Module 3: Genes and Sequences (NCBI)

ii - Does My Gene Have Known Homologs/Orthologs?

Aims

- Introduce tools to mine homology data
- Suggest ways to identify homologs
- Provide alternative ways to navigate
- Show examples of pre-computed homology comparisons

Introduction

You can mine the pre-computed sequence comparisons identifying putative orthologs (highly similar sequences across genomes) in Homologene. Begin your search for homologs by submitting a search on the Entrez home page (http://www.ncbi.nlm.nih.gov/gquery/gquery.fcgi) or by navigating to Homologene (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=homologene) to view results or submit a text query against the Homologene database. You can also following Links to Homologene from related records in other Entrez databases, such as Entrez Gene or UniGene.

Pre-computed protein comparisons are also available for each protein in Entrez Protein in the BLink (BLAST Link) database. You can view a graphical display of similar proteins by following the BLink link from any Entrez protein record. On the BLink page you can view a blast2 alignment between your protein and each protein identified by BLink as highly similar. Scroll down the list of Protein Descriptions to view the protein names for these proteins.

Homologs can also be identified through cross-species BLAST searches, as described in Module 2_iv.

Since homologs often share similar naming conventions, querying Entrez Gene with a gene name or gene symbol may yield homologous gene records, as seen in the exercise in Module3_i.

Additionally, you can determine if a curated homolog has been identified for a zebrafish gene by following the link to ZFIN found on Entrez Gene and UniGene pages.

Cross-species genome comparisons may also be used to identify homologs. For example, mouse homlogs for human genes can be putatively identified based on the placement of mouse genes on the human genome. To see these comparative maps for human, mouse and rat, navigate to the Map Viewer home page (http://www.ncbi.nlm.nih.gov/mapview/), choose one of these organisms and select a chromosome to view. The “Maps & Options” button will provide a pop-up window where you can then add maps from human or rat to the mouse Map Viewer page. See Module2_iii to view the zebrafish Map Viewer page. Zebrafish Map Viewer does not currently include comparative maps.

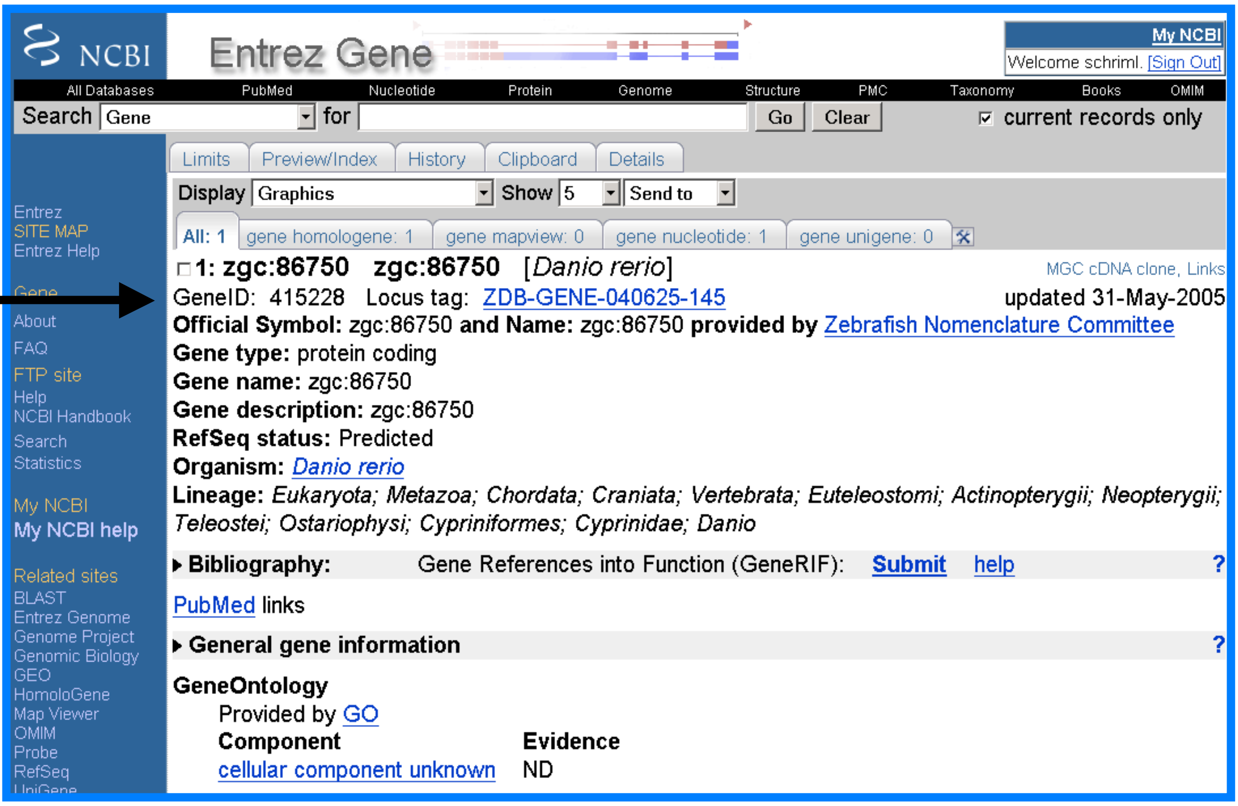
Exercises

1. Homologene: Identify putative homologs based on sequence similarity using pre-computed comparisons in Homologene.

2. BLink: Identify putative homologs in other fish species.

1. Homologene: Identify putative homologs based on sequence similarity using pre-computed comparisons in Homologene.

Starting with an anonymous Entrez Gene record, zgc:86750 (GeneID:415228, http://ww.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=415228), follow the link to Homologene.



□ 1: zgc:86750 zgc:86750 [*Danio rerio*]

GeneID: 415228 Locus tag: ZDB-GENE-040625-145 updated 31-May-2005

Official Symbol: zgc:86750 **and Name:** zgc:86750 **provided by** Zebrafish Nomenclature Committee

Gene type: protein coding

Gene name: zgc:86750

Gene description: zgc:86750

RefSeq status: Predicted

Organism: *Danio rerio*

Lineage: *Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Actinopterygii; Neopterygii; Teleostei; Ostariophysi; Cypriniformes; Cyprinidae; Danio*

▶ **Bibliography:** Gene References into Function (GeneRIF): **Submit** help ?

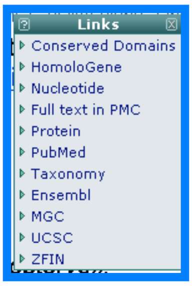
PubMed links

▶ **General gene information** ?

GeneOntology

Provided by GO

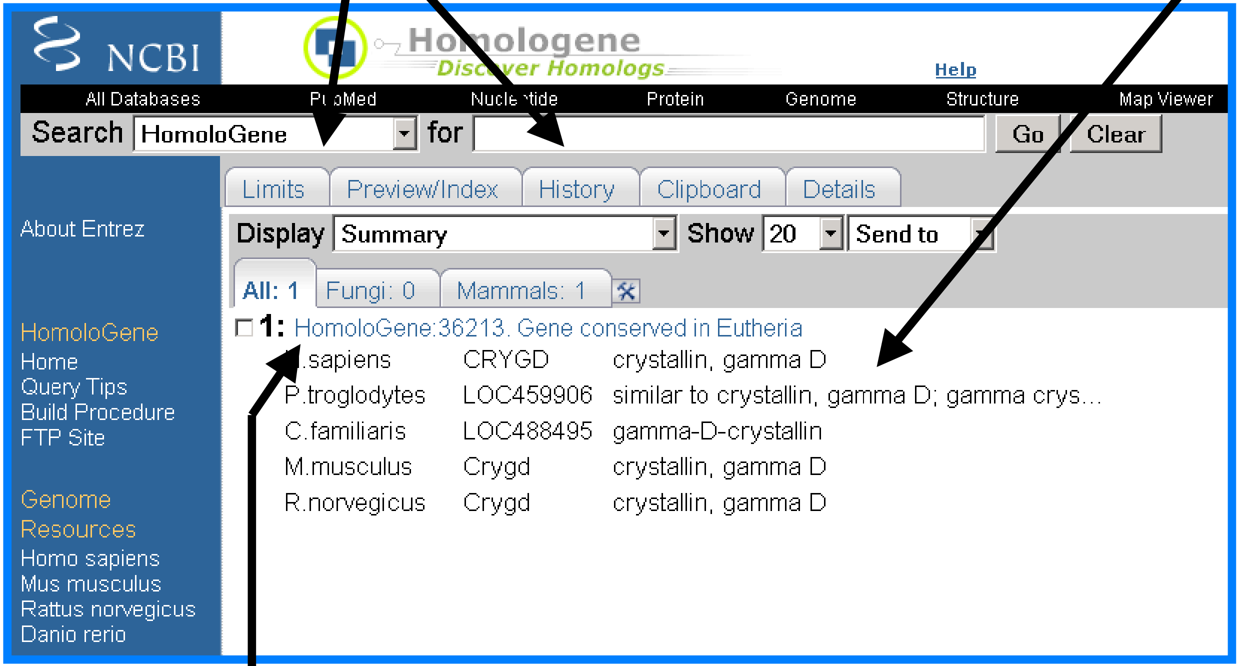
Component	**Evidence**
cellular component unknown	ND



Click on Homologene link to view results of pre-computed sequence comparisons

You can also submit a text search against the Homologene database from any Entrez page

View Homologene record links to zgc:86750

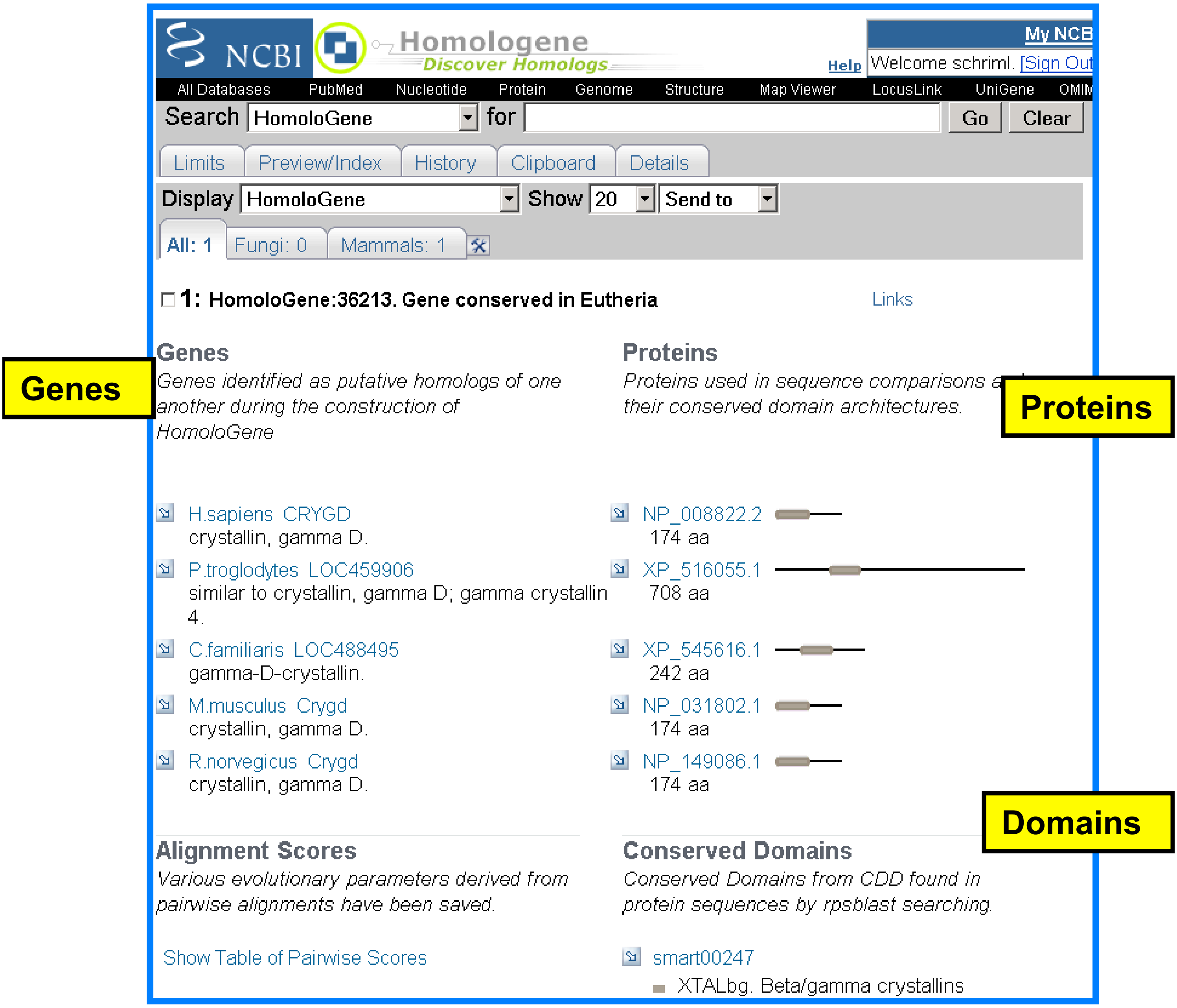


□ 1: HomoloGene:36213. Gene conserved in Eutheria

H.sapiens	CRYGD	crystallin, gamma D
P.troglodytes	LOC459906	similar to crystallin, gamma D; gamma crys...
C.familiaris	LOC488495	gamma-D-crystallin
M.musculus	Crygd	crystallin, gamma D
R.norvegicus	Crygd	crystallin, gamma D

Click on Homologene:35213 to view the detailed HomoloGene record

- **View related Genes, their Proteins, related Phenotypes and PubMed entries**
- **View conserved domains identified in these proteins**
- **View curated homology data**
- **View related UniGene clusters**



Welcome schriml. [Sign Out

Search HomoloGene for

Display HomoloGene Show 20 Send to

All: 1 Fungi: 0 Mammals: 1

□ 1: HomoloGene:36213. Gene conserved in Eutheria

Genes

Genes identified as putative homologs of one another during the construction of HomoloGene

Proteins

Proteins used in sequence comparisons a their conserved domain architectures.

H.sapiens CRYGD crystallin, gamma D.	NP_008822.2 174 aa
P.troglodytes LOC459906 similar to crystallin, gamma D; gamma crystallin 4.	XP_516055.1 708 aa
C.familiaris LOC488495 gamma-D-crystallin.	XP_545616.1 242 aa
M.musculus Crygd crystallin, gamma D.	NP_031802.1 174 aa
R.norvegicus Crygd crystallin, gamma D.	NP_149086.1 174 aa

Alignment Scores

Various evolutionary parameters derived from pairwise alignments have been saved.

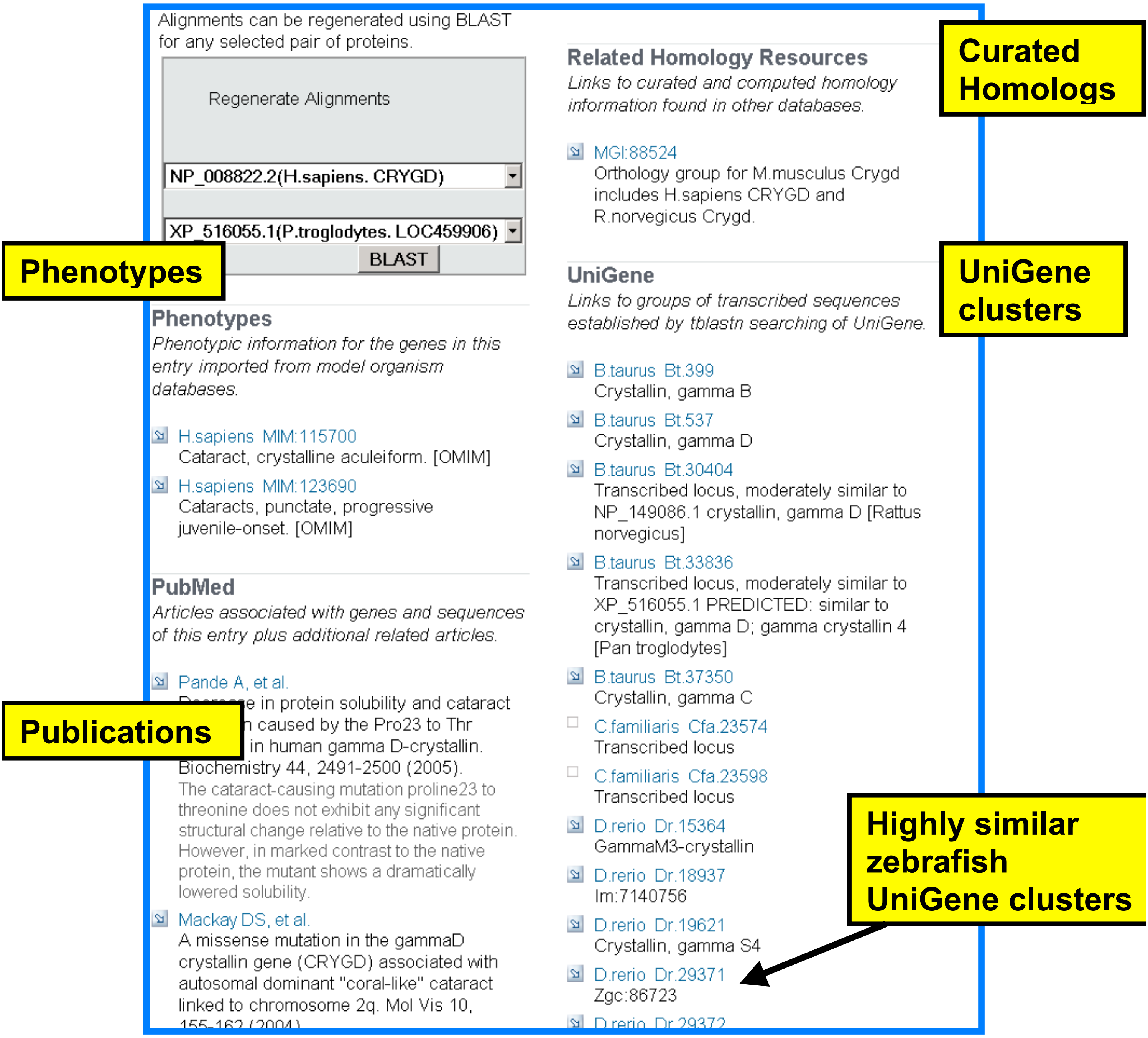
Show Table of Pairwise Scores

Conserved Domains

Conserved Domains from CDD found in protein sequences by rpsblast searching.

smart00247

▬ XTALbg. Beta/gamma crystallins



Alignments can be regenerated using BLAST for any selected pair of proteins.

Regenerate Alignments

NP_008822.2(H.sapiens. CRYGD)

XP_516055.1(P.troglodytes. LOC459906)

BLAST

Phenotypes

Phenotypic information for the genes in this entry imported from model organism databases.

H.sapiens MIM:115700
Cataract, crystalline aculeiform. [OMIM]

H.sapiens MIM:123690
Cataracts, punctate, progressive juvenile-onset. [OMIM]

PubMed

Articles associated with genes and sequences of this entry plus additional related articles.

Pande A, et al.
e in protein solubility and cataract n caused by the Pro23 to Thr in human gamma D-crystallin. Biochemistry 44, 2491-2500 (2005).
The cataract-causing mutation proline23 to threonine does not exhibit any significant structural change relative to the native protein. However, in marked contrast to the native protein, the mutant shows a dramatically lowered solubility.

Mackay DS, et al.
A missense mutation in the gammaD crystallin gene (CRYGD) associated with autosomal dominant "coral-like" cataract linked to chromosome 2q. Mol Vis 10, 155-162 (2004).

Related Homology Resources

Links to curated and computed homology information found in other databases.

MGI:88524
Orthology group for M.musculus Crygd includes H.sapiens CRYGD and R.norvegicus Crygd.

UniGene

Links to groups of transcribed sequences established by tblastn searching of UniGene.

B.taurus Bt.399
Crystallin, gamma B

B.taurus Bt.537
Crystallin, gamma D

B.taurus Bt.30404
Transcribed locus, moderately similar to NP_149086.1 crystallin, gamma D [Rattus norvegicus]

B.taurus Bt.33836
Transcribed locus, moderately similar to XP_516055.1 PREDICTED: similar to crystallin, gamma D; gamma crystallin 4 [Pan troglodytes]

B.taurus Bt.37350
Crystallin, gamma C

C.familiaris Cfa.23574
Transcribed locus

C.familiaris Cfa.23598
Transcribed locus

D.rerio Dr.15364
GammaM3-crystallin

D.rerio Dr.18937
Im:7140756

D.rerio Dr.19621
Crystallin, gamma S4

D.rerio Dr.29371
Zgc:86723

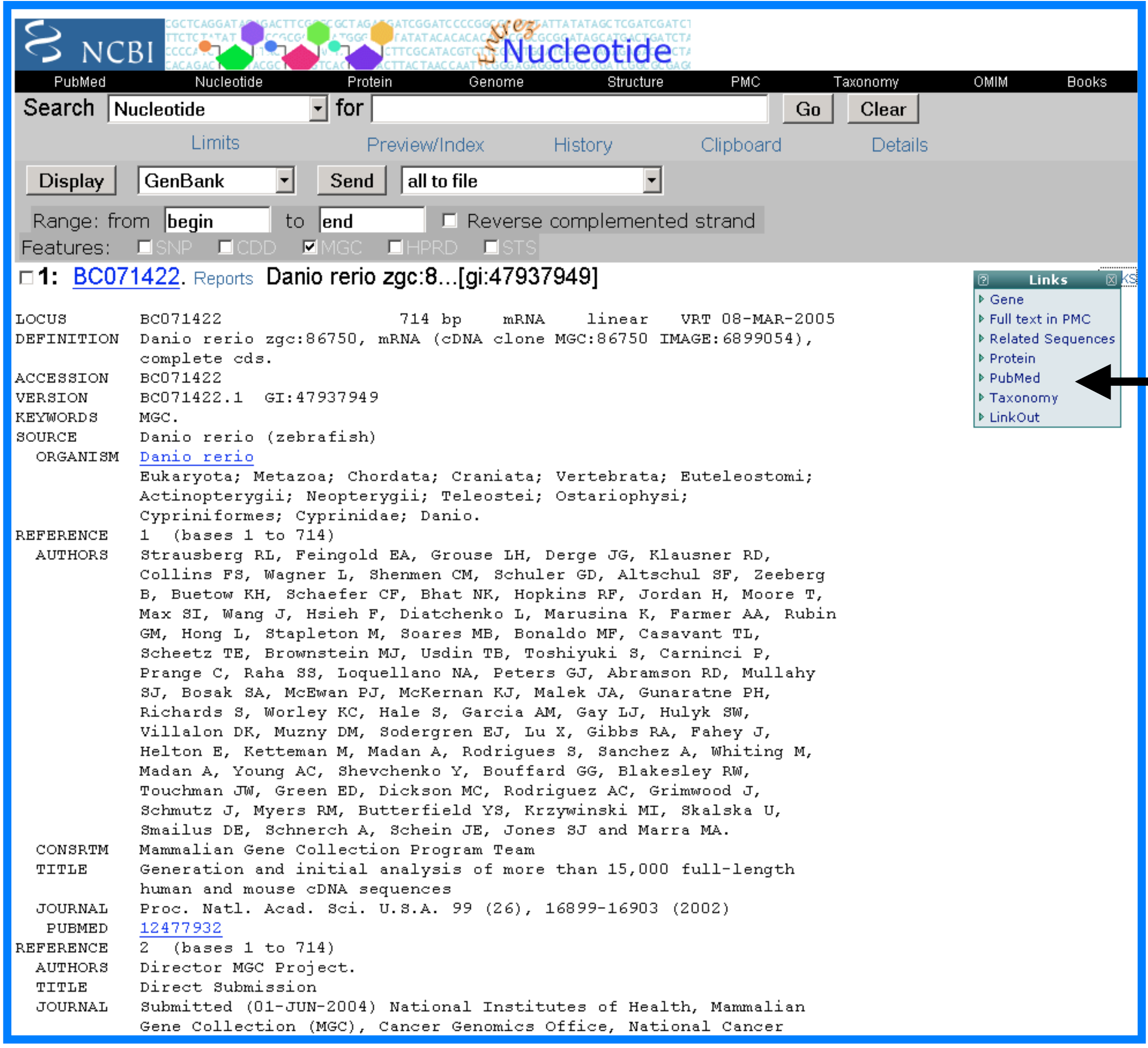
D.rerio Dr.29372

Homologene comparisons have shown that the Entrez Gene zgc:86723 record is highly similar to members of the gamma crystallin gene family.

2. BLink: Identify putative homologs in other fish species.
Begin your search from mRNA accession.

For example: BC071422 (http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=BC071422.1)

Click on the Links menu and select 'Protein' to go to the corresponding Entrez Protein record



□ 1: BC071422. Reports Danio rerio zgc:8...[gi:47937949]

```
LOCUS       BC071422                 714 bp    mRNA    linear   VRT 08-MAR-2005
DEFINITION  Danio rerio zgc:86750, mRNA (cDNA clone MGC:86750 IMAGE:6899054),
            complete cds.
ACCESSION   BC071422
VERSION     BC071422.1  GI:47937949
KEYWORDS    MGC.
SOURCE      Danio rerio (zebrafish)
  ORGANISM  Danio rerio
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Actinopterygii; Neopterygii; Teleostei; Ostariophysi;
            Cypriniformes; Cyprinidae; Danio.
REFERENCE   1  (bases 1 to 714)
  AUTHORS   Strausberg RL, Feingold EA, Grouse LH, Derge JG, Klausner RD,
            Collins FS, Wagner L, Shenmen CM, Schuler GD, Altschul SF, Zeeberg
            B, Buetow KH, Schaefer CF, Bhat NK, Hopkins RF, Jordan H, Moore T,
            Max SI, Wang J, Hsieh F, Diatchenko L, Marusina K, Farmer AA, Rubin
            GM, Hong L, Stapleton M, Soares MB, Bonaldo MF, Casavant TL,
            Scheetz TE, Brownstein MJ, Usdin TB, Toshiyuki S, Carninci P,
            Prange C, Raha SS, Loquellano NA, Peters GJ, Abramson RD, Mullahy
            SJ, Bosak SA, McEwan PJ, McKernan KJ, Malek JA, Gunaratne PH,
            Richards S, Worley KC, Hale S, Garcia AM, Gay LJ, Hulyk SW,
            Villalon DK, Muzny DM, Sodergren EJ, Lu X, Gibbs RA, Fahey J,
            Helton E, Ketteman M, Madan A, Rodrigues S, Sanchez A, Whiting M,
            Madan A, Young AC, Shevchenko Y, Bouffard GG, Blakesley RW,
            Touchman JW, Green ED, Dickson MC, Rodriguez AC, Grimwood J,
            Schmutz J, Myers RM, Butterfield YS, Krzywinski MI, Skalska U,
            Smailus DE, Schnerch A, Schein JE, Jones SJ and Marra MA.
  CONSRTM   Mammalian Gene Collection Program Team
  TITLE     Generation and initial analysis of more than 15,000 full-length
            human and mouse cDNA sequences
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)
   PUBMED   12477932
REFERENCE   2  (bases 1 to 714)
  AUTHORS   Director MGC Project.
  TITLE     Direct Submission
  JOURNAL   Submitted (01-JUN-2004) National Institutes of Health, Mammalian
            Gene Collection (MGC), Cancer Genomics Office, National Cancer
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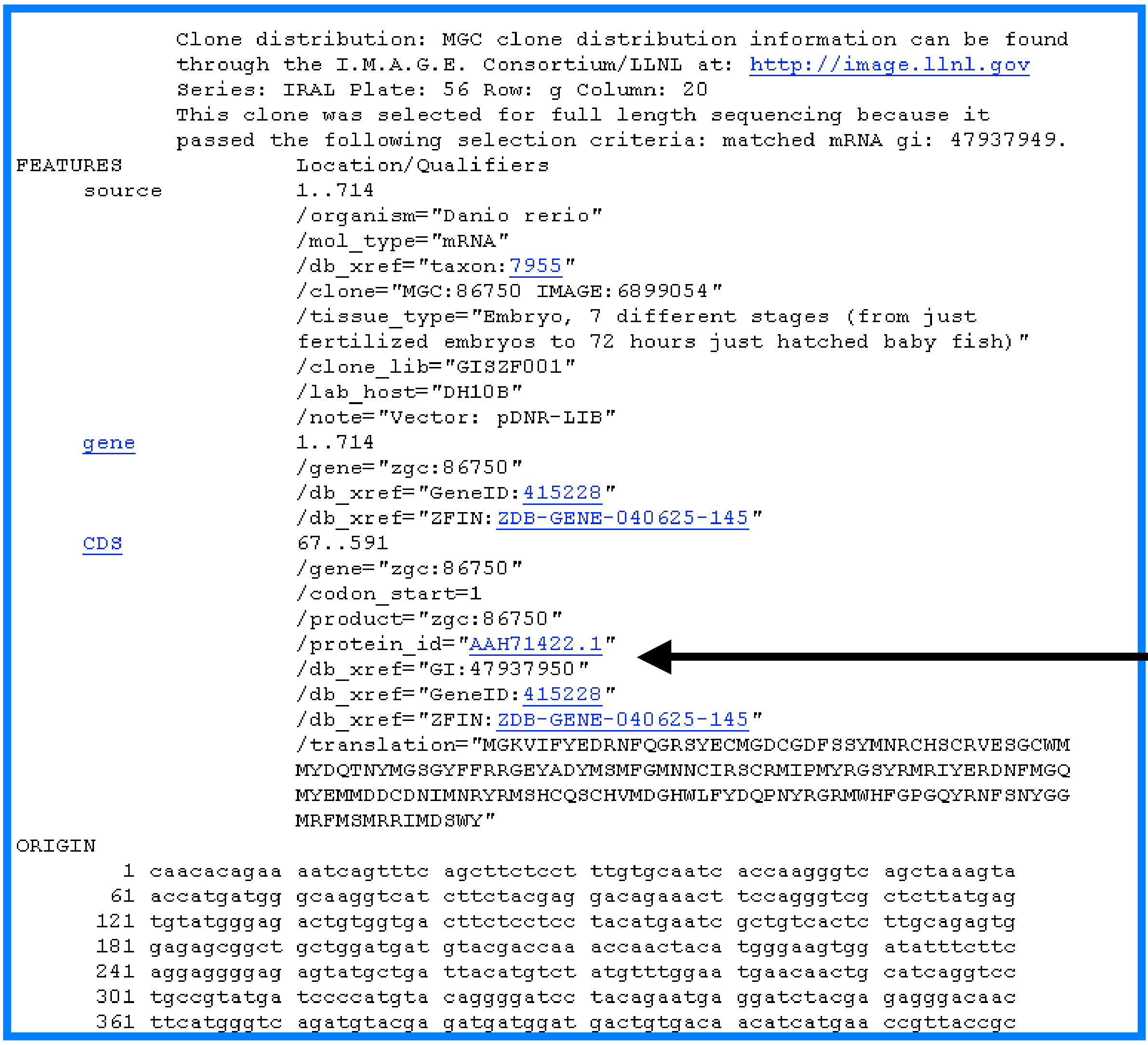
To navigate to the corresponding Entrez Protein record: first scroll down the page to the Protein Link

Now click on the Protein Link



```
             Clone distribution: MGC clone distribution information can be found
             through the I.M.A.G.E. Consortium/LLNL at: http://image.llnl.gov
             Series: IRAL Plate: 56 Row: g Column: 20
             This clone was selected for full length sequencing because it
             passed the following selection criteria: matched mRNA gi: 47937949.
FEATURES             Location/Qualifiers
     source          1..714
                     /organism="Danio rerio"
                     /mol_type="mRNA"
                     /db_xref="taxon:7955"
                     /clone="MGC:86750 IMAGE:6899054"
                     /tissue_type="Embryo, 7 different stages (from just
                     fertilized embryos to 72 hours just hatched baby fish)"
                     /clone_lib="GISZF001"
                     /lab_host="DH10B"
                     /note="Vector: pDNR-LIB"
     gene            1..714
                     /gene="zgc:86750"
                     /db_xref="GeneID:415228"
                     /db_xref="ZFIN:ZDB-GENE-040625-145"
     CDS             67..591
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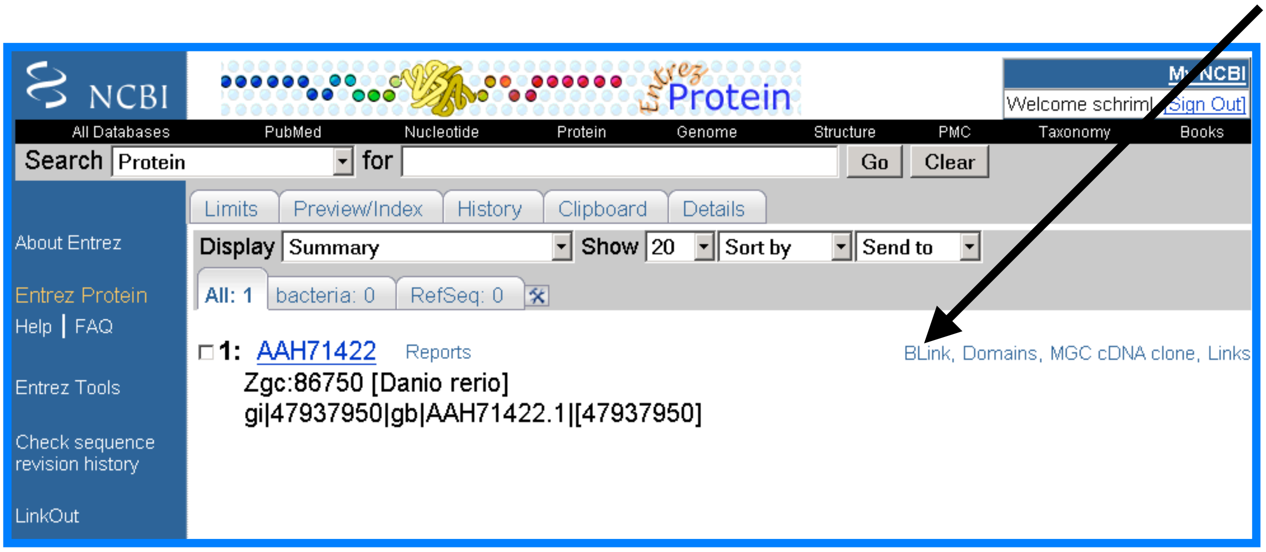
                     /product="zgc:86750"
                     /protein_id="AAH71422.1"
                     /db_xref="GI:47937950"
                     /db_xref="GeneID:415228"
                     /db_xref="ZFIN:ZDB-GENE-040625-145"
                     /translation="MGKVIFYEDRNFQGRSYECMGDCGDFSSYMNRCHSCRVESGCWM
                     MYDQTNYMGSGYFFRRGEYADYMSMFGMNNCIRSCRMIPMYRGSYRMRIYERDNFMGQ
                     MYEMMDDCDNIMNRYRMSHCQSCHVMDGHWLFYDQPNYRGRMWHFGPGQYRNFSNYGG
                     MRFMSMRRIMDSWY"
ORIGIN
        1 caacacagaa aatcagtttc agcttctcct ttgtgcaatc accaagggtc agctaaagta
       61 accatgatgg gcaaggtcat cttctacgag gacagaaact tccagggtcg ctcttatgag
      121 tgtatgggag actgtggtga cttctcctcc tacatgaatc gctgtcactc ttgcagagtg
      181 gagagcggct gctggatgat gtacgaccaa accaactaca tgggaagtgg atatttcttc
      241 aggaggggag agtatgctga ttacatgtct atgtttggaa tgaacaactg catcaggtcc
      301 tgccgtatga tccccatgta caggggatcc tacagaatga ggatctacga gagggacaac
      361 ttcatgggtc agatgtacga gatgatggat gactgtgaca acatcatgaa ccgttaccgc
```

Navigate to BLink by the provided link



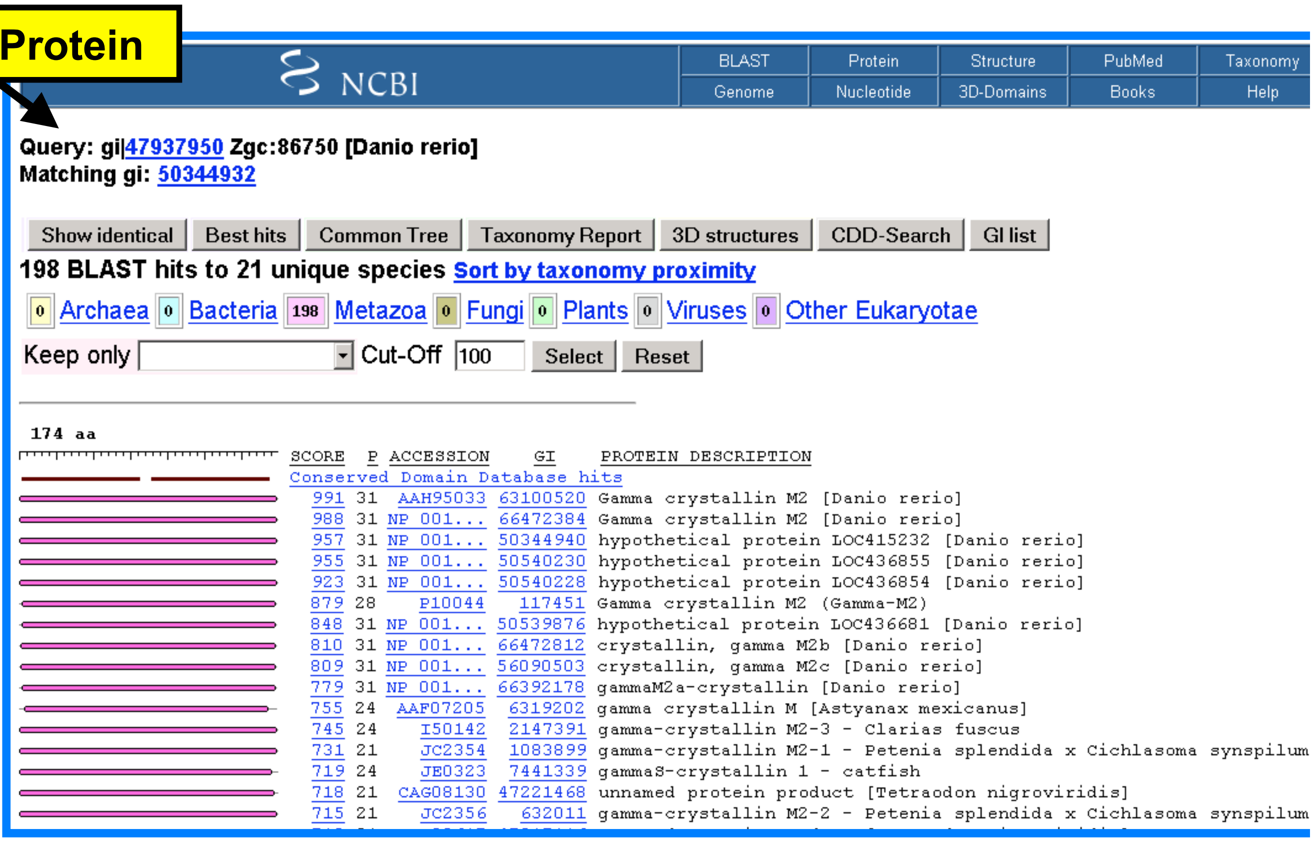
□ 1: AAH71422 Reports BLink, Domains, MGC cDNA clone, Links

Zgc:86750 [Danio rerio]

gi|47937950|gb|AAH71422.1|[47937950]

- **View the graphical display of protein hits**
- **Click on the BLAST score to see the alignment**
- **Click on the Accession to go to the Entrez Protein record**
- **Scroll down the Protein Descriptions to protein names**
- **Click on "Show identical" to include all identical hits in the display**
- **Click on "Best hits" to view the hits grouped by organism**
- **Click on "Conserved Domain Database hits" to view domain details**

Query Protein



Query: gi|47937950 Zgc:86750 [Danio rerio]
Matching gi: 50344932

198 BLAST hits to 21 unique species Sort by taxonomy proximity

0 Archaea 0 Bacteria 198 Metazoa 0 Fungi 0 Plants 0 Viruses 0 Other Eukaryotae

Keep only Cut-Off 100

```
174 aa
                SCORE  P ACCESSION    GI     PROTEIN DESCRIPTION
                Conserved Domain Database hits
                  991 31  AAH95033 63100520 Gamma crystallin M2 [Danio rerio]
                  988 31 NP 001... 66472384 Gamma crystallin M2 [Danio rerio]
                  957 31 NP 001... 50344940 hypothetical protein LOC415232 [Danio rerio]
                  955 31 NP 001... 50540230 hypothetical protein LOC436855 [Danio rerio]
                  923 31 NP 001... 50540228 hypothetical protein LOC436854 [Danio rerio]
                  879 28    P10044   117451 Gamma crystallin M2 (Gamma-M2)
                  848 31 NP 001... 50539876 hypothetical protein LOC436681 [Danio rerio]
                  810 31 NP 001... 66472812 crystallin, gamma M2b [Danio rerio]
                  809 31 NP 001... 56090503 crystallin, gamma M2c [Danio rerio]
                  779 31 NP 001... 66392178 gammaM2a-crystallin [Danio rerio]
                  755 24  AAF07205  6319202 gamma crystallin M [Astyanax mexicanus]
                  745 24    I50142  2147391 gamma-crystallin M2-3 - Clarias fuscus
                  731 21    JC2354  1083899 gamma-crystallin M2-1 - Petenia splendida x Cichlasoma synspilum
                  719 24    JE0323  7441339 gammaS-crystallin 1 - catfish
                  718 21  CAG08130 47221468 unnamed protein product [Tetraodon nigroviridis]
                  715 21    JC2356   632011 gamma-crystallin M2-2 - Petenia splendida x Cichlasoma synspilum
```

BLink has identified highly similar proteins in several fish including: zebrafish, Mexican tetra, whitespotted clarias, catfish and freshwater pufferfish