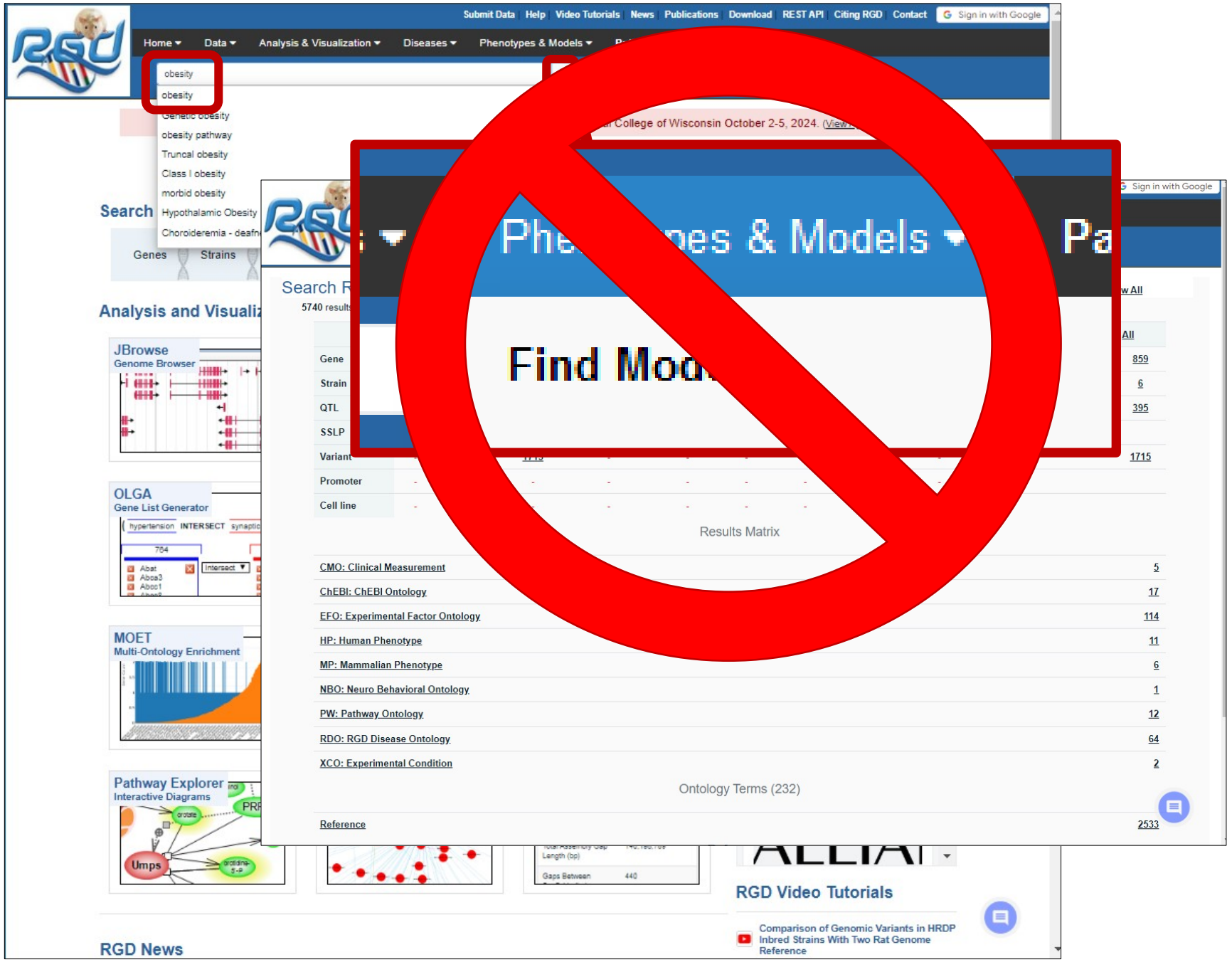
Using RGD to find a rat model of obesity

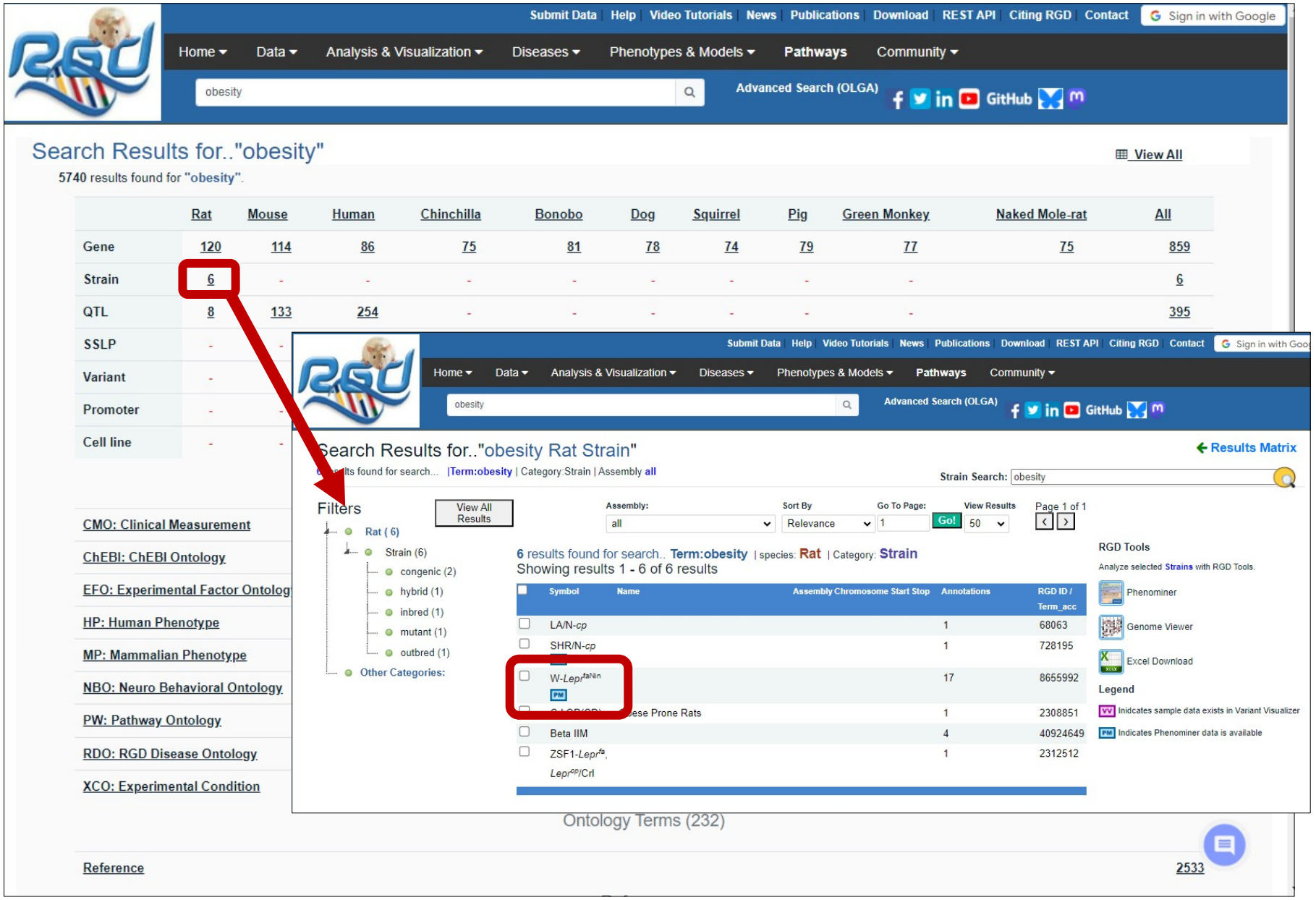
Resources Workshop, Use Case 2

Jennifer Smith and Mary Kaldunski
Rat Genome Database
Medical College of Wisconsin

Complex Trait Community and Rat Genomics Meeting

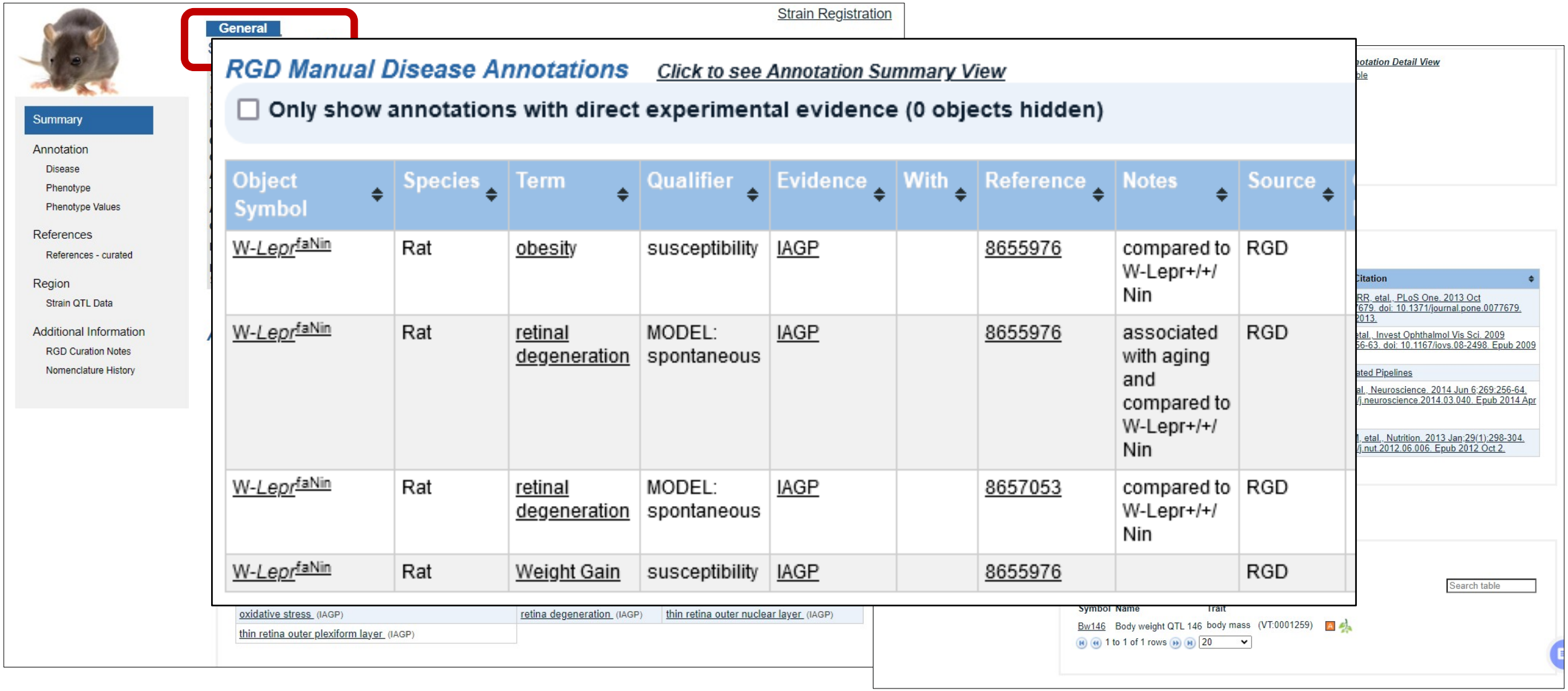


- For the "Find Models" portal, see the poster by M. Kaldunski, et al.
- **Method 1:** Keyword/general search
  - Search bar at the top of most RGD pages
  - Simple
  - Straightforward
  - Returns results in multiple different categories
- Enter “obesity” and click the magnifying glass search icon button to open a results page with a categorized table of data for the term.
- Note this is a keyword search, not a search of the ontology annotations.



- Primary results
  - Genes for all RGD species
  - Rat strains
  - Rat/human/mouse QTL
  - Variants
  - Ontology terms
  - References
    - Note the over 2500 references in RGD for this disease term.
- Click the number for Rat+Strain to open a table with the rat strains related to “obesity”.
- Each strain symbol is clickable and will open the rat strain report page.
- A blue PM icon denotes quantitative phenotype data in PhenoMiner.
- A purple VV icon denotes variant data in RGD's Variant Visualizer.

The strain report page is the primary comprehensive location for any information in RGD for that strain. Strain nomenclature, IDs, and available information for the provenance of strain creation are described. RGD manual annotations for disease and phenotype, evidence codes for the annotations, and clickable links to related references are listed. Available information related to PhenoMiner quantitative data and related QTL are given.



Strain Registration

General

Summary

Annotation
- Disease
- Phenotype
- Phenotype Values

References
- References - curated

Region
- Strain QTL Data

Additional Information
- RGD Curation Notes
- Nomenclature History

RGD Manual Disease Annotations

Click to see Annotation Summary View

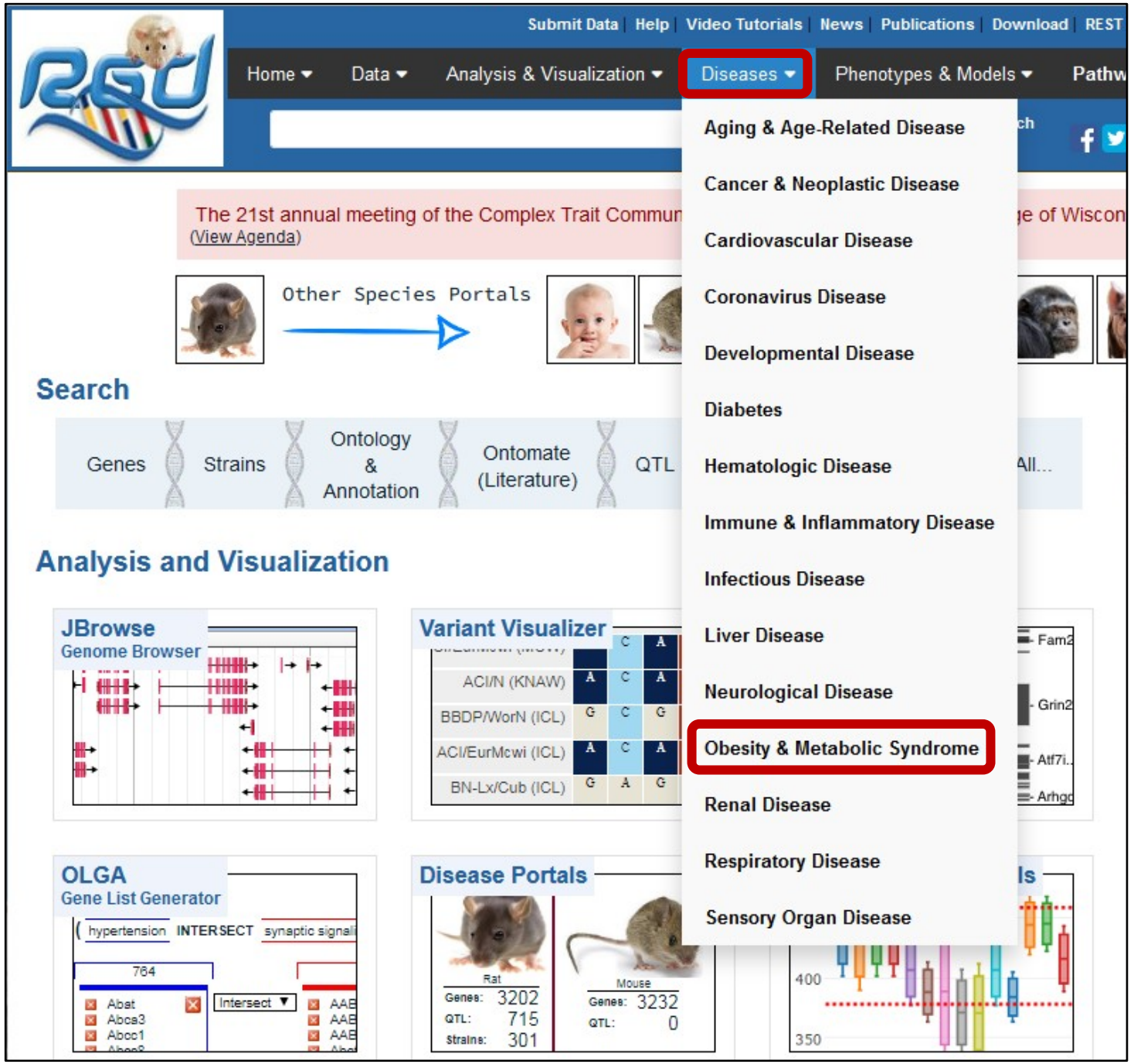
Only show annotations with direct experimental evidence (0 objects hidden)

Object Symbol	Species	Term	Qualifier	Evidence	With	Reference	Notes	Source
W-*Lepr*^{faNin}	Rat	obesity	susceptibility	IAGP		8655976	compared to W-Lepr+/+/ Nin	RGD
W-*Lepr*^{faNin}	Rat	retinal degeneration	MODEL: spontaneous	IAGP		8655976	associated with aging and compared to W-Lepr+/+/ Nin	RGD
W-*Lepr*^{faNin}	Rat	retinal degeneration	MODEL: spontaneous	IAGP		8657053	compared to W-Lepr+/+/ Nin	RGD
W-*Lepr*^{faNin}	Rat	Weight Gain	susceptibility	IAGP		8655976		RGD

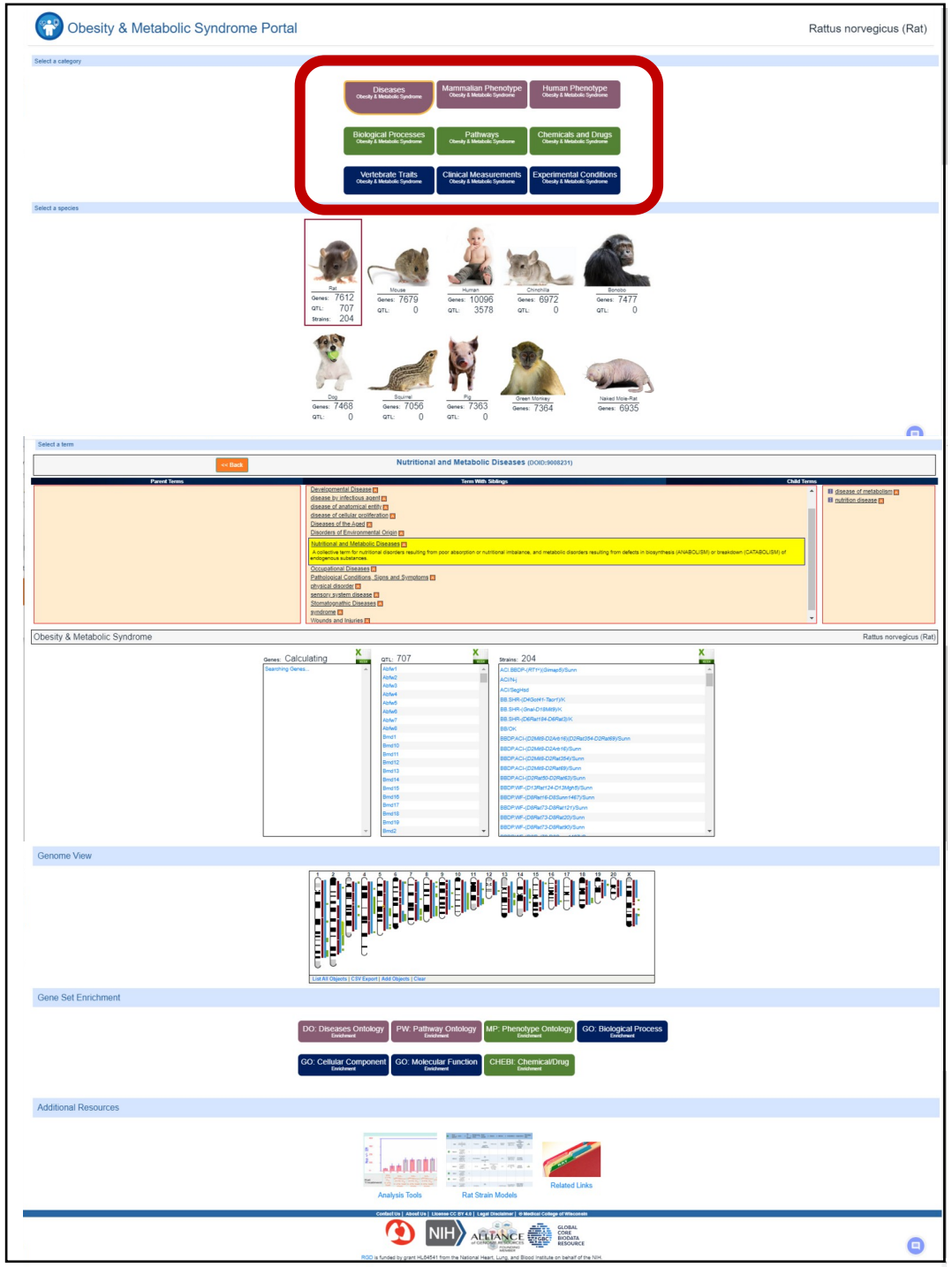
oxidative stress (IAGP) | retina degeneration (IAGP) | thin retina outer nuclear layer (IAGP)
thin retina outer plexiform layer (IAGP)

Search table

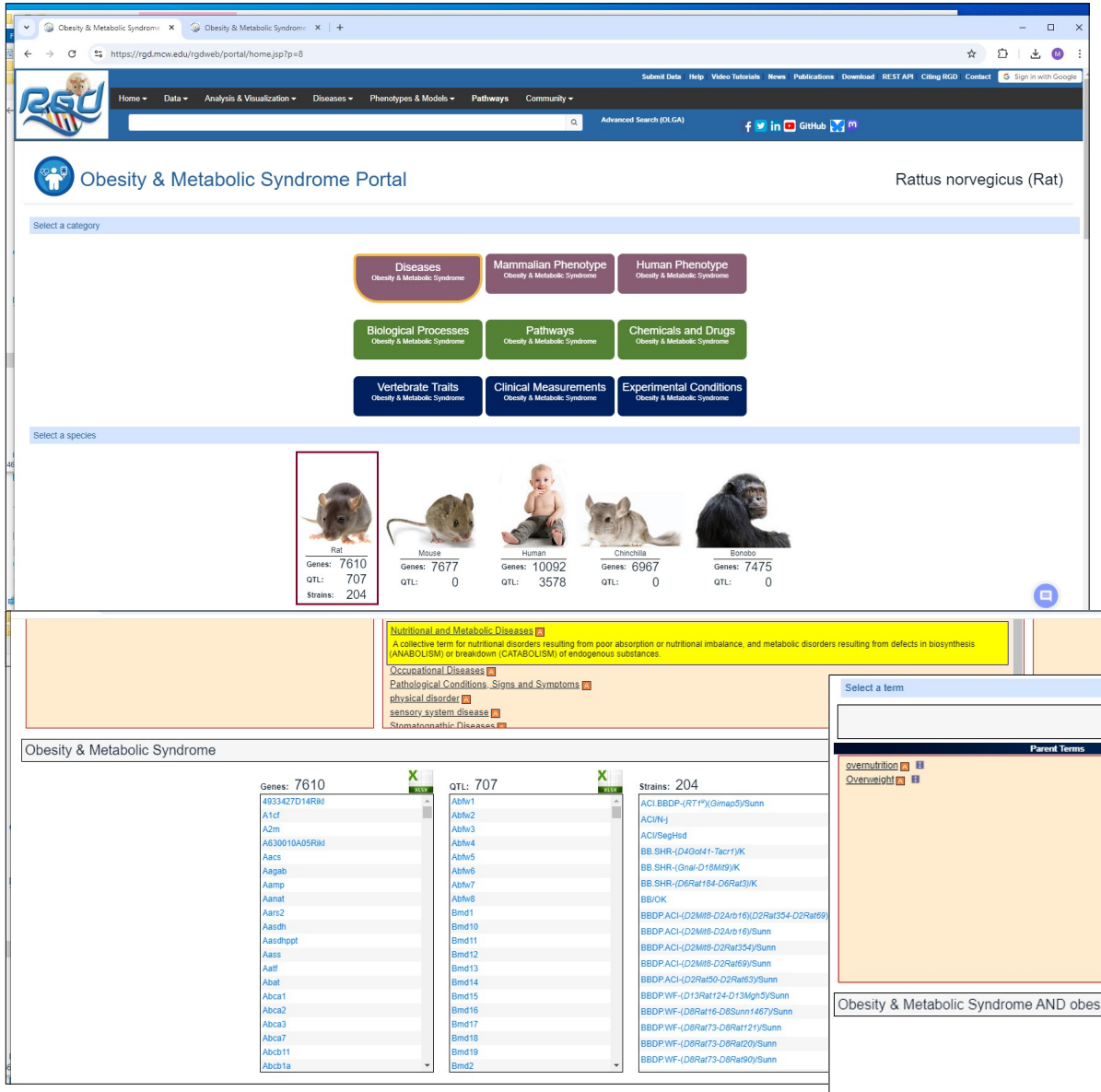
Symbol Name Trait
Bw146 Body weight QTL 146 body mass (VT:0001259)
1 to 1 of 1 rows 20

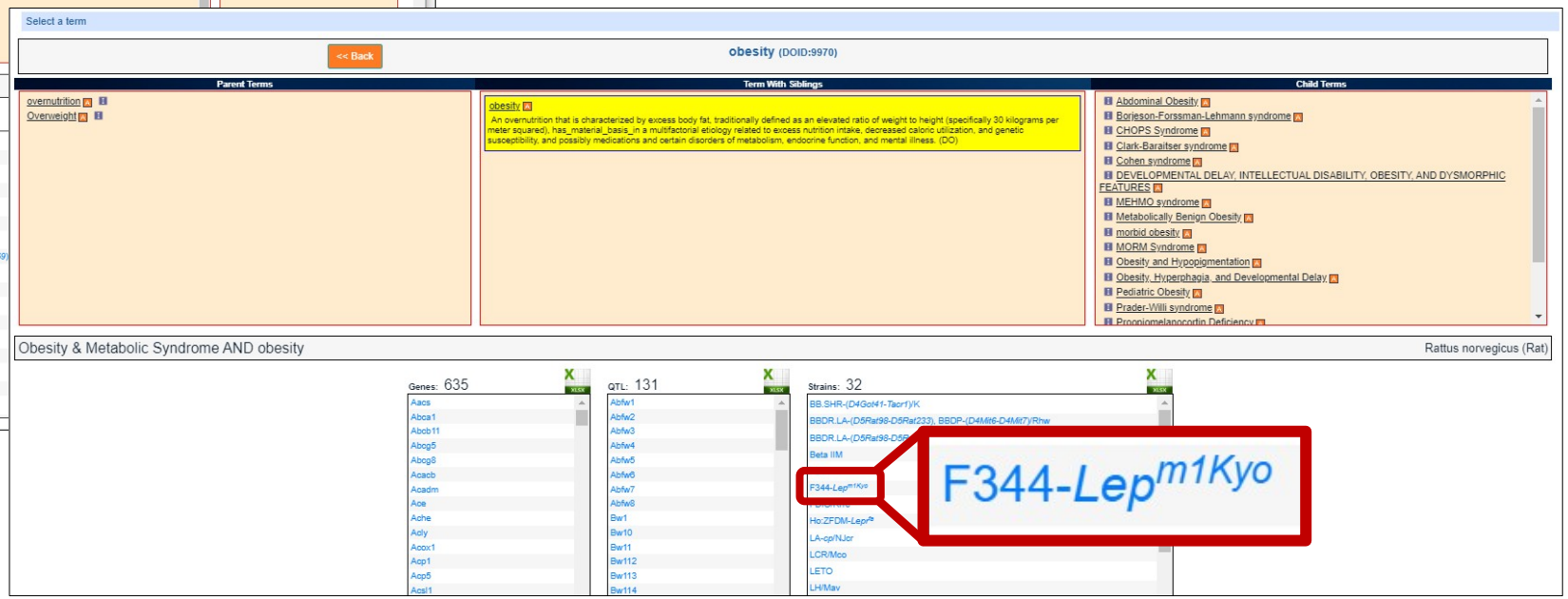


- **Method 2:** The RGD Disease Portals.
- Organize information for the most highly annotated disease categories.
- For today's example of OBESITY, look at the Obesity and Metabolic Syndrome Portal



- On the Disease Portal page are toggles to alter the page information to be focused on each possible ontology:
  - Diseases
  - Mammalian Phenotypes
  - Human Phenotypes
  - Biological Processes
  - Pathways
  - Chemicals and Drugs
  - Vertebrate Traits
  - Clinical Measurements
  - Experimental Conditions
- Click a toggle to update the information on the page accordingly
- The appropriate ontology browser will be displayed allowing selection of a more specific term if desired.
- Any of the 10 species for which RGD carries data can be selected and the page will update with the relevant data.





- The default ontology displayed is the Disease Ontology.
- The page default term will be for the least granular term that fits the Portal category, in this case, "Nutritional and Metabolic Diseases".
- For "Nutritional and Metabolic Diseases", 204 strains are listed
- For the more specific term "obesity" (selected by drilling into the ontology tree), there are 32 strains.
- Note that these include those that are models for the disease, and also strains used as controls.
- Click a gene, QTL, or strain symbol to access the appropriate report page.

Strain Registration

General

Strain: F344-*Lep*^{m1Kyo}

Symbol:	F344-*Lep*^{m1Kyo}
Strain:	F344-*Lep*^{m1}
Substrain:	Kyo
Full Name:	F344 OB rat
RGD ID:	8549776
Citation ID:	RRID:RGD_8549776
Ontology ID:	RS:0003644
Alleles:	*Lep*^{m1Kyo}; *Lep*
Also Known As:	F344-Lepm1Kyo; F344 OB rat; NBRP Rat No: 0628; F344-Lep^[m1Kyo]
Type:	mutant
Available Source:	National BioResource Project for the Rat in Japan
Origination:	National BioResource Project for the Rat in Japan
Description:	Established by ENU mutagenesis in F344/NSlc rats. This strain has Lep missense mutation (Q92X).
Coat Color:	albino
Inbred Generations:	N10
Last Known Status:	Live Animals (as of 2017-03-17)
Research Usage	Diabetes Obesity

Position

Rat Assembly	Chr	Position (strand)	Source	JBrowse
mRatBN7.2	4	57,672,294 - 57,672,294	RGD_MAPPER_PIPELINE	mRatBN7.2
Rnor_6.0	4	56,348,850 - 56,348,850	RGD_MAPPER_PIPELINE	Rnor6.0
Rnor_5.0	4	56,085,079 - 56,099,209	RGD_MAPPER_PIPELINE	Rnor5.0
RGSC_v3.4	4	55,943,837 - 55,945,938	RGD_MAPPER_PIPELINE	RGSC3.4

Summary
- Congenic Strains
- Mutant Strains

Annotation
- RGD Manual Disease
- Phenotype
- Mammalian Phenotype

References
- References - curated

Region
- Allelic Variants

Congenic Strains

F344.NER-(D1Mgh6-D1Rat73)(D5Mgh4-D5Rat36)Lgi1m1/Kyo

Mutant Strains

F344.NER-(D1Mgh6-D1Rat73)(D5Mgh4-D5Rat36)Lgi1m1/Kyo

Annotation

Click to see Annotation Summary View

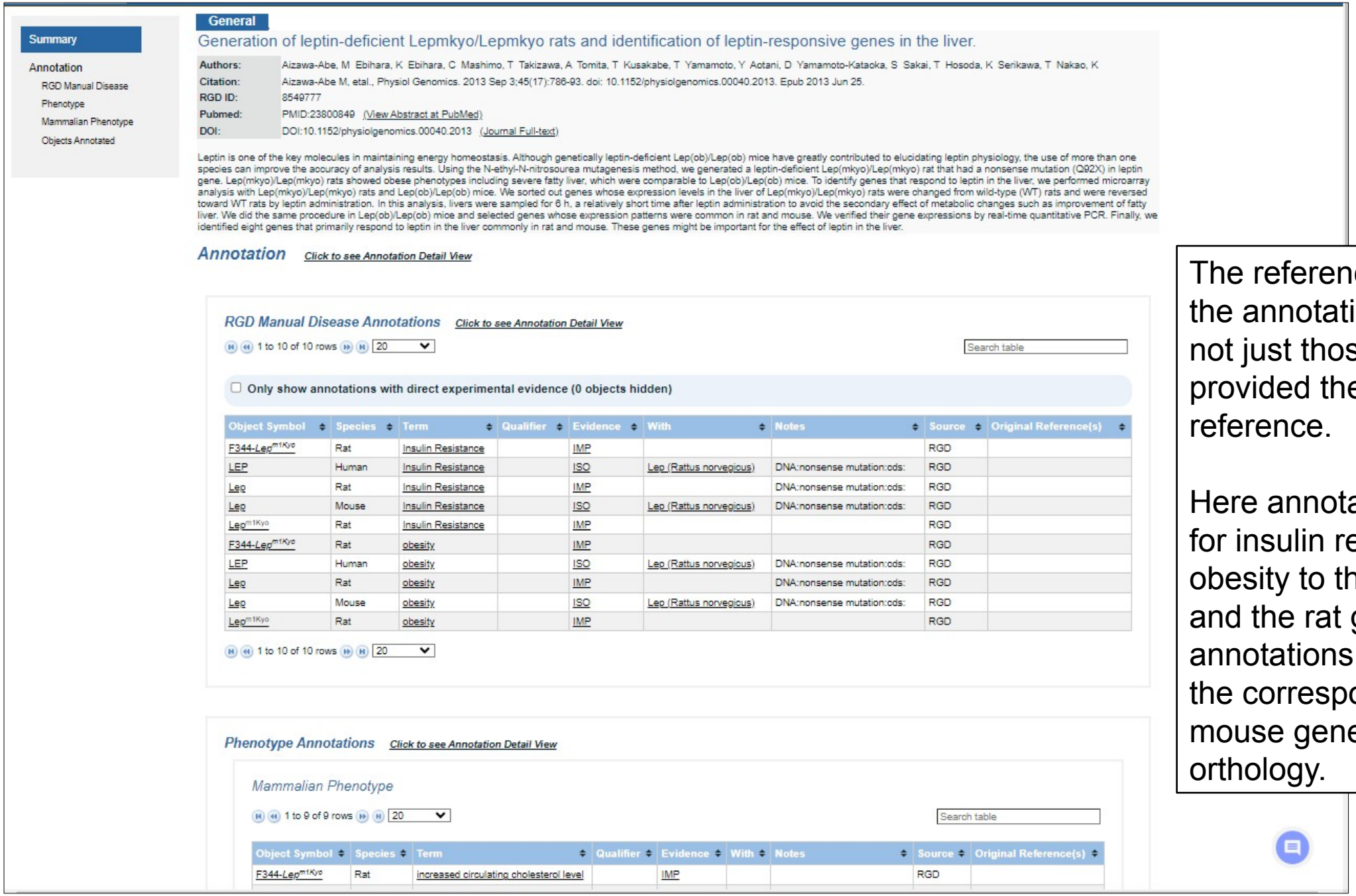
RGD Manual Disease Annotations

Click to see Annotation Summary View

Only show annotations with direct experimental evidence (0 objects hidden)

Object Symbol	Species	Term	Qualifier	Evidence	With	Reference	Notes	Source	Original Reference(s)
F344-*Lep*^{m1Kyo}	Rat	Insulin Resistance		IMP		8549777		RGD	
F344-*Lep*^{m1Kyo}	Rat	obesity		IMP		8549777		RGD	

- As mentioned before, the strain report page is formatted to provide access to all information in RGD for that strain.
  - Persistent identifiers
  - Allele and gene information
  - Strain type (mutant, inbred, etc)
  - **Source where the strain is available**
  - Strain description
  - Related strains
- Annotations include clickable links to related references for data provenance.



Summary

Annotation
- RGD Manual Disease
- Phenotype
- Mammalian Phenotype
- Objects Annotated

General

Generation of leptin-deficient Lepmkyo/Lepmkyo rats and identification of leptin-responsive genes in the liver.

Authors:	Aizawa-Abe, M Ebihara, K Ebihara, C Mashimo, T Takizawa, A Tomita, T Kusakabe, T Yamamoto, Y Aotani, D Yamamoto-Kataoka, S Sakai, T Hosoda, K Serikawa, T Nakao, K
Citation:	Aizawa-Abe M, etal., Physiol Genomics. 2013 Sep 3;45(17):786-93. doi: 10.1152/physiolgenomics.00040.2013. Epub 2013 Jun 25.
RGD ID:	8549777
Pubmed:	PMID:23800849 (View Abstract at PubMed)
DOI:	DOI:10.1152/physiolgenomics.00040.2013 (Journal Full-text)

Leptin is one of the key molecules in maintaining energy homeostasis. Although genetically leptin-deficient Lep(ob)/Lep(ob) mice have greatly contributed to elucidating leptin physiology, the use of more than one species can improve the accuracy of analysis results. Using the N-ethyl-N-nitrosourea mutagenesis method, we generated a leptin-deficient Lep(mkyo)/Lep(mkyo) rat that had a nonsense mutation (Q92X) in leptin gene. Lep(mkyo)/Lep(mkyo) rats showed obese phenotypes including severe fatty liver, which were comparable to Lep(ob)/Lep(ob) mice. To identify genes that respond to leptin in the liver, we performed microarray analysis with Lep(mkyo)/Lep(mkyo) rats and Lep(ob)/Lep(ob) mice. We sorted out genes whose expression levels in the liver of Lep(mkyo)/Lep(mkyo) rats were changed from wild-type (WT) rats and were reversed toward WT rats by leptin administration. In this analysis, livers were sampled for 6 h, a relatively short time after leptin administration to avoid the secondary effect of metabolic changes such as improvement of fatty liver. We did the same procedure in Lep(ob)/Lep(ob) mice and selected genes whose expression patterns were common in rat and mouse. We verified their gene expressions by real-time quantitative PCR. Finally, we identified eight genes that primarily respond to leptin in the liver commonly in rat and mouse. These genes might be important for the effect of leptin in the liver.

Annotation *Click to see Annotation Detail View*

RGD Manual Disease Annotations *Click to see Annotation Detail View*

1 to 10 of 10 rows 20 Search table

Only show annotations with direct experimental evidence (0 objects hidden)

Object Symbol	Species	Term	Qualifier	Evidence	With	Notes	Source	Original Reference(s)
F344-Lep^{m1Kyo}	Rat	Insulin Resistance		IMP			RGD	
LEP	Human	Insulin Resistance		ISO	Lep (Rattus norvegicus)	DNA:nonsense mutation:cds:	RGD	
Lep	Rat	Insulin Resistance		IMP		DNA:nonsense mutation:cds:	RGD	
Lep	Mouse	Insulin Resistance		ISO	Lep (Rattus norvegicus)	DNA:nonsense mutation:cds:	RGD	
Lep^{m1Kyo}	Rat	Insulin Resistance		IMP			RGD	
F344-Lep^{m1Kyo}	Rat	obesity		IMP			RGD	
LEP	Human	obesity		ISO	Lep (Rattus norvegicus)	DNA:nonsense mutation:cds:	RGD	
Lep	Rat	obesity		IMP		DNA:nonsense mutation:cds:	RGD	
Lep	Mouse	obesity		ISO	Lep (Rattus norvegicus)	DNA:nonsense mutation:cds:	RGD	
Lep^{m1Kyo}	Rat	obesity		IMP			RGD	

1 to 10 of 10 rows 20

Phenotype Annotations *Click to see Annotation Detail View*

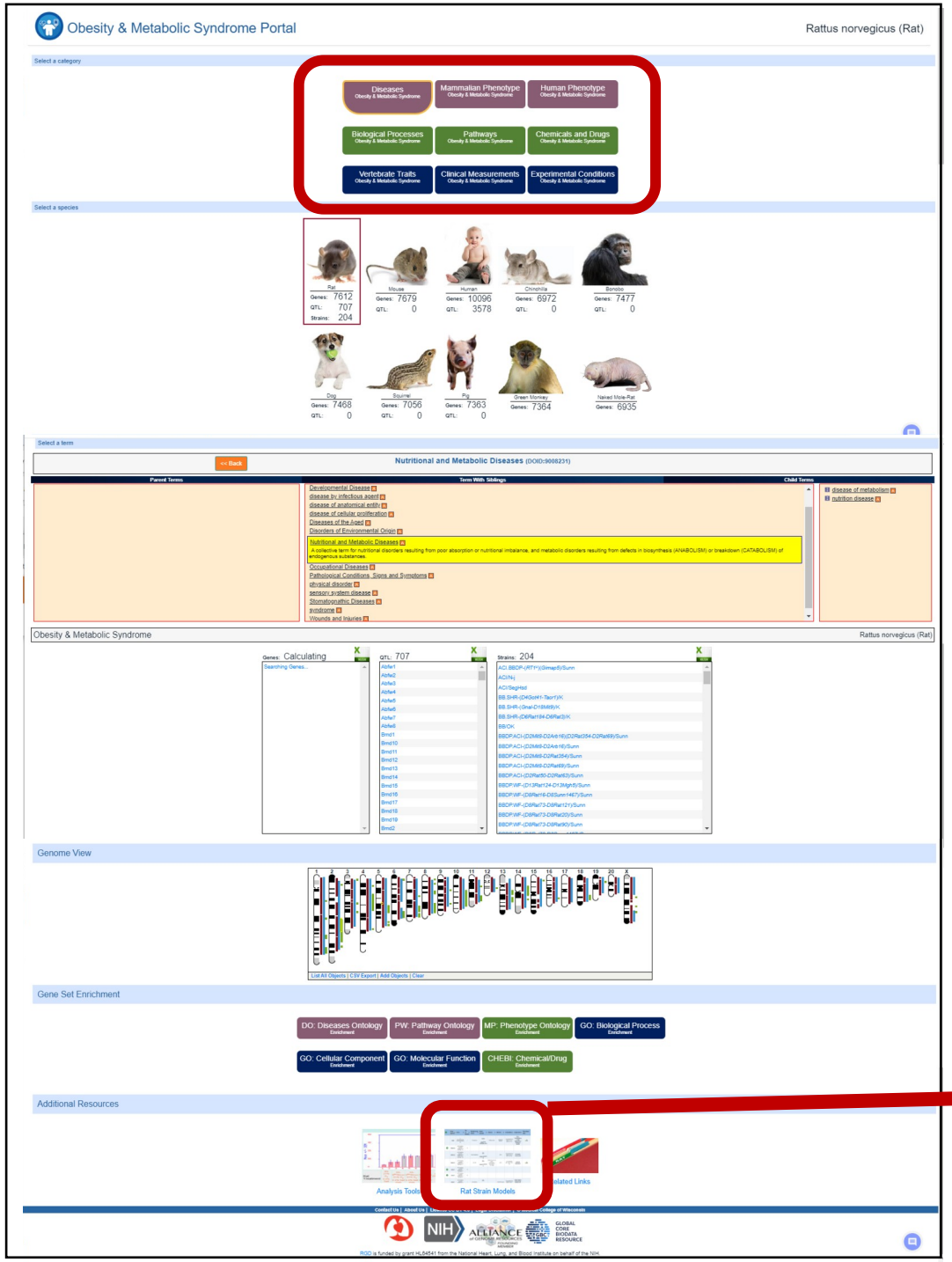
Mammalian Phenotype

1 to 9 of 9 rows 20 Search table

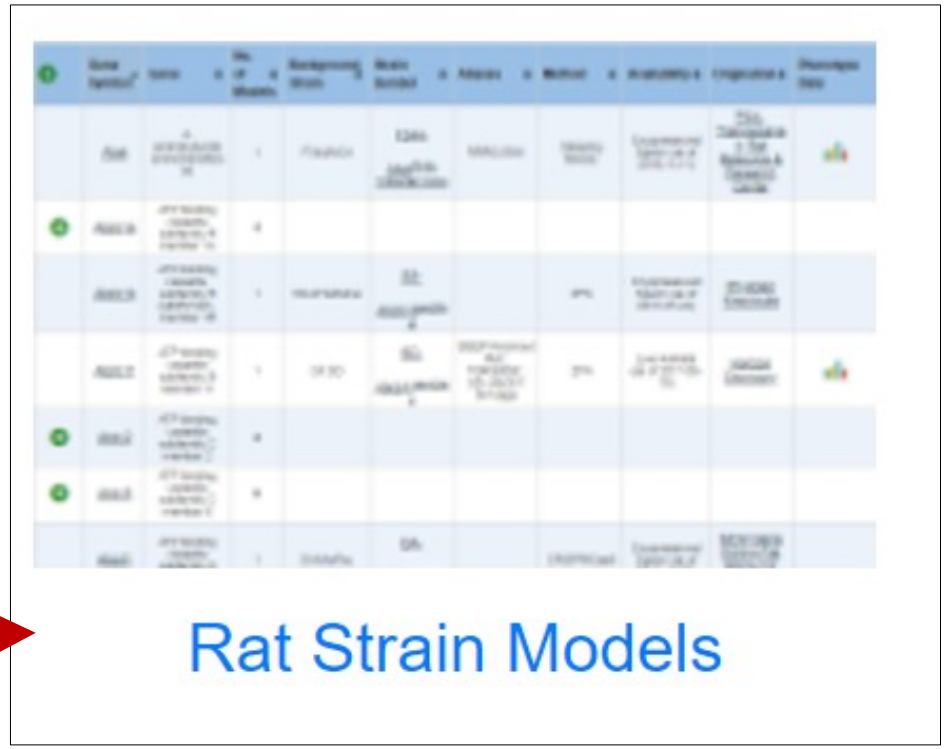
Object Symbol	Species	Term	Qualifier	Evidence	With	Notes	Source	Original Reference(s)
F344-Lep^{m1Kyo}	Rat	increased circulating cholesterol level		IMP			RGD	

The reference report shows all the annotations for that paper, not just those of the strain that provided the link to the reference.

Here annotations were made for insulin resistance and obesity to the strain, the allele and the rat gene, plus annotations were assigned to the corresponding human and mouse genes based on orthology.



Going back to the Disease Portal page, in addition to the strains given in the interactive list, there is a link at the bottom of the page to RGD's Find Models tool.



Rat Models Results

Enter a Disease or Phenotype or Strain or Condition to find the rat models

obesity

Examples: Hypertension Cancer MHS/Gib

(OR) Browse Ontology Tree, Select Term & Search:

Browse Disease Ontology Browse Mammalian Phenotype Ontology Browse Strain Ontology

For more about the Find Models tool, see the poster presented by M. Kaldunski, later today.

Filter by ...

All Results(50)

Models

Disease (35)
- MODEL: spontaneous (9)
- MODEL: control (5)
- susceptibility (2)
- MODEL: induced (1)
- MODEL: treatment (1)
- disease_progression (1)
- sexual_dimorphism (1)
- treatment (1)

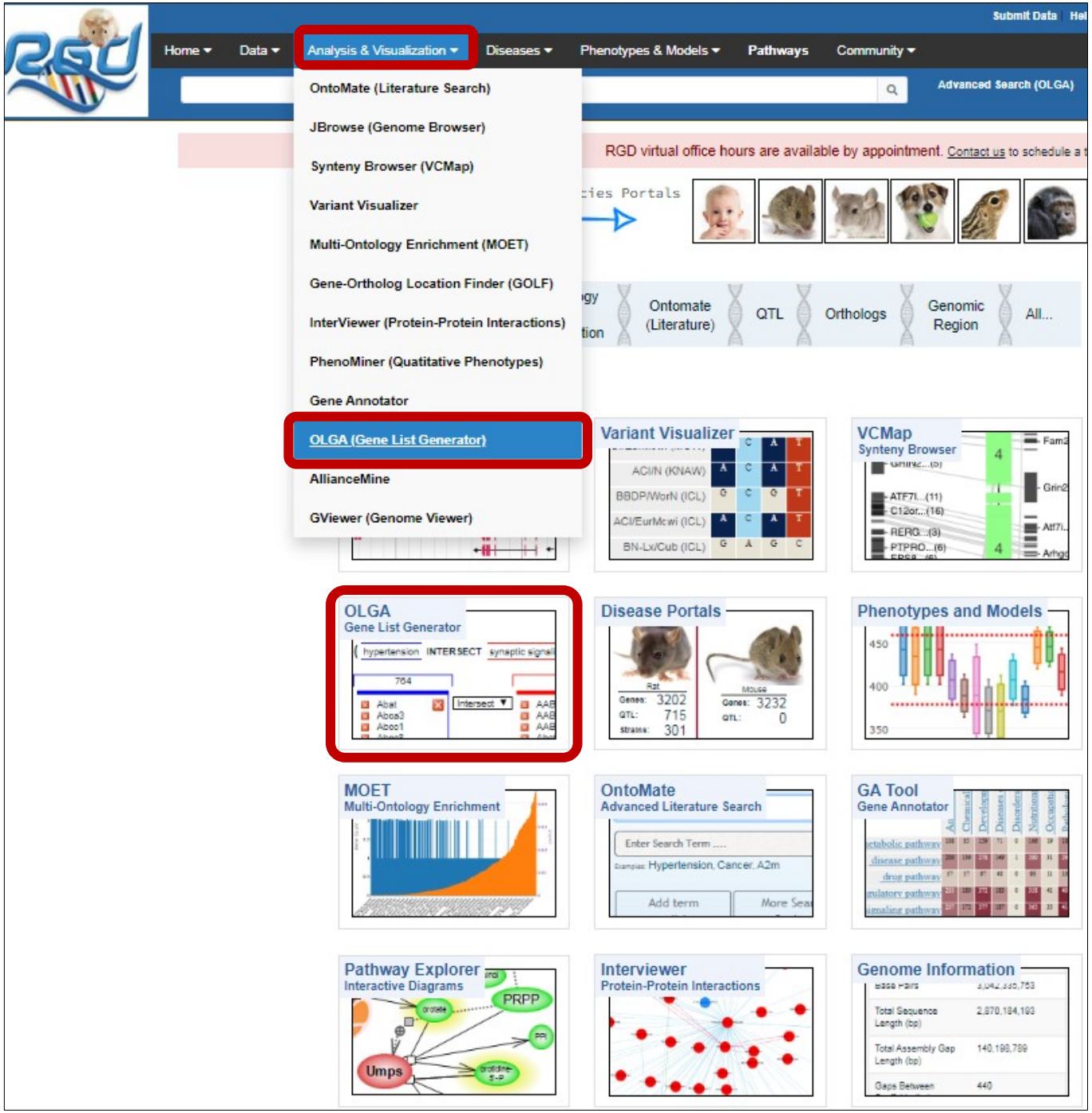
Phenotype (15)
- treatment (2)
- induced (1)
- susceptibility (1)

Strain Types
- mutant (17)
- inbred (18)
- congenic (9)
- hybrid (5)
- outbred (2)
- transgenic (1)

Conditions
- controlled calorie content diet (4)
- controlled fat content diet (1)
- dehydroepiandrosterone (1)
- quinapril (1)
- rosiglitazone (1)

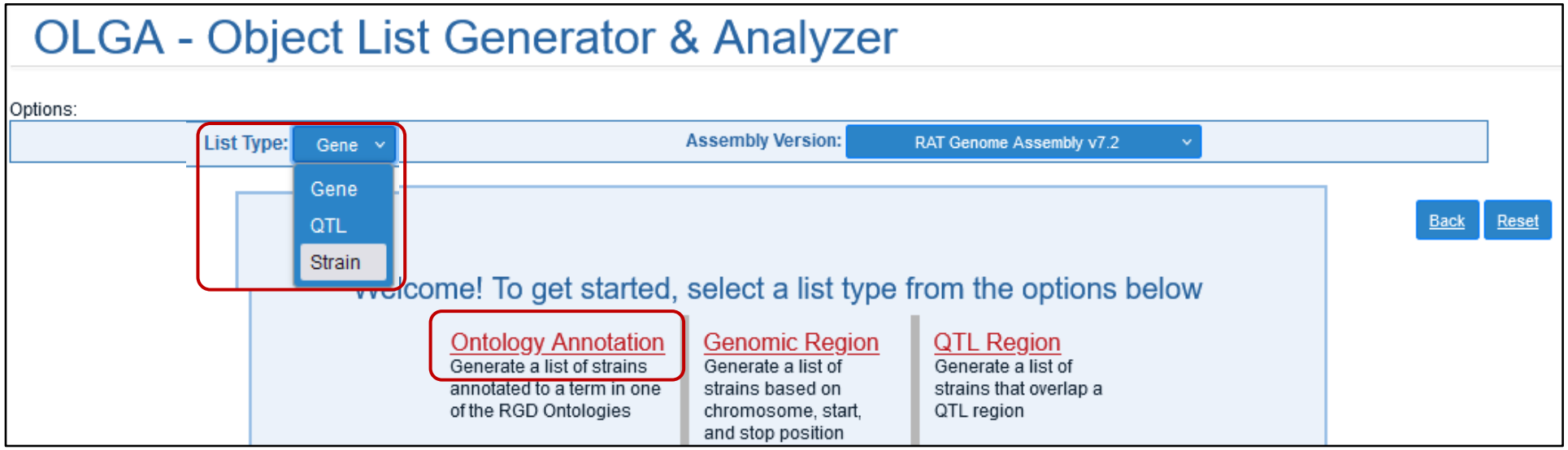
50 results for term "obesity "

Strain	Considered as type ...	Disease/Phenotype	With conditions	Evidence Code	Reference
Search for strain...					
LA-*cp*/NJcr	MODEL: spontaneous	obesity		IAGP	1642391 21408584 21408581
ZSF1-*Lepr*$^{fa/cp}$/Crl	MODEL: spontaneous	obesity		IAGP	401960103 401965413 401965414
WI-*Mc4r*^{tm1Hubr}	MODEL: spontaneous	obesity		IMP	13825242 6478803
Slc:ZUC-*Lepr*$^{fa/+}$	MODEL: spontaneous	obesity		IAGP	12859276 2300017
SDDR/Rrrc	MODEL: control	obesity		IAGP	1302371 21408576
SDDIO/Rrrc	MODEL: spontaneous	obesity		IAGP	1302371 21408576
ZSF1-*Lepr*^{lean}/Crl	MODEL: control	obesity		IAGP	401960103 401965414 401965413
FDIO/Rrrc	MODEL: induced	obesity	controlled calorie content diet | controlled fat content diet	IAGP	6482246 24922212
FDIO/Rrrc	MODEL: spontaneous	obesity		IAGP	24922212
LETO	MODEL: control	obesity		IAGP	21406435
ZUC-*Lepr*$^{faSteJrpz+/+}$	MODEL: spontaneous	obesity		IAGP	628436 24922198
ZUC-*Lepr*$^{+Ste}$	MODEL: control	obesity		IAGP	628581 628910
ZUC-*Lepr*$^{faSte-/-}$	MODEL: spontaneous	obesity		IAGP	628581 628910
F344	MODEL: control	obesity		IAGP	6482246 24922212
OLETF	MODEL: treatment	obesity	rosiglitazone	IAGP	21406435
SDT.Cg-*Lepr*^{fa}/Utt	MODEL: spontaneous	obesity		IAGP	2314025 2314024 2314022
SHRSP.ZUC-(*D5Rat4-D5Rat36*)/IzmDmcr	susceptibility	obesity		IAGP	2300017
ZUC-*Lepr*$^{faSte-/-}$	sexual_dimorphism	obesity		IAGP	7365117
LH/Mav		obesity		IAGP	1580389
SD-*Lepr*^{em3}		obesity		IMP	12910507
SD-*Lep*$^{em1Sage-/-}$		obesity		IMP	12904911
SS-*Lepr*^{em2Mcw}	disease_progression	obesity		IMP	12911217
ZSF1-*Lepr*$^{fa/cp}$/Crl	treatment	obesity		IAGP	401965412
SD-*Lepr*^{em2}		obesity		IMP	12910507
Beta IIM		obesity		IAGP	724733

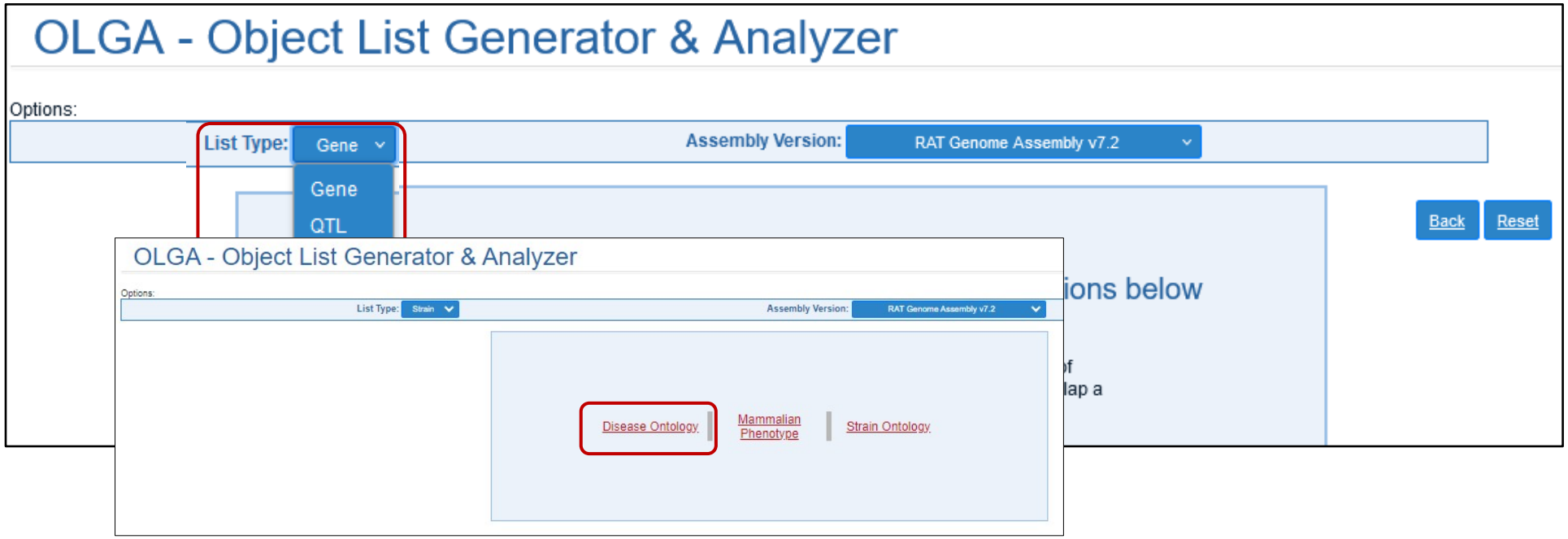


Method 3: Search for strains for a specific disease or for the intersection of more than one disease using the **Object List Generator & Analyzer**, or OLGA tool.

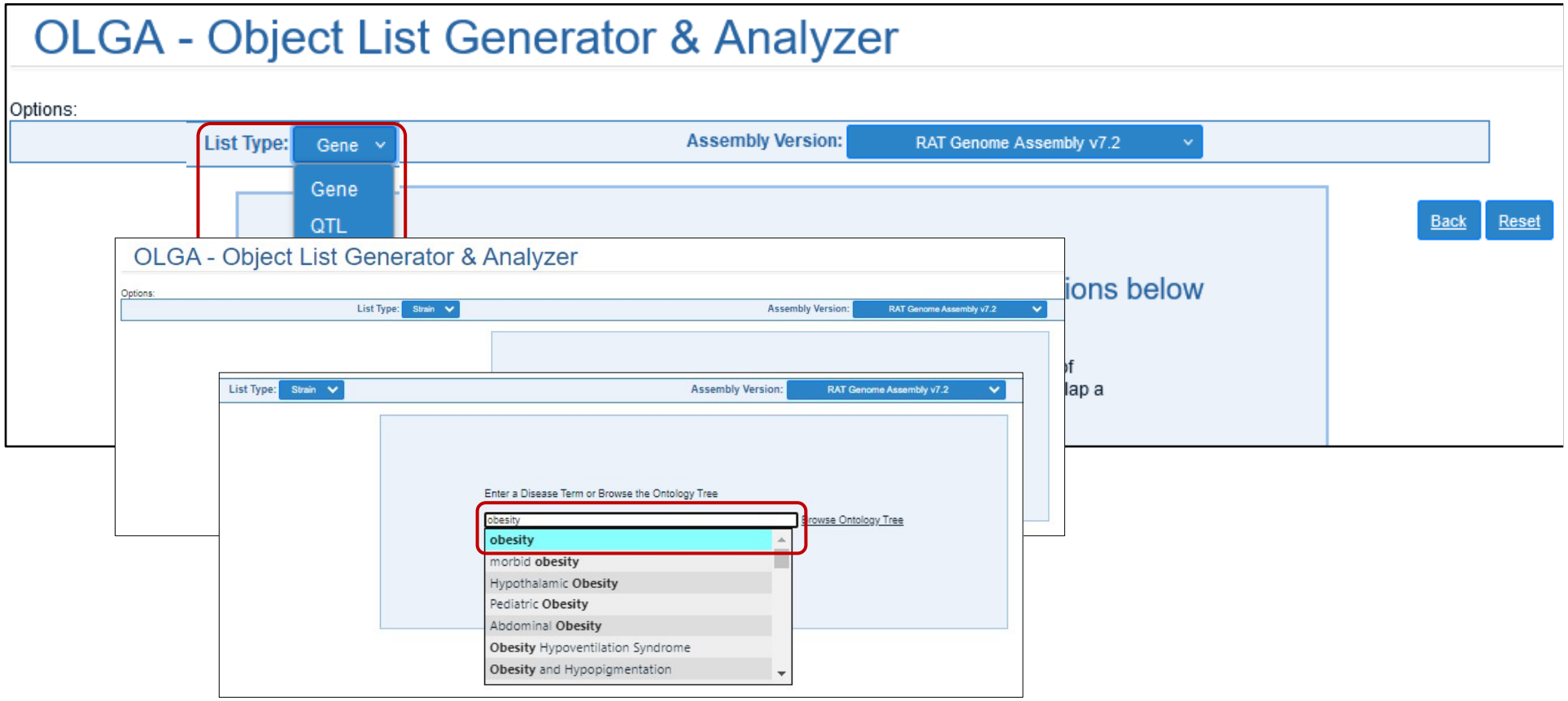
- From the Analysis & Visualization menu in the top black bar, choose "OLGA"
- Or use the prominent button on the RGD home page



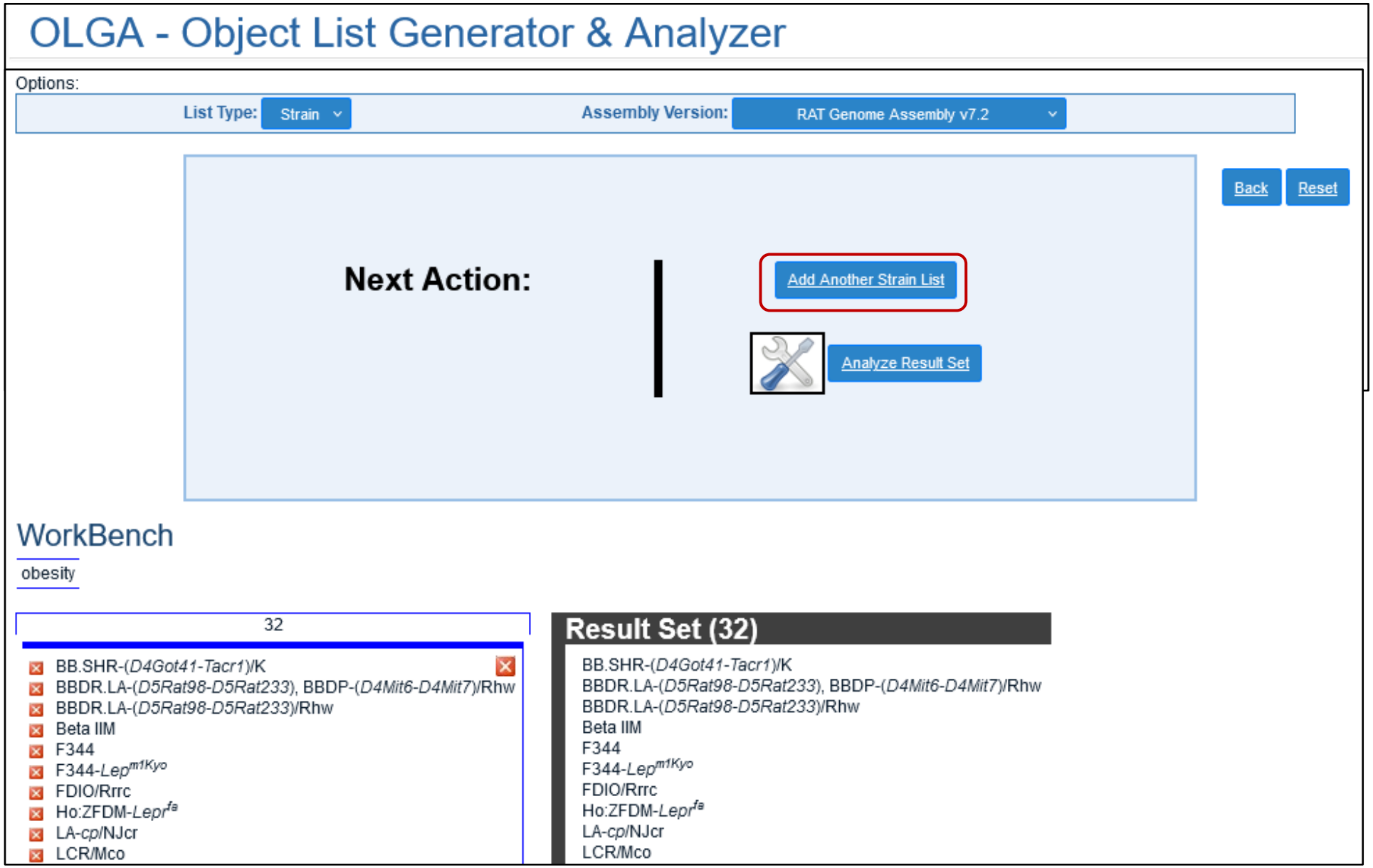
- Select Strain from the "List type" dropdown and "Ontology Annotation" from the options below.



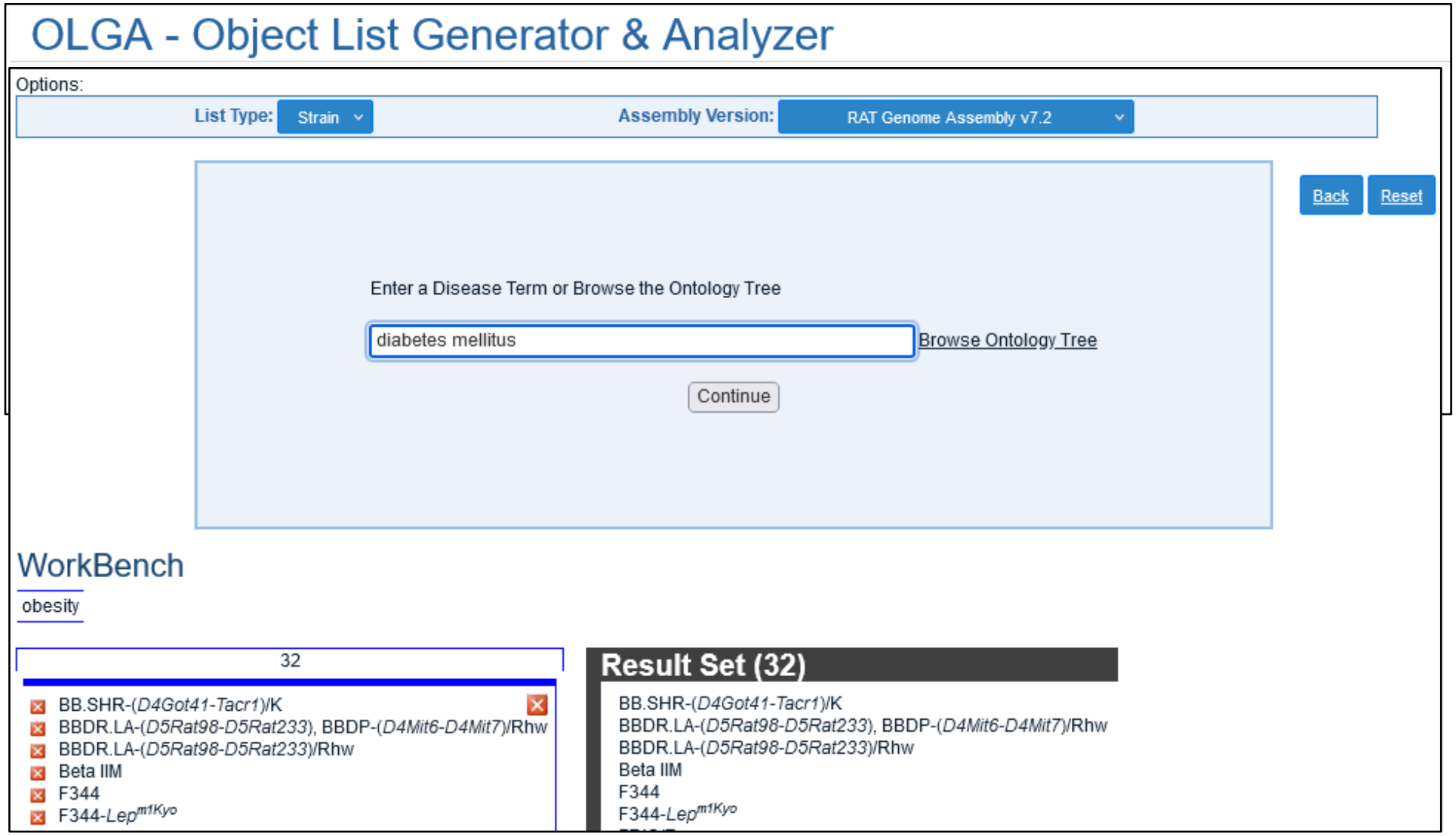
- Select Strain from the "List type" dropdown and "Ontology Annotation" from the options below.
- Choose the Disease Ontology



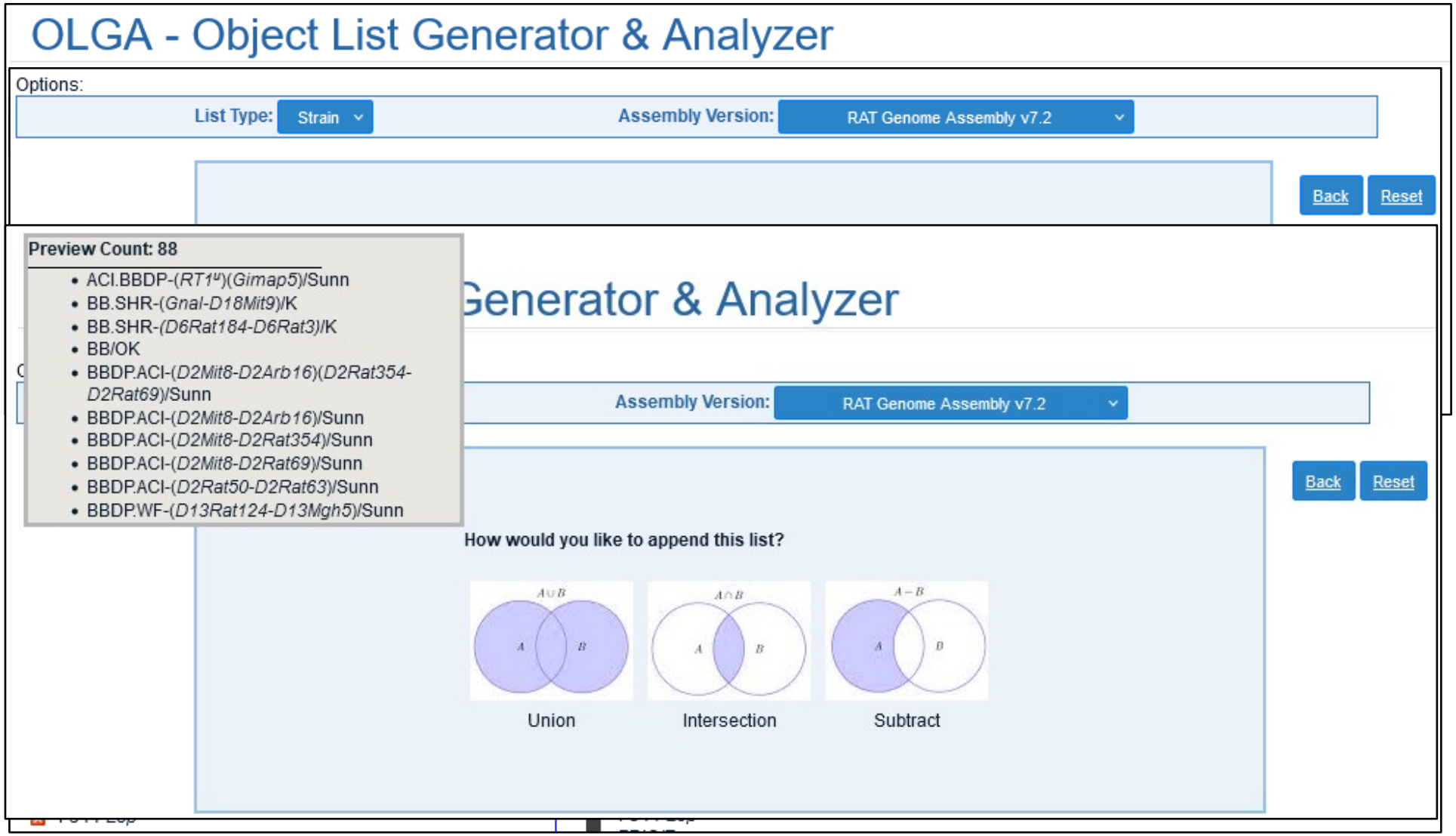
- Select Strain from the "List type" dropdown and "Ontology Annotation" from the options below.
- Choose the Disease Ontology
- Autocomplete options are provided. Choose "obesity" and click "Continue".



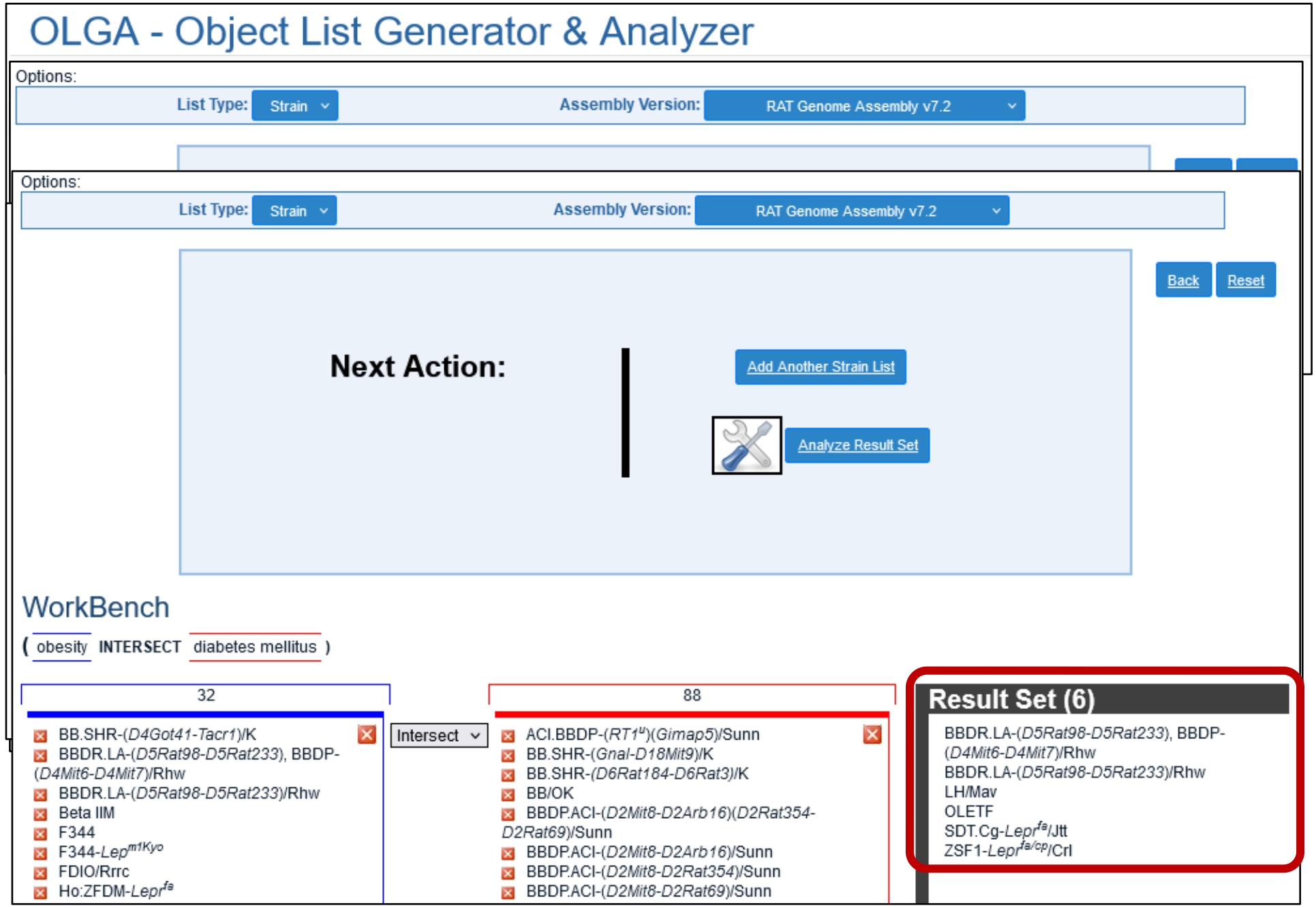
- Select Strain from the "List type" dropdown and "Ontology Annotation" from the options below.
- Choose the Disease Ontology
- Autocomplete options are provided. Choose "obesity" and click "Continue".
- The result set shows the same 32 strains found on the Disease Portal page for obesity.
- Select "Add Another Strain List" to bring back the term entry box.



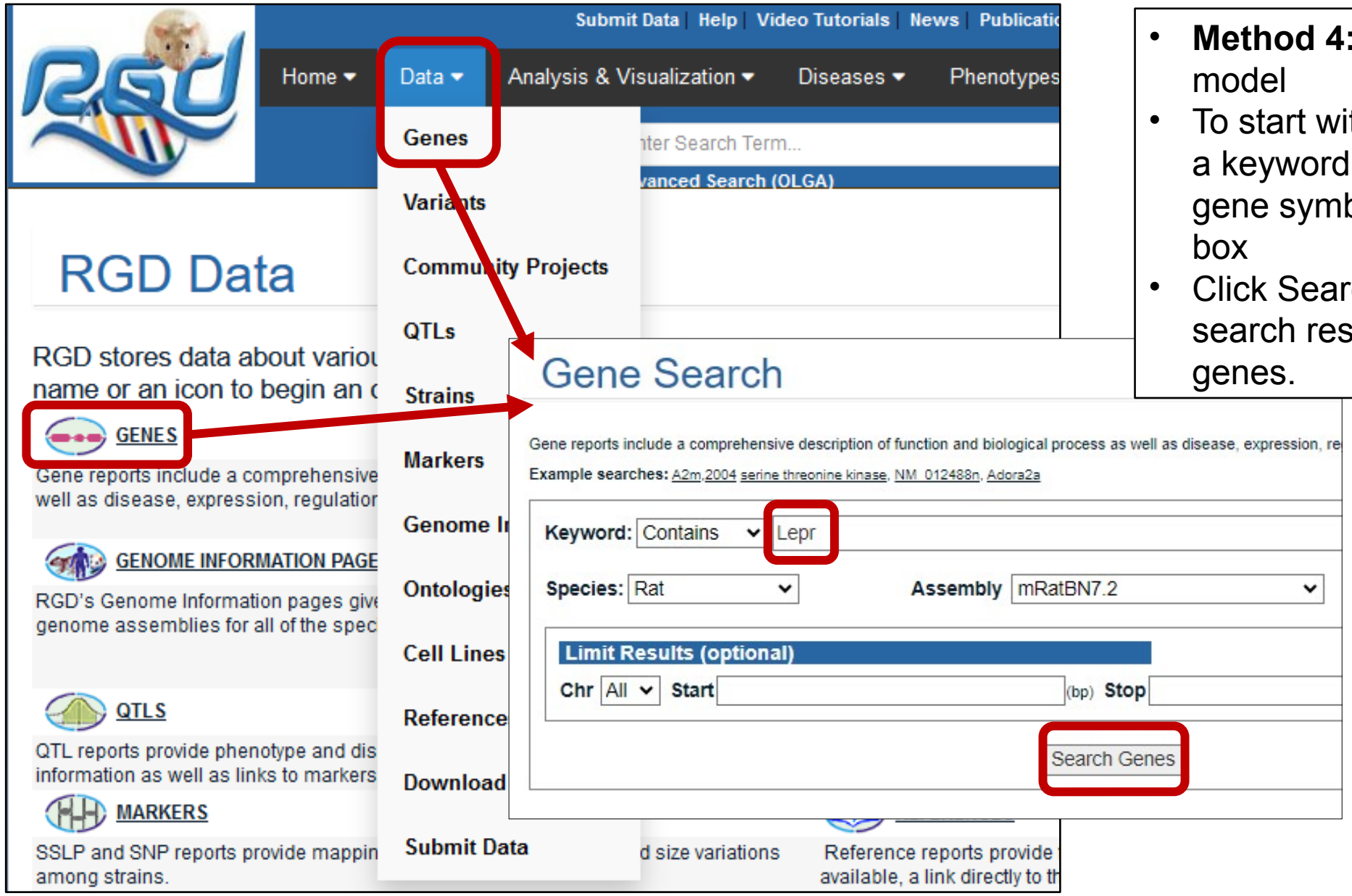
- Enter "diabetes mellitus" (DM) in the search box.



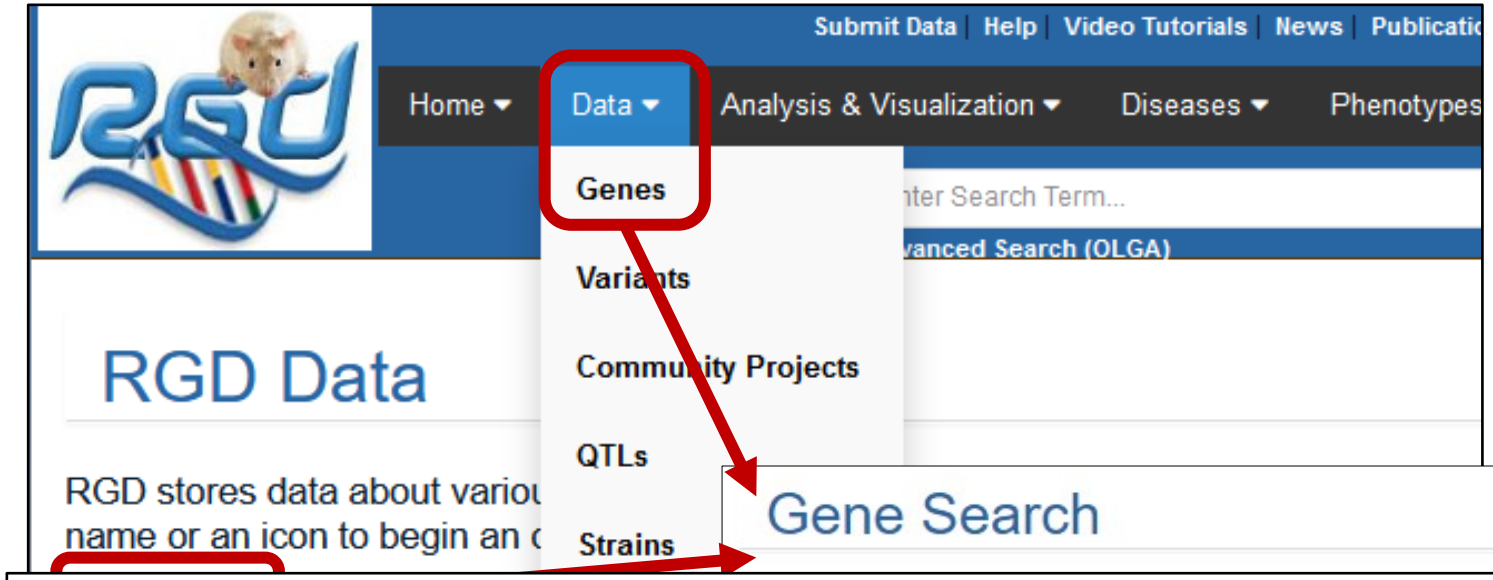
- Enter "diabetes mellitus" (DM) in the search box.
- The tool gives a preview of the 88 strains for diabetes and options for how to combine the two lists
  - Union
  - Intersection
  - Subtraction



- Enter "diabetes mellitus" (DM) in the search box.
- The tool gives a preview of the 88 strains for diabetes and options for how to combine the two lists
  - Union
  - Intersection
  - Subtraction
- Choose "Intersection" to get the list of six strains annotated to both obesity and diabetes.



- **Method 4:** Use a gene to find a model
- To start with a gene of interest, enter a keyword such as all or part of a gene symbol or name in the search box
- Click Search Genes to open a search result page with all related genes.



- **Method 4:** Use a gene to find a model
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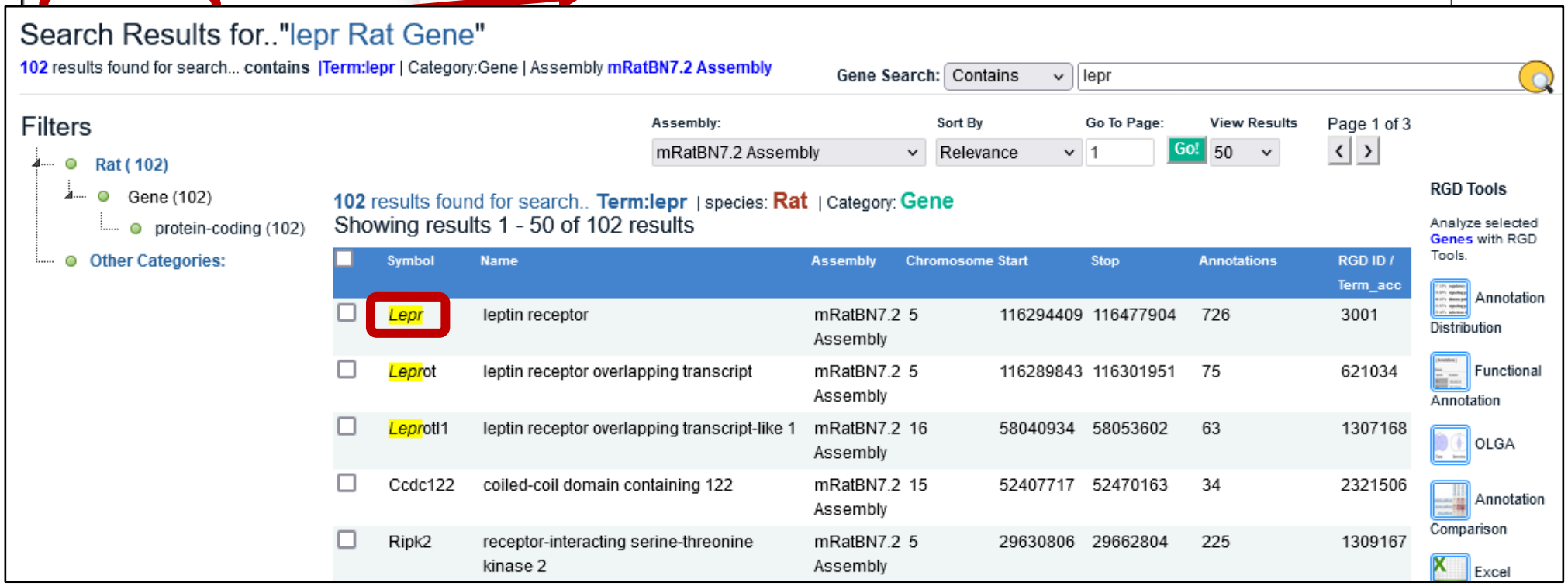
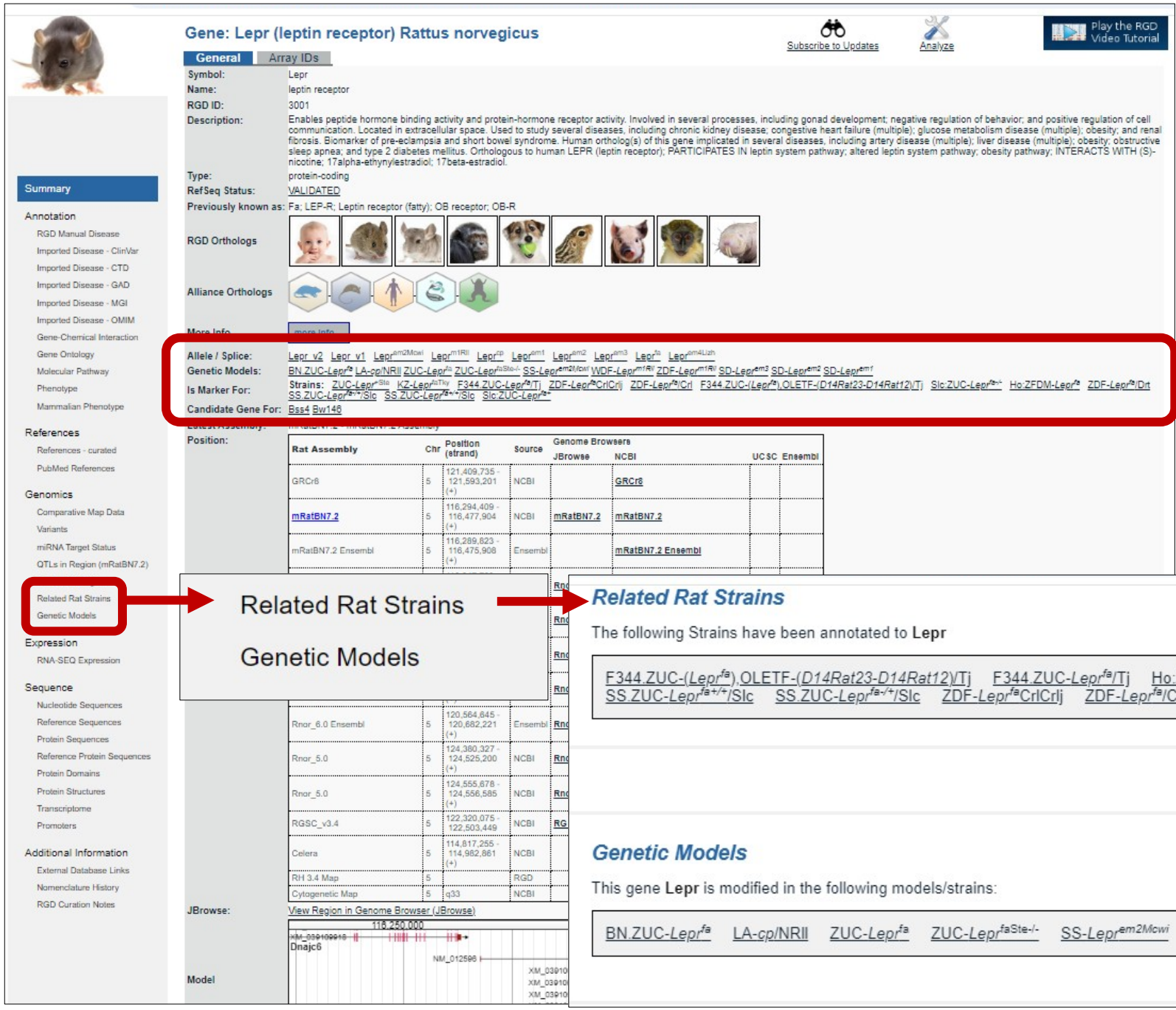


- Click the gene symbol to access the report page for that gene.



Related Rat Strains

Genetic Models

Related Rat Strains

The following Strains have been annotated to **Lepr**

F344.ZUC-(*Lepr*^{fa}),OLETF-(*D14Rat23-D14Rat12*)/Tj F344.ZUC-*Lepr*^{fa}/Tj Ho:ZFDM-*Lepr*^{fa} KZ-*Lepr*^{faTky} Slc:ZUC-*Lepr*$^{fa+}$ Slc:ZUC-*Lepr*$^{fa-/-}$ SS.ZUC-*Lepr*$^{fa+/+}$/Slc SS.ZUC-*Lepr*$^{fa-/+}$/Slc ZDF-*Lepr*^{fa}CrlCrlj ZDF-*Lepr*^{fa}/Crl ZDF-*Lepr*^{fa}/Drt ZUC-*Lepr*$^{+Ste}$

Genetic Models

This gene **Lepr** is modified in the following models/strains:

BN.ZUC-*Lepr*^{fa} LA-*cp*/NRll ZUC-*Lepr*^{fa} ZUC-*Lepr*$^{faSte-/-}$ SS-*Lepr*^{em2Mcwi} WDF-*Lepr*^{m1Rll} ZDF-*Lepr*^{m1Rll} SD-*Lepr*^{em3} SD-*Lepr*^{em2} SD-*Lepr*^{em1}

- The gene report page is formatted similarly to a strain report page
- Entries in the menu down the left side jump to sections and information by categories.
- There is a listing of genetic models at the top of the page.
- Click "Related Rat Strains" or "Genetic Models" in the left sidebar to move down to that region of the report page.
- Click a Strain symbol from the list to open the relevant strain report page.