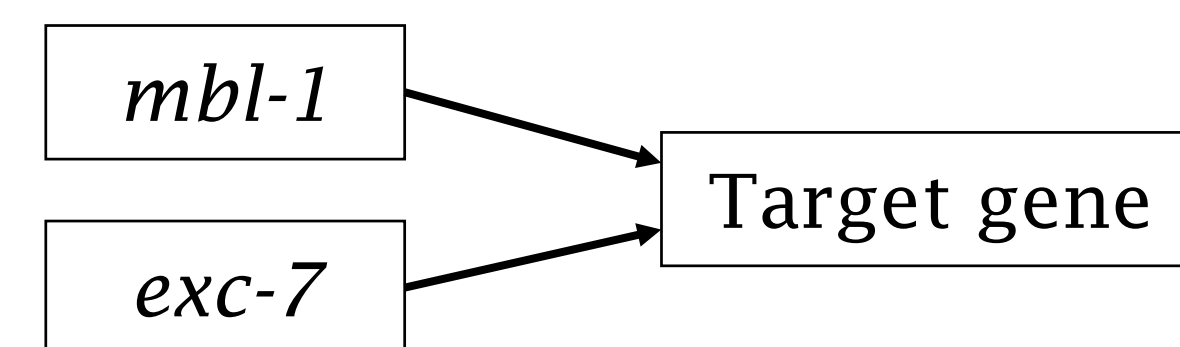




Genetic Interactions Can Give Insights into Pathways

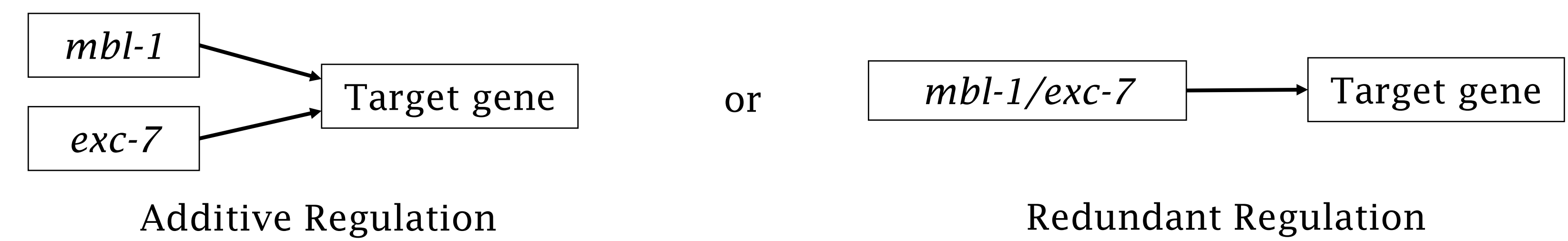
Many diseases arise from multiple genetic factors. Discovering how multiple genes contribute to an unexpected phenotype is crucial for understanding these diseases. In particular, genetic interactions from simultaneous mutations in two genes can lead to cardiac, mitochondrial, and neurodegenerative diseases.

In *C. elegans*, the double mutant for RNA binding proteins MBL-1 and EXC-7 has a significantly shortened lifespan than either single mutant. RNA sequencing data identified target genes that are regulated differently in the double mutant to determine the cause of the phenotype. We are working to characterize the genetic interactions occurring in these target genes.



Do *mbl-1* and *exc-7* work additively or redundantly?

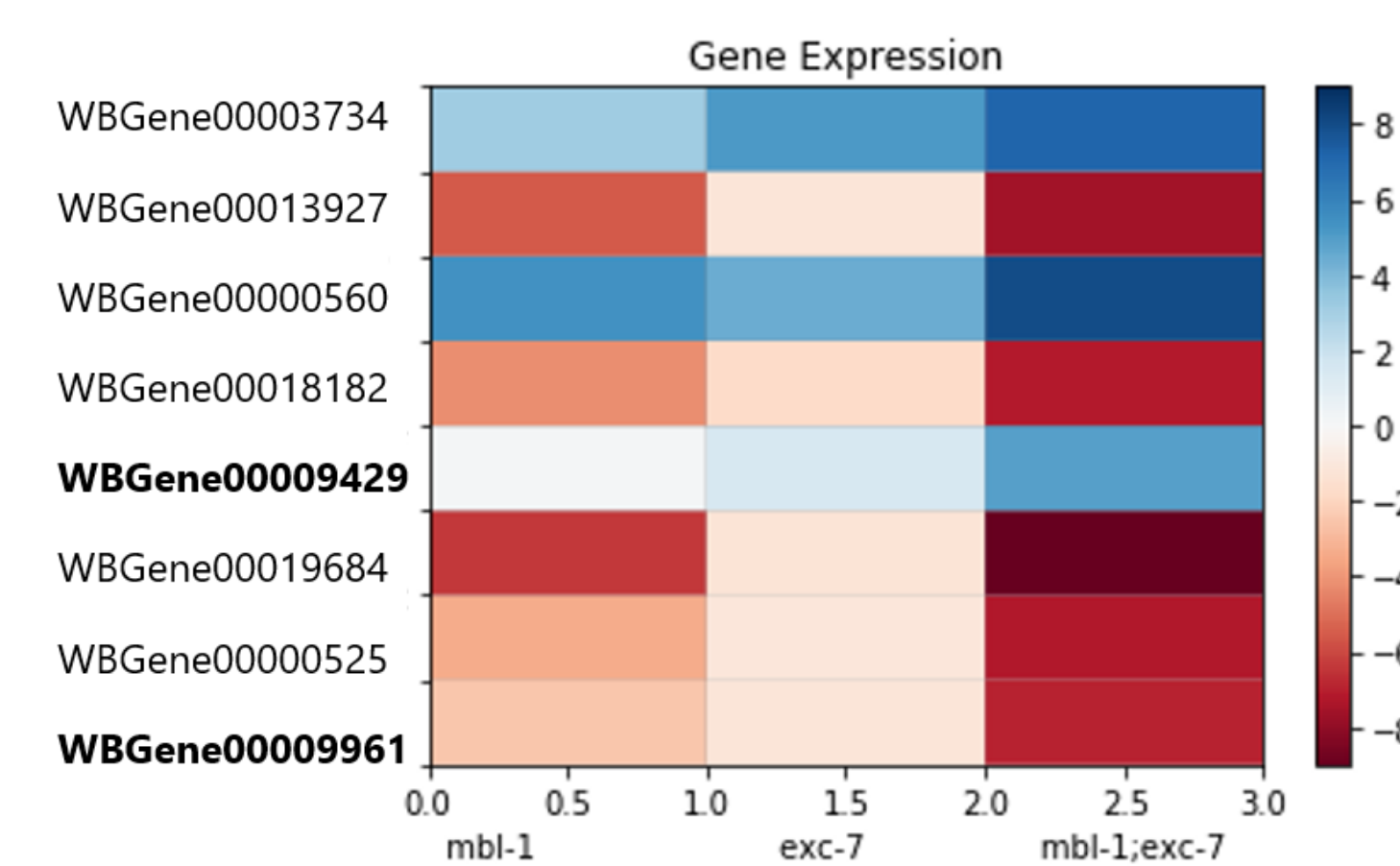
The RNA sequencing data shows that the effect that *mbl-1* and *exc-7* together have on *irg-5* and *cutl-7* is greater than an additive effect.



Conclusion: *mbl-1* and *exc-7* likely work redundantly.

Genetic Interactions In Double Mutants

- We examined log(2) change in gene expression from wild type.
- We are particularly interested in cases where the gene expression in the double mutant is significantly different than either single mutant.
- We have identified the target genes *irg-5* and *cutl-7*.

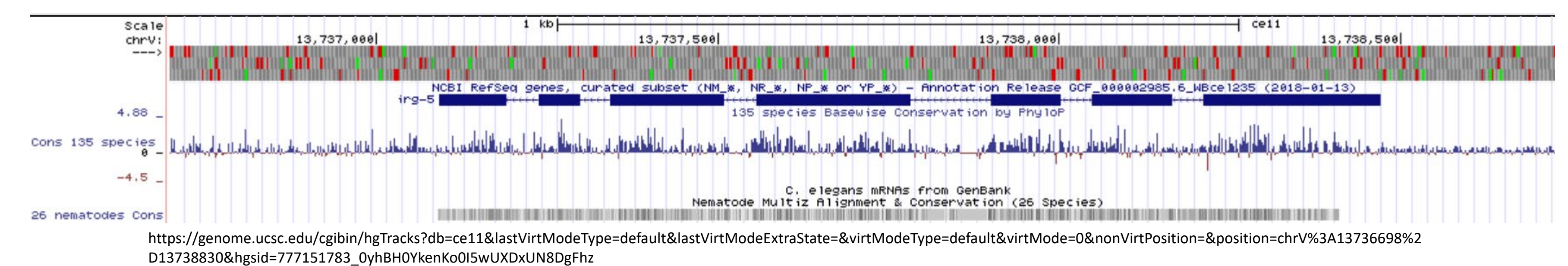
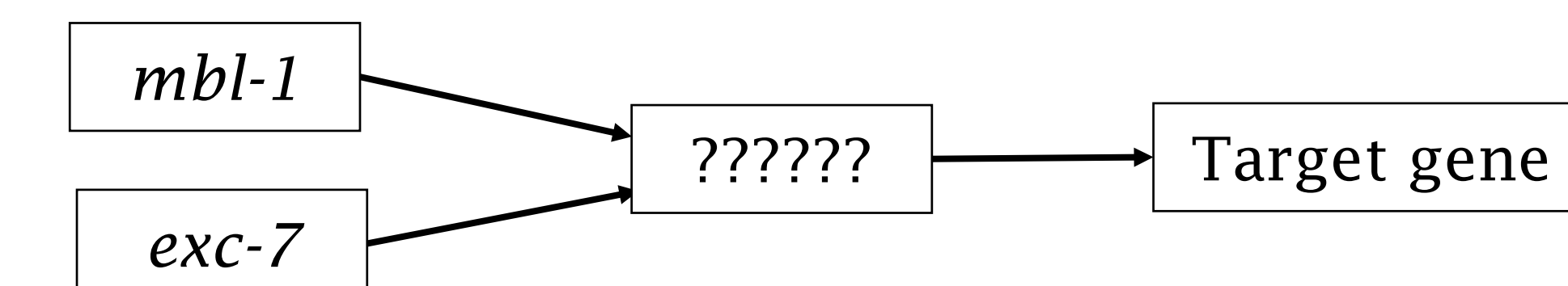


Gene Expression Levels

Mutant 1	Mutation 2	Double Mutant	Interaction
X	Y	X+Y	Additive effect: mutants function independently on similar processes
X	Y	X	Epistasis: Y negatively regulates X
X	Y	>X and Y	X and Y contribute independently to the same process. They are partially the same
X	Y	< X and Y	X and Y contribute independently to the same process: Negative epistasis
X	Y	>>>X and Y	X and Y have redundant function. Independent or dependent regulation
X	Y	<<<X and Y	X and Y have redundant function. Independent or dependent regulation
X	Y	Between X & Y	Mild epistasis of one gene

Is there an intermediate?

- We did not find any promising binding sites for *mbl-1* or *exc-7* in the *irg-5* and *cutl-7* sequences indicating there may be an intermediate.
- We searched Wormbase for known genes that interact with *irg-5* and *cutl-7*.
- No genes matched genes that were also dysregulated in *mbl-1* or *exc-7*.
- We also looked at genes affected by both *mbl-1* and *exc-7* knockouts but none of them had regulatory functions.



Conclusions and Future Work

Conclusions

- We have laid out rules for determining the type of genetic interaction based on gene expression.
- We have come up with a process to test for independent or dependent regulation, determine if the effect is additive or redundant, and search for possible intermediates.
- This work can be used in future analysis of RNA sequencing data to further uncover the mechanisms of genetic interactions.

Future Work

- We will continue to characterize other target genes of *mbl-1* and *exc-7*.
- We will use this analysis framework to analyze other interesting double mutants.
- Once we have fully determined the mechanism of *mbl-1* and *exc-7*, we can determine if this pathway is similar in humans and can give new information about muscular disorders.

Do *mbl-1* and *exc-7* work dependently or independently?

- We searched for preferred binding sites of *mbl-1* and *exc-7* and found no significant binding sites.
- We checked gene expression and splicing data from RNA sequencing and found *mbl-1* expression and splicing is not changed in *exc-7* and vice versa.

Common Name	WBGene	Log2 change gene exp in <i>mbl-1</i>	Log2 change gene exp in <i>exc-7</i>	Log2 change gene exp in <i>mbl-1;exc-7</i>	Function
<i>cutl-7</i>	WBGene00009961	-2.471	-1.1651	-6.9230	zona pellucida domain, enriched in males
<i>irg-5</i>	WBGene00009429	0.2002	1.5447	4.9219	defense response to graham positive bacteria
<i>mbl-1</i>	WBGene00019347	-0.9147	0.1263	-1.1280	RNA binding protein
<i>exc-7</i>	WBGene00001368	0.2010	0.3389	-1.1324	RNA binding protein

Conclusion: *mbl-1* and *exc-7* likely work independently.

References and Acknowledgements

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D RayH KazanKB CookMT WeirauchHS NajafabadiX LIS GuerousovM AlbuH ZhengA YangH NaM IrimiaLH MatzatRK DaleSA SmithCA YaroshSM KellyB NabetD MecnasW LiRS LaishramM QiaoHD LipshitzF PianoAH CorbettRP CarstensBJ FreyRA AndersonKW LynchLO PenalvaEP LeiAG FraserBJ BlencoweQD MorrisTR Hughes, *A compendium of RNA-binding motifs for decoding gene regulation* (2013)

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