

Question 12

How does a user find characterized mouse mutants corresponding to human genes?

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The NCBI provides a set of maps that show chromosomal regions homologous between mouse and human. This resource can be accessed directly at <http://www.ncbi.nlm.nih.gov/Homology/>. For this example using a known, mapped human gene, however, it is easier to start the search from the LocusLink entry for tyrosinase. The LocusLink¹⁰ query page can be found at <http://www.ncbi.nlm.nih.gov/LocusLink/>. Select *Human* from the *Organism* pull-down menu, enter 'tyrosinase' into the *Query* box and click *Go*. To view the entry for tyrosinase (*TYR*), click on its LocusLink ID, 7299.

On the resulting page (Fig. 12.1), links to the mouse homology maps are in the section of the LocusLink summary page marked *Relationships*. In this case, there are four maps available for *TYR* showing mouse alignments: *NCBI vs MGD* aligns the current NCBI assembly of the human genome with the MGD (Mouse Genome Database²¹, at The Jackson Laboratory) genetic map, *UCSC vs. MGD* aligns the current UCSC genome assembly with the MGD genetic map, *NCBI vs. EST-based RH Map* aligns the NCBI assembly with the Whitehead–MRC RH map, and *UCSC vs. Hudson et al.* aligns the 7 October 2001 UCSC assembly with the Whitehead–MRC RH Map²². The *Hs* and *Mm* links adjacent to each map name show the mouse–human homology map with the master chromosome as human or mouse, respectively. Click on the *Hs* link next to the *NCBI vs. MGD* map.

The resulting mouse–human map shows the mouse genes that are the likely orthologs of human genes on human chromosome 11 (Fig. 12.2). Depending on the browser being used, one may have to click the *View as text* box to obtain the output; the resulting output will appear in text format, slightly different from what is shown in Fig. 12.2. Chromosomal locations of the mouse genes are shown, where known. The green circles link to the UniSTS entry for each locus; those on the left link to the human UniSTS entry, whereas those on the right link to the mouse UniSTS entry. The cytogenetic positions are hyperlinked to either the human or mouse Map Viewer, as appropriate. Gene symbols are linked to LocusLink¹⁰. The tyrosinase gene, highlighted in pink, maps to mouse chromosome 7 at 44 cM, a piece of information that will be needed in the next step.

The mouse models themselves are described at the Mouse Genome Informatics site at the Jackson Laboratory. Go to the Mouse Genome Informatics home page, at <http://www.informatics.jax.org/>, and use the *Advanced search for...* pull-down

menu to select *Linkage Maps*. On the resulting page, customize the search to find the region around the mouse gene *Tyr*. Under *Chromosome*, set the number to 7; then set the chromosomal region to between 40 and 48 cM.

Many of the uncloned mouse mutants are not mapped in high-resolution crosses, and many are carried out with a small number of mice relative to another easy-to-score phenotype for another mouse mutant that maps to the same chromosome. It is thus necessary to be lenient in looking for potential uncloned mouse mutants (± 4 cM relative to the location). In this case, as the NCBI data tells us that the gene is at 44 cM, the region from 40 to 48 cM should be searched.

Further down the page (Fig. 12.3), under *Markers*, set *Include DNA segments* to *No* to reduce the number of markers shown. Do include *syntenic markers*, which are DNA markers and mutant alleles linked to chromosome 7 that have not been finely mapped but that may be associated with a phenotype of interest relative to *TYR*. Under *Comparative Maps*, *Show orthologs from species*, choose *human (Homo sapiens)*. Select *Show all markers*. Use the default setting for all other options, and hit *Retrieve*.

The gene *Tyr* is found on page 2 of the output, at 44 cm (Fig. 12.4). The mouse chromosome is shown schematically on the left and expands as one moves to the right. In the rightmost columns are the names of the mouse markers in a particular region in blue and, if there is a corresponding human ortholog, the name of that ortholog in black. Some of the displayed mouse markers are genes, some are STSs, some are recessive mutants (all small letters) and some are dominant alleles (initial capital letter). At the bottom of the page are syntenic markers, those which have been mapped to chromosome 7 but not to an exact position.

Clicking the blue *Tyr* link at 44 cm opens up a summary of the *Genes, Markers, and Phenotypes* for that gene (Fig. 12.5). Of particular interest in this case are the phenotypic alleles. There are 100 mouse strains with mutations in the *Tyr* gene.

Users can also view chromosomal regions that are homologous between mouse and human or rat and human by using Ensembl's SyntenyView, available from the ContigView by clicking the *Jump to →syntenyview* link (Fig. 1.12, center yellow bar).

Figure 12.1

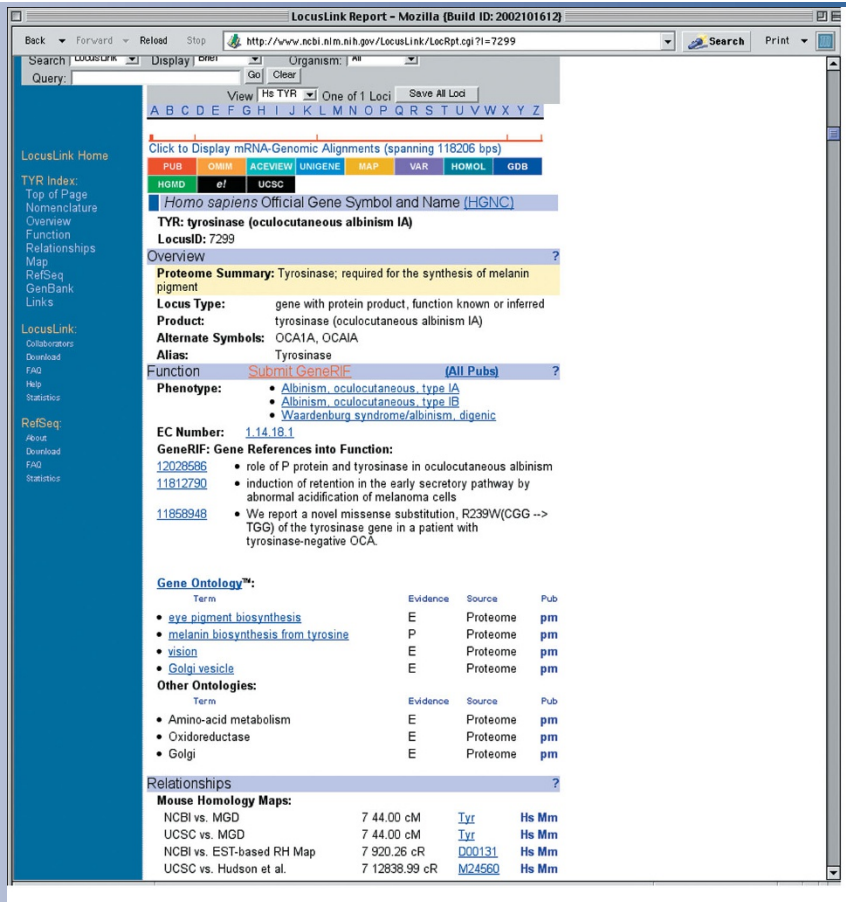
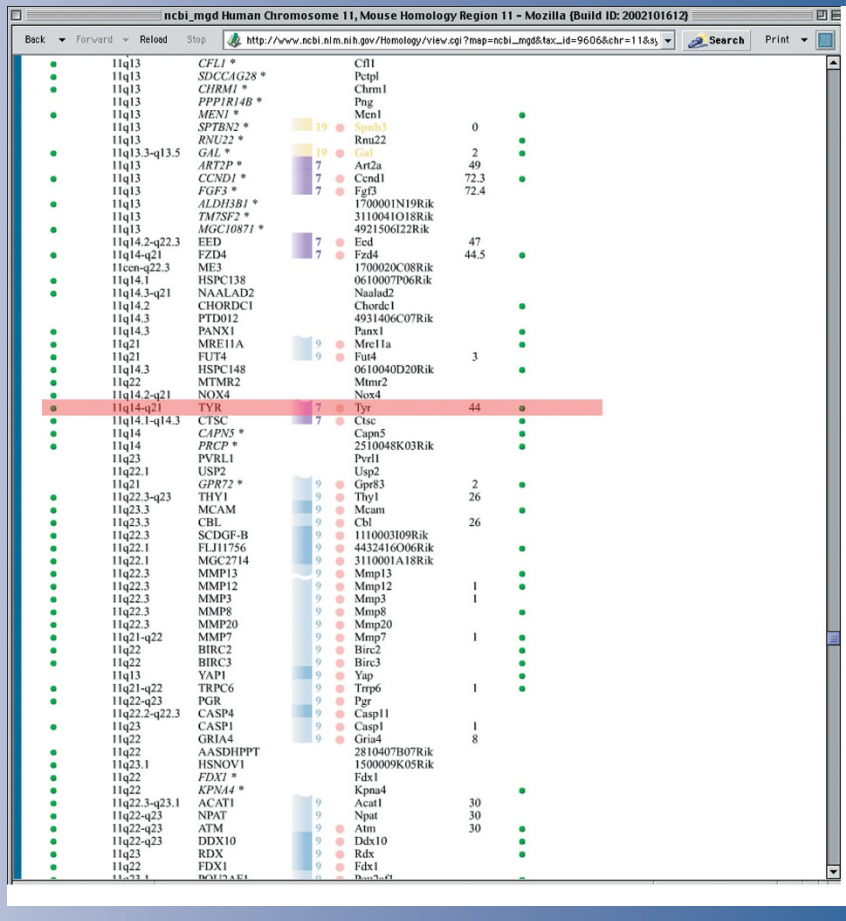


Figure 12.2



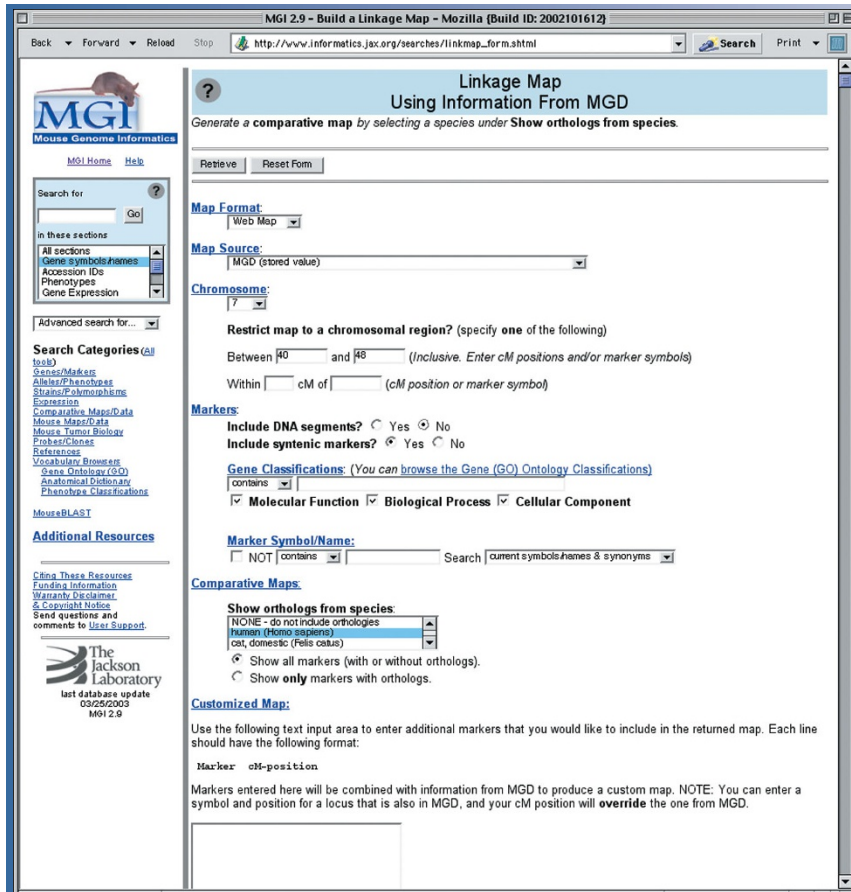


Figure 12.3

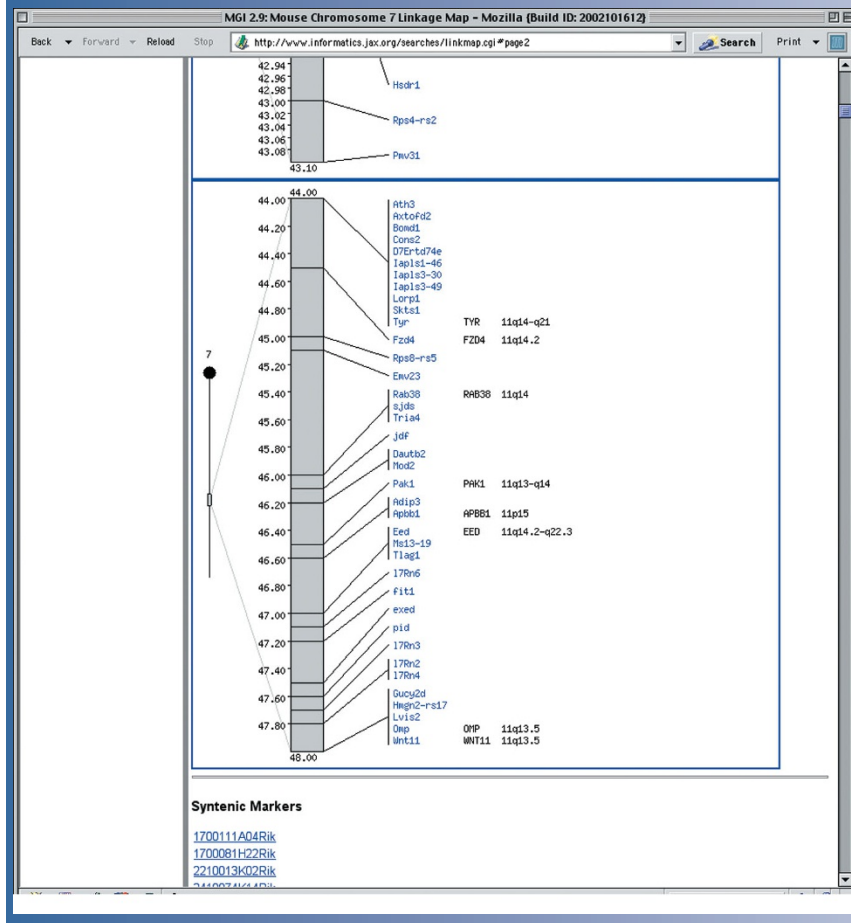


Figure 12.4

Figure 12.5

Gene Detail Your Input Welcome

Symbol Name	Tyr tyrosinase	MGI:98880
STS	D7Mit19, D7Mit31	
Synonyms	albino, c	
Map position	Chromosome 7 44.0 cM Detailed Map \pm 1 cM Mapping data(14)	
Mammalian orthology	human; cattle; rat (orthology data) Comparative Map (Mouse/Human Tyr \pm 2 cM)	
Sequences	Nucleotide NM_011661 Protein P11344 All sequences(13)	
Phenotypes	All phenotypic alleles(100) : Spontaneous(23) Chemically induced(3) Other(74) Mouse Locus Catalog	
Polymorphisms	All(26) : PCR(2) RFLP(26)	
Gene Ontology (GO) classifications	Process melanin biosynthesis from tyrosine, metabolism... Component extracellular space, integral to membrane... Function monooxygenase activity, monophenol monooxygenase activity... All GO classifications(3)	
Expression	Theiler Stage(2) Tissues(1) Assay Type Results(2) Assays(1) RNA In Situ 3 1 GXD literature index(6) cDNA source data(6)	
Other database links	TIGR TC655262 UniGene 1365 EC 1.14.18.1 LocusLink 22173 ENSEMBL ENSMUSG00000004651 InterPro IPR002227 DoTS DT 5031519Z, DT 9133752Z	
Molecular reagents	All nucleic(116) Genomic(62) cDNA(32) Primer pair(2) Other(31)	
References	(Earliest) J100 Haldane JBS <i>et al.</i> , "Reduplication in mice" J Genet 1915;50:133-135 (Latest) J8000 The FANTOM Consortium and The RIKEN Genome Exploration Research Group Phase I & II Team, "Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs" Nature 2002;420:563-573 All references(369)	
Other accession IDs	MGD-MRK-15315, MGD-MRK-1695	