Using RNAi screens to predict phenotypes of orthologous genes

MMG1001 Assignment 3 – Group Heather

Corresponding reading

Kamath *et. al.* 2003. Systematic functional analysis of the *Caenorhabditis elegans* genome using RNAi. Nature 42:231-237

Tools

- Wormbase: Nematode genome database
- Ensembl: Genome browser and database for many species
- OMIM: (Online Mendelian Inheritance in Man) catalog of human genetic disorders

Overview

RNAi screens in model organisms can provide useful information for other organisms given the similarity of homologous genes. We will look at the results of a genome-wide RNAi screen in *C. elegans*, make predictions about phenotypes in humans, and explore other homolog information.

Predict human phenotypes from *C. elegans* RNAi screen results

The following table is a subset of Supplementary Table 3 (RNAi phenotypes for 1528 genepairs corresponding to a single predicted gene) from the paper, with content modified for clarity. These genes were predicted to match to a single human ortholog.

Predicted Gene	Functional Class	Embryonic lethality	Sterility	Post-embryonic phenotypes			Development Issue
				1	2	3	
B0035.5	Metabolism	50-80%	-	Clear	-	-	Slow post-embryonic growth
C17E4.5	RNA binding	90%	-	Uncoordinated	-	-	Larval arrest
C29A12.3	DNA cell cycle	100%	-	-	-	-	-
D2045.1	Unknown	50-80%	-	-	-	-	-
F01G10.1	Metabolism	50-80%	-	Clear	-	-	Slow post-embryonic growth

1. Fill out the following table:
    a. Given the information in the above table, make a prediction about what **phenotype** might be observed if the gene was knocked down or less functional in humans.
    b. Using **Wormbase**:
        i. search for the *C. elegans* predicted gene to find out the **human ortholog** by clicking on the *Homology* tab on the left and scrolling down to the *Other Orthologs* table (search "*sapiens*" if human results aren't on the first page. If more than one ortholog is present, select the one(s) predicted by multiple tools).
        ii. write brief descriptions of the **human gene function** and **associated disorder** by clicking on the *Human Disease* tab on the left and visiting the appropriate **OMIM** links

Predicted Gene	**Predicted phenotype in humans**	**Human ortholog**	**Brief description of gene function from OMIM**	**Name and brief description of associated disorder from OMIM**
B0035.5				
C17E4.5				
C29A12.3				
D2045.1				
F01G10.1				

2. Do the disorders match your predicted phenotypes? Do the disorders make sense given the *C. elegans* phenotype information?
   B0035.5:
   C17E4.5:
   C29A12.3:
   D2045.1:
   F01G10.1:

3. Compare your results to Table 1 in the paper. Which genes in your table *do not* match the human disease and/or human gene ortholog in Table 1 in the paper?

Determine orthologs for *C. elegans* genes

4. The following pairs of *C. elegans* and human genes are listed as orthologs in Table 1 in the paper. **Are they still orthologs**? Search for the human gene in **Ensembl** to find out for the following pairs (it might help to learn the common gene name from Wormbase first):

Human gene from Table 1	***C. elegans* gene from Table 1**	**Common *C. elegans* name (Wormbase)**	***C. elegans* ortholog in Ensembl**	***Ortholog type***
DNA ligase1	*C29A12.3*			
KRT9	*W10G6.3*			
MADH4	*R12B2.1*			

5. Why might there be **discrepancies** between Table 1 and what you found in Ensembl?

6. For *C. elegans* ***lig-1***, search **Ensembl** for the following ortholog information (Hint: from the Ensembl home page, select *Caenorhabditis elegans* from the species list and then search for *lig-1*):

***H. sapiens* (human)**		**N. leucogenys (gibbon)**		***R. norvegicus* (rat)**		***M. musculus* (mouse)**	
Type	**Ortholog**	**Type**	**Ortholog**	**Type**	**Ortholog**	**Type**	**Ortholog**

7. For which species should you *not* use *C. elegans* as a **model** to study DNA ligase 1 activity and function? Why not?

Additional questions to ponder

1. Why is it difficult to match RNAi phenotypes between *C. elegans* and humans?
2. Why is it important to keep databases up to date?