

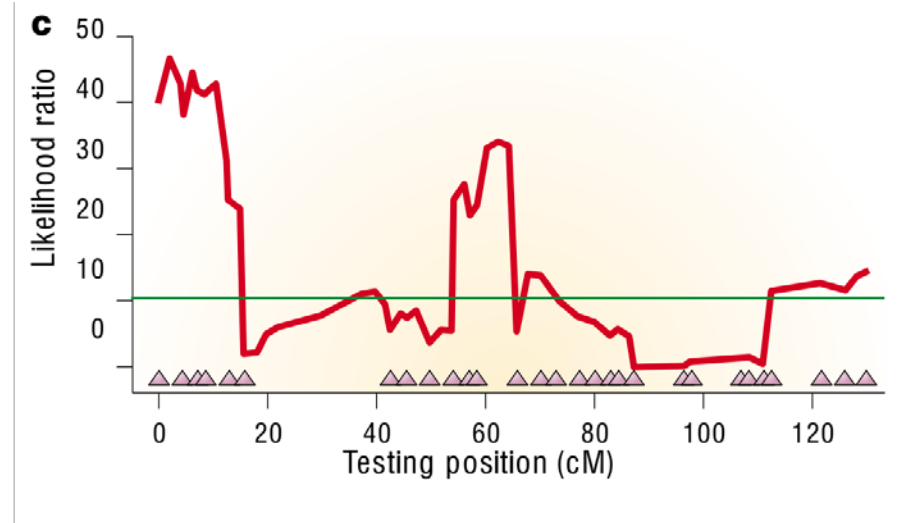
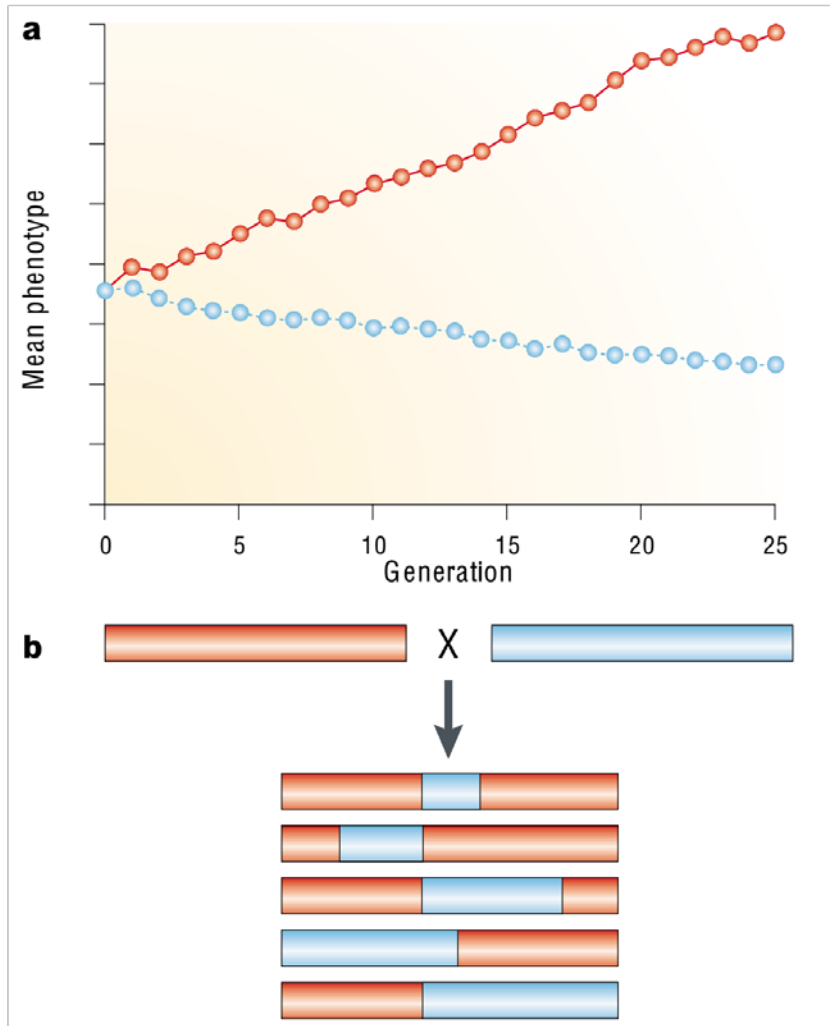
Quantitative Trait Locus (QTL) Mapping: Principles and Applications

Technical Journal Club

Tingting Liu

07-08-2020

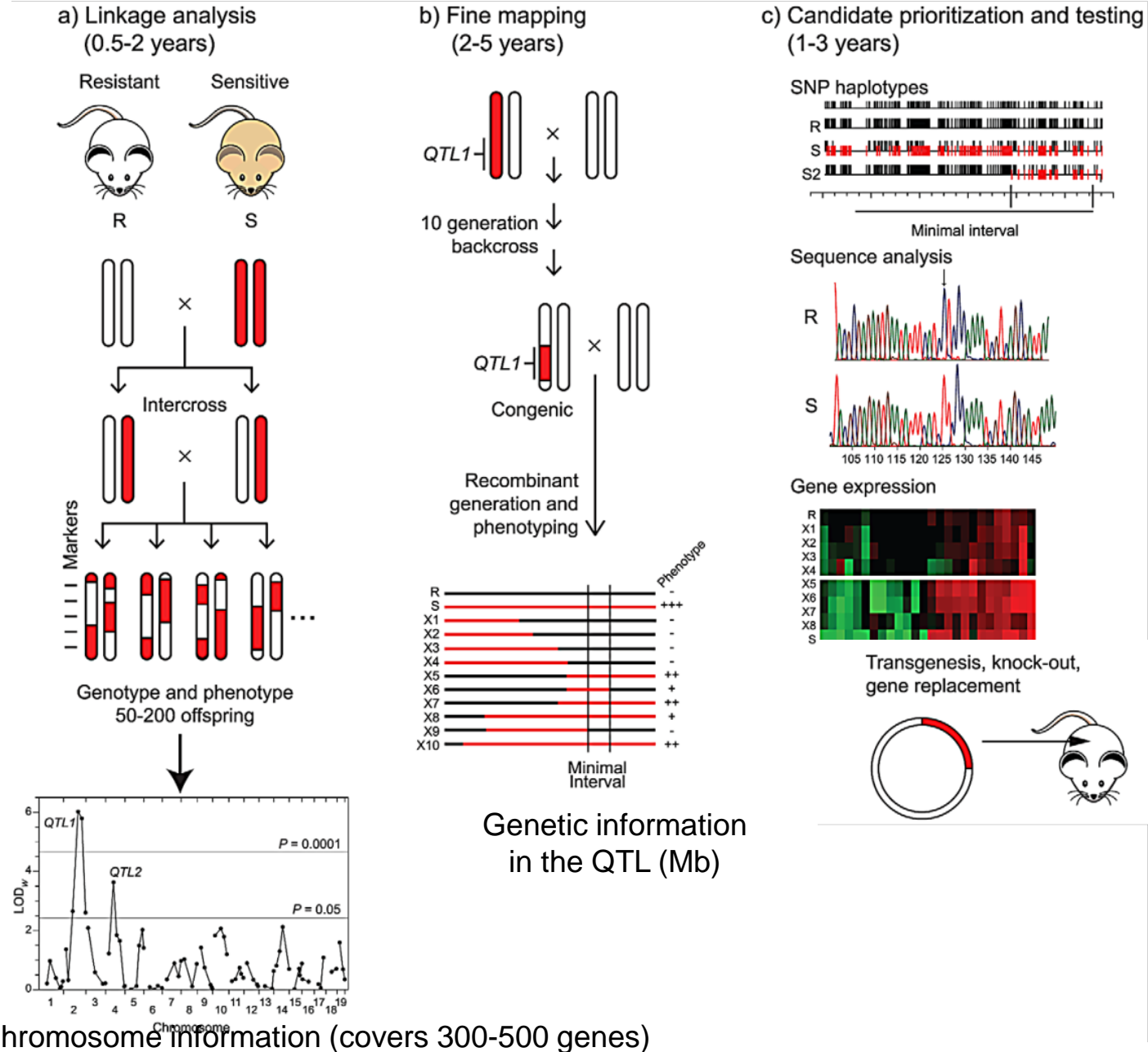
Quantitative Trait Locus (QTL) Mapping



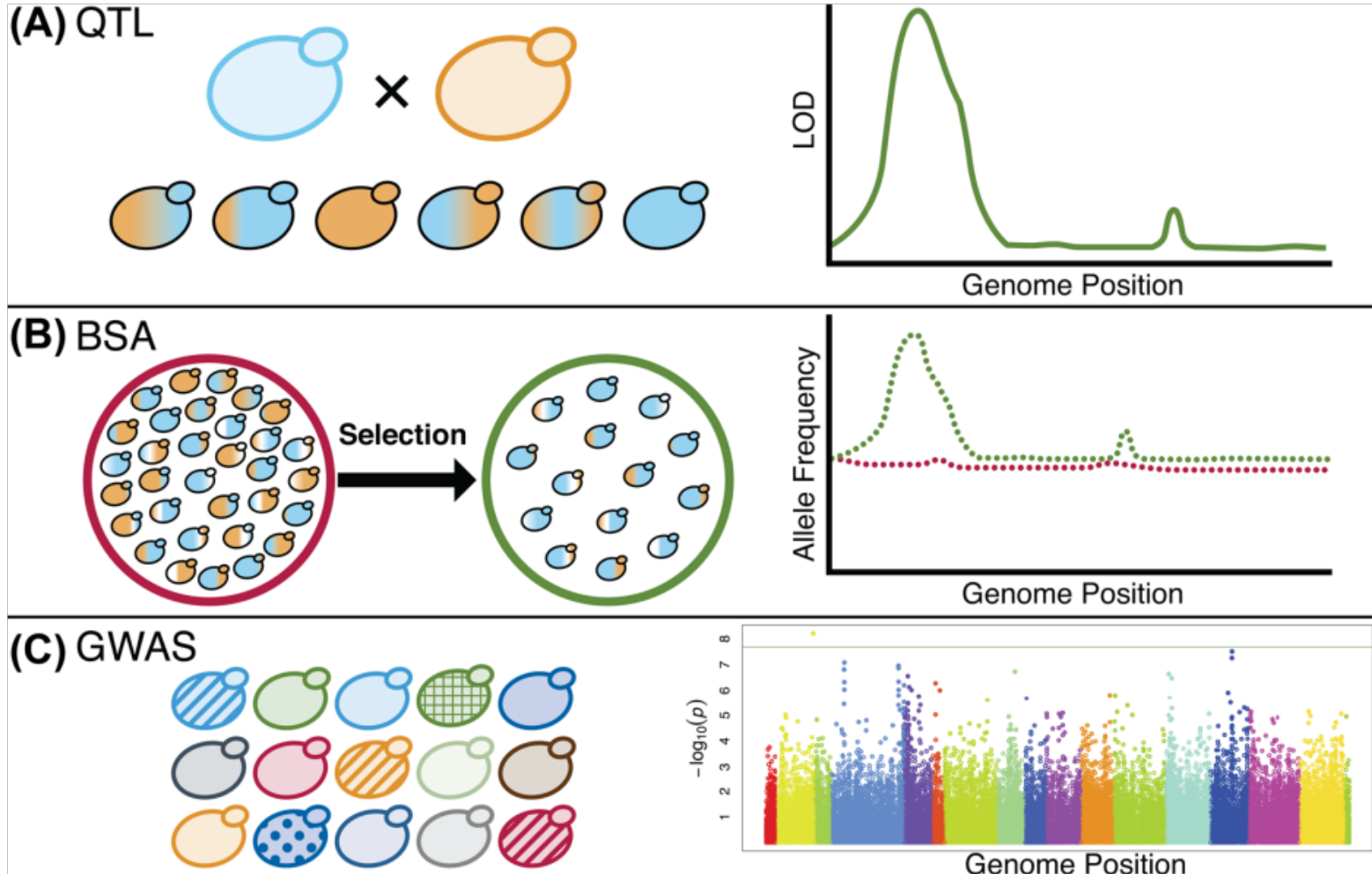
$$\text{LOD}(z) = \log_{10} \left\{ \frac{\Pr(\text{data} | \text{QTL at } z, \hat{\mu}_A, \hat{\mu}_B, \hat{\sigma})}{\Pr(\text{data} | \text{no QTL})} \right\}$$

The LOD score measures the strength of the evidence for the presence of a QTL at the location z , compared to there being no segregating QTL in the backcross. Larger LOD scores correspond to greater evidence for the presence of a QTL. The LOD score is calculated at each position of the genome (or, in practice, just every 0.5 cM or so).

The long path from QTL to causative gene



Genetic mapping methods



Shared literature:

1. QTL

Ackermann, 2016, Nature. (Mice)

Bargman, 2009, Neuron. (C.elegans)

Bargman, 2009, Neuron. (C.elegans)

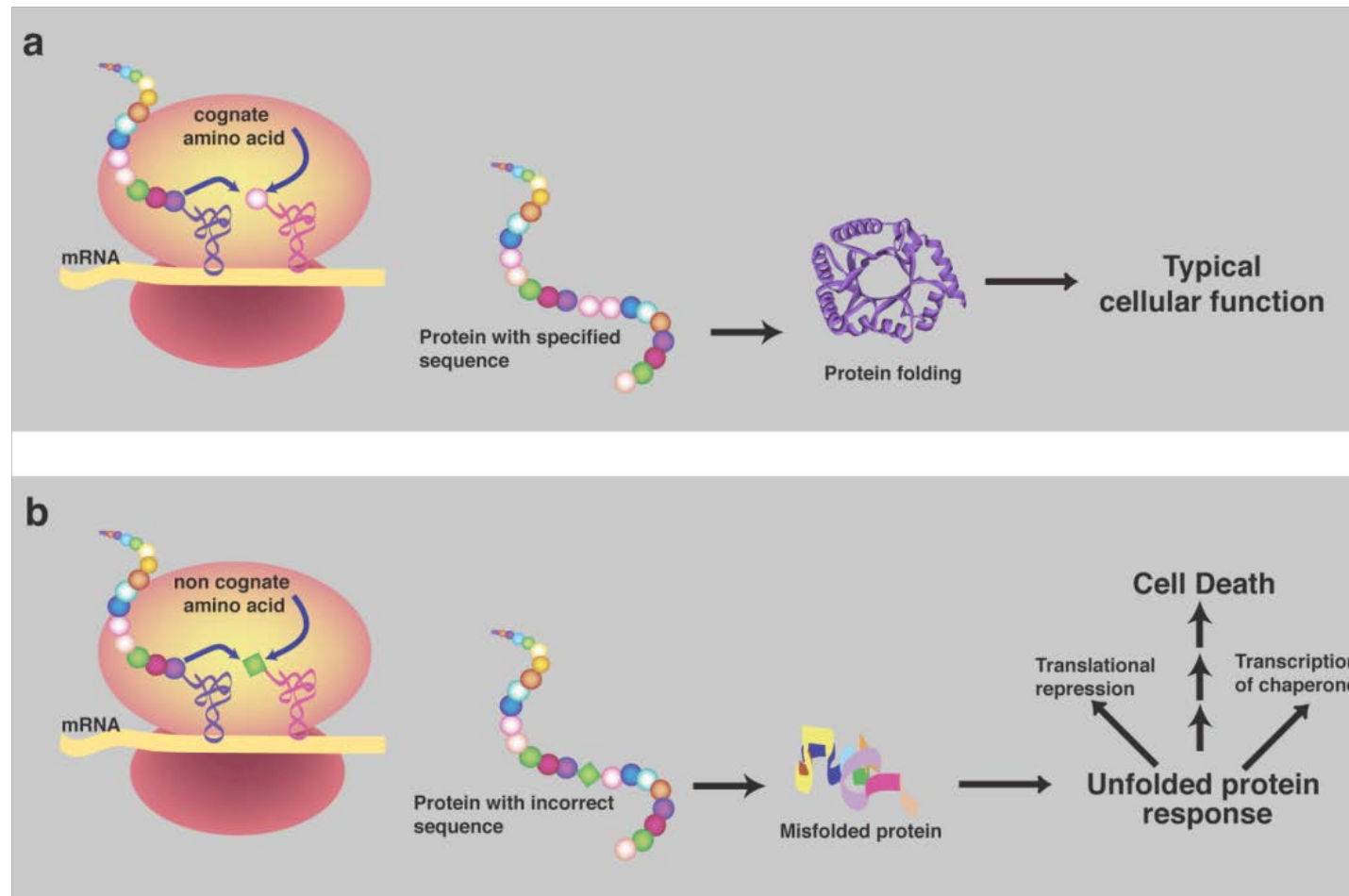
2. BSA / ceX-QTL

Kruglyak, 2019, Nature Communications

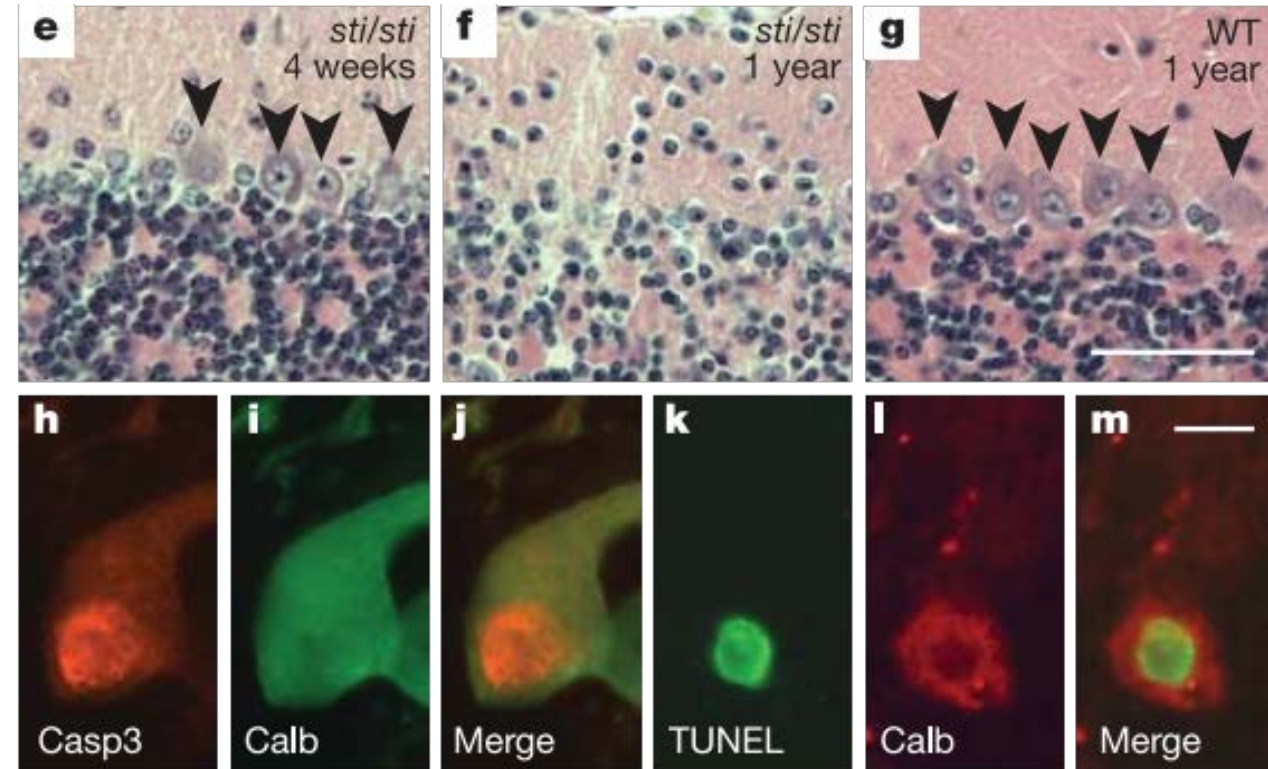
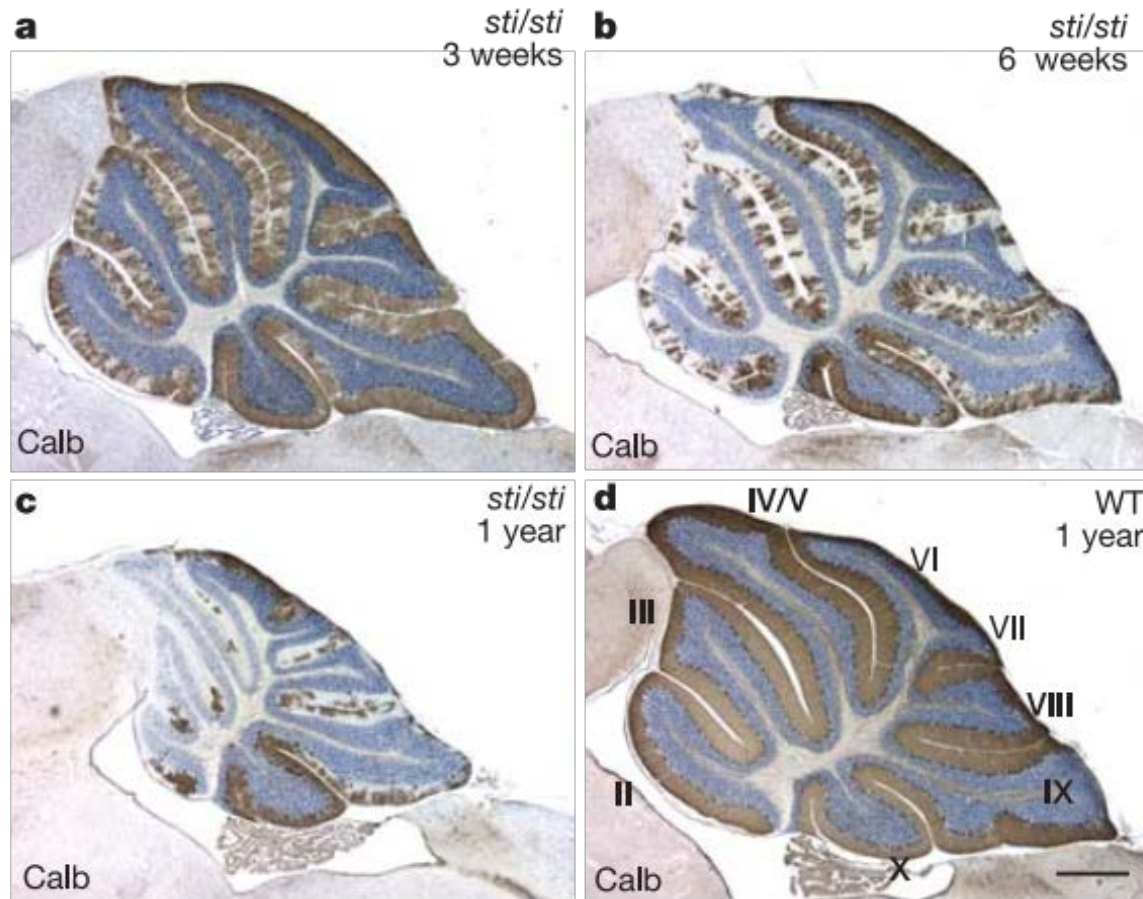
(C.elegans)

Editing-defective tRNA synthetase causes protein misfolding and neurodegeneration

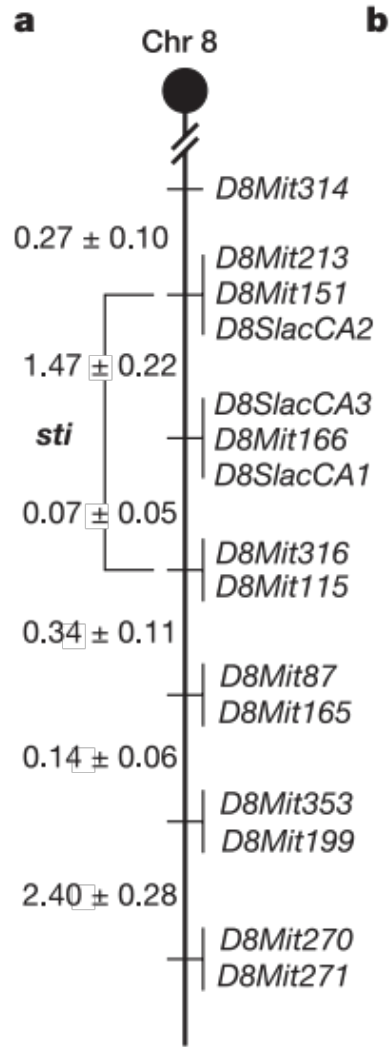
Jeong Woong Lee¹, Kirk Beebe², Leslie A. Nangle², Jaeseon Jang¹†, Chantal M. Longo-Guess¹, Susan A. Cook¹, Muriel T. Davisson¹, John P. Sundberg¹, Paul Schimmel² & Susan L. Ackerman^{1,3}



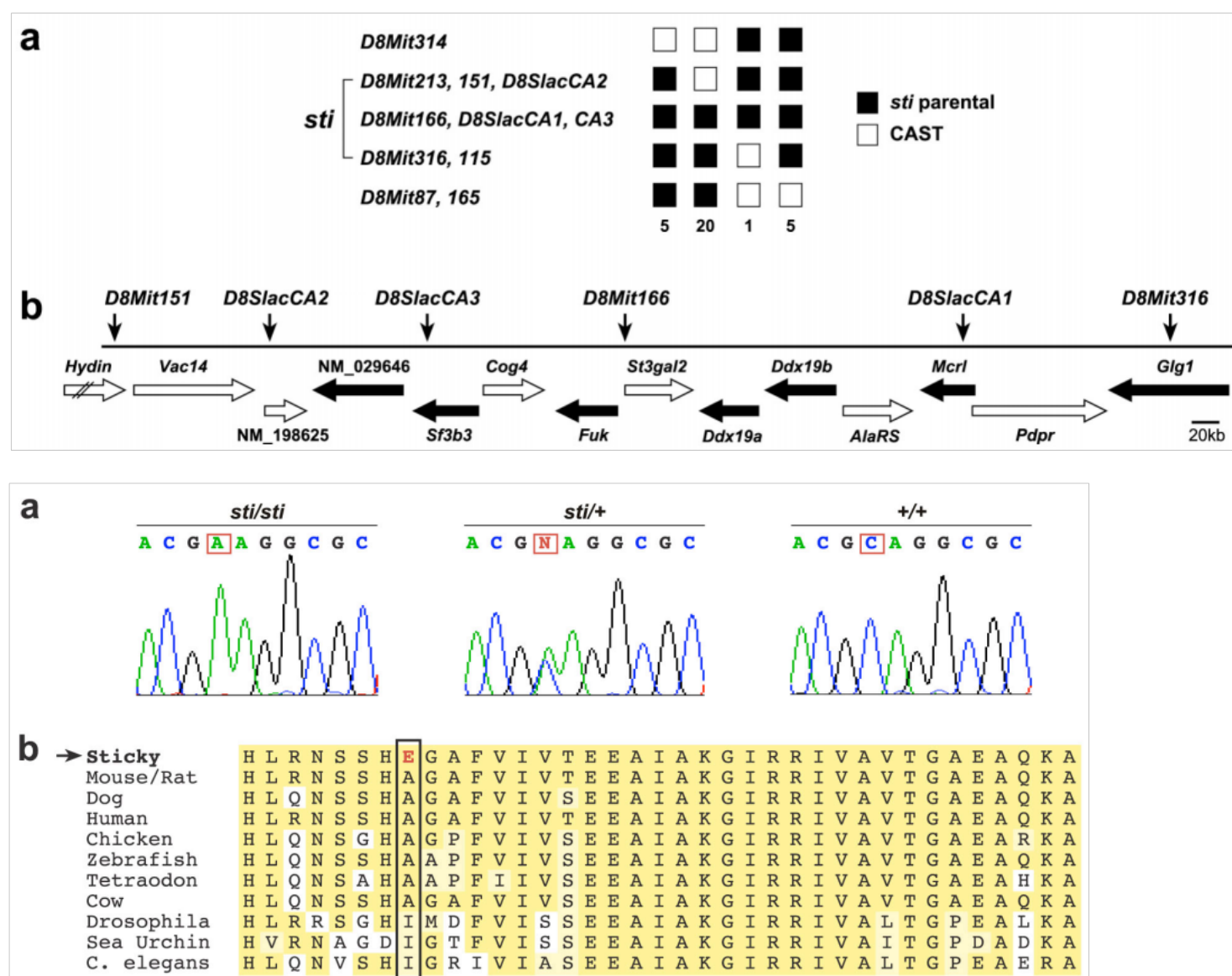
Purkinje cell loss in sticky mutant mice



The *sti* mutation is identified in the alanyl-tRNA synthetase (*Aars*) gene

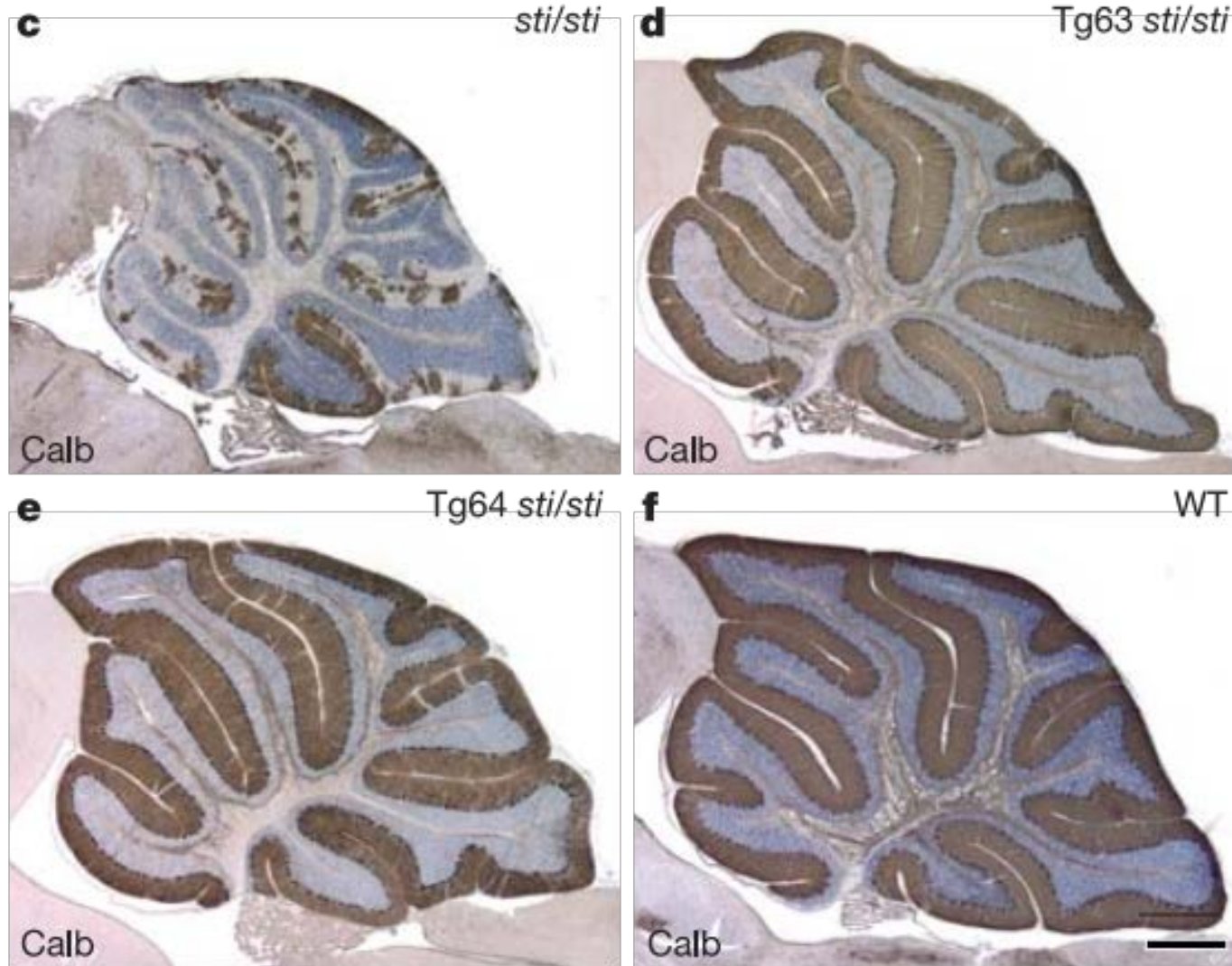


The *sti* locus resides in a 1.54 centimorgan (cM) region

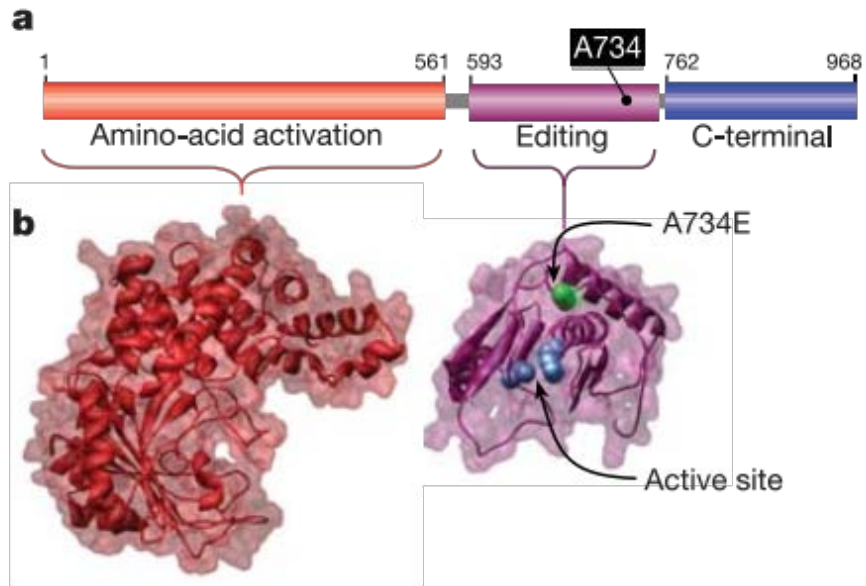


Point mutation in *Aars* gene predict a cause an Ala to Glu, a residue that is evolutionarily conserved

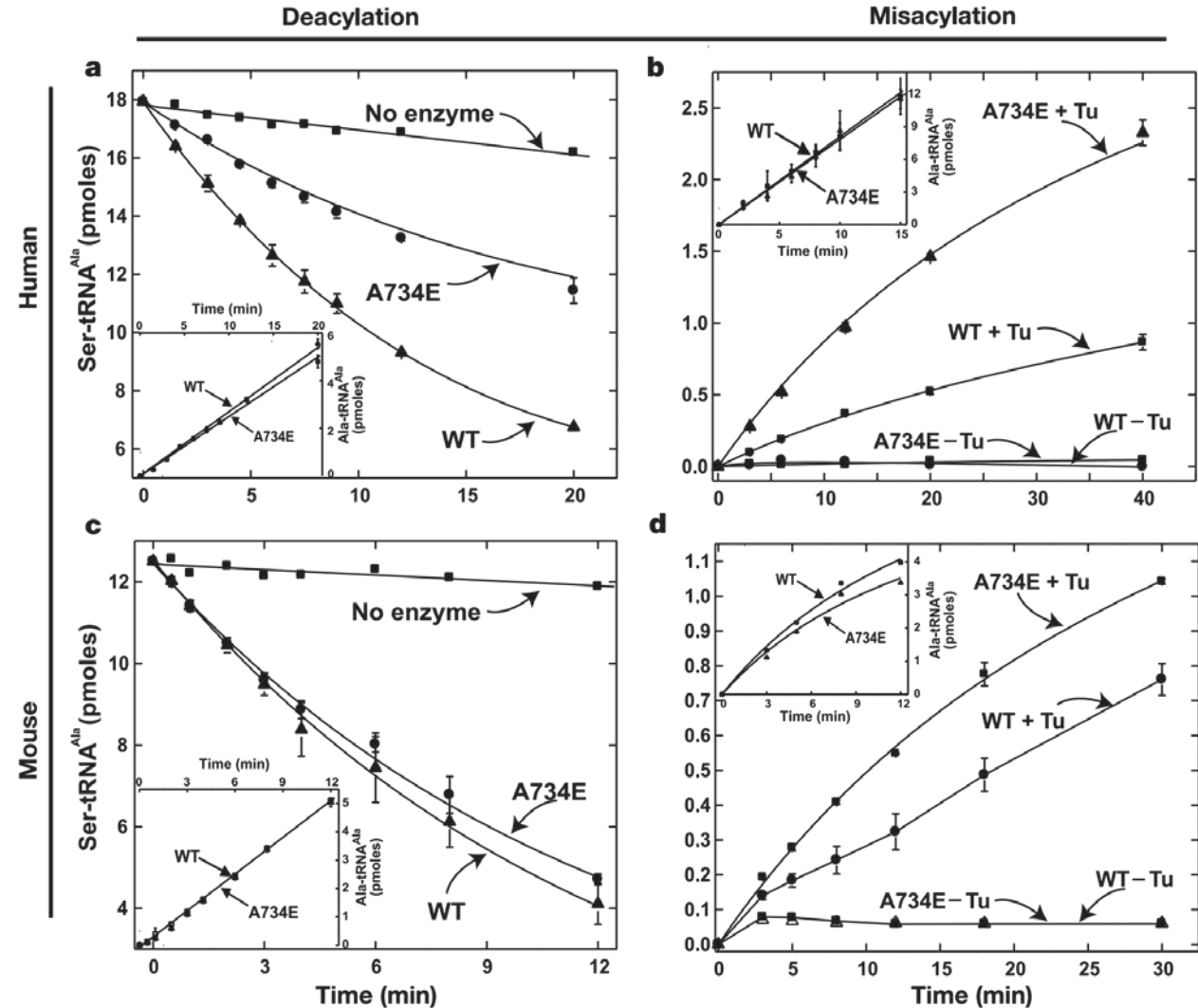
Wild typed *Aars* gene rescues neuronal degeneration in *sti* mutants



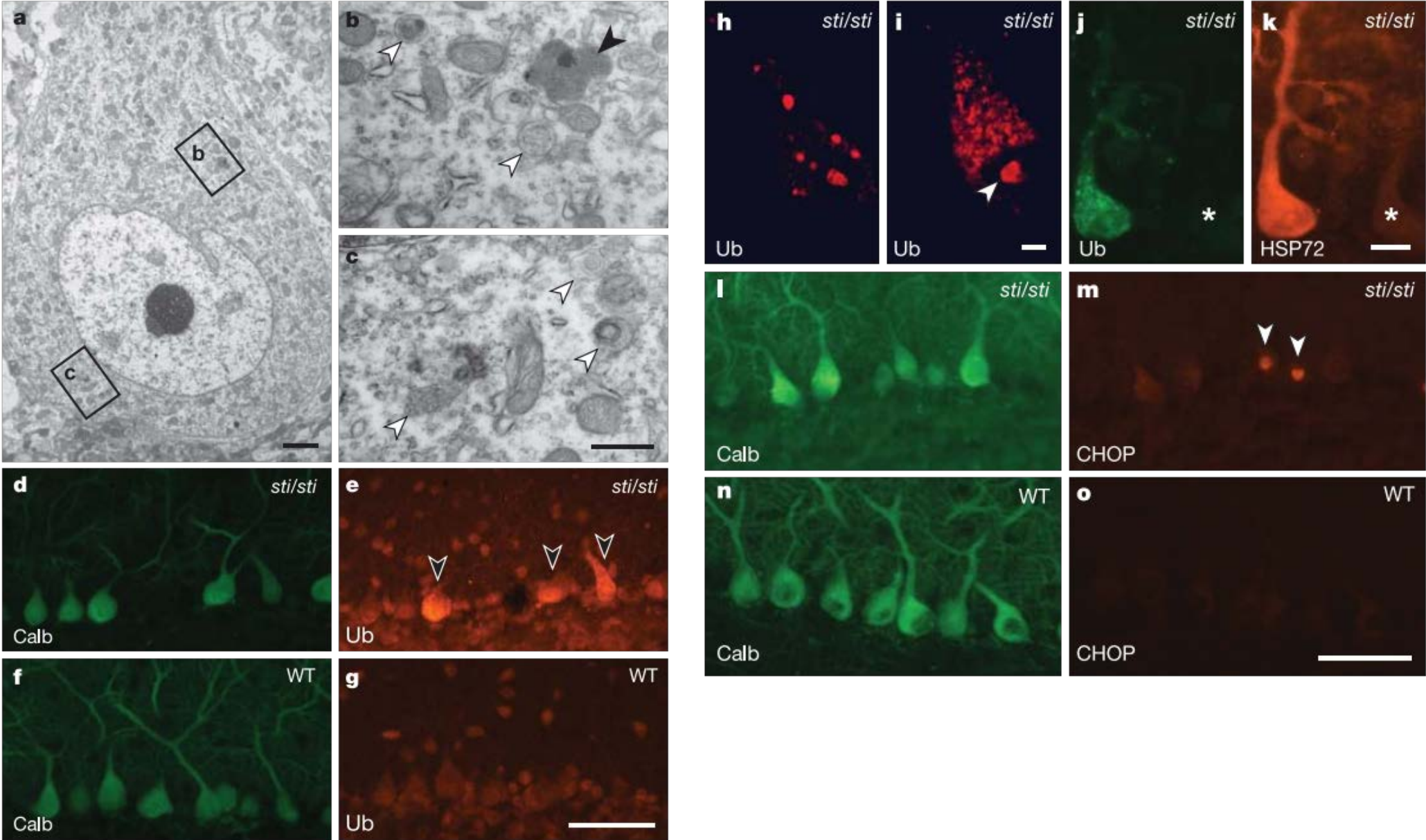
The *sti* mutation disrupts Serine-sensitive AlaRS editing



AlaRS functions in amino-acid activation and tRNA aminoacylation.



Accumulation of misfolded proteins in *sti/sti* Purkinje cells



ANKRD16 prevents neuron loss caused by an editing-defective tRNA synthetase

My-Nuong Vo^{1,17}, Markus Terrey^{2,3,4,5,17}, Jeong Woong Lee^{5,12}, Bappaditya Roy^{6,7}, James J. Moresco^{8,13}, Litao Sun¹, Hongjun Fu^{5,14,15}, Qi Liu^{6,7,9,16}, Thomas G. Weber¹⁰, John R. Yates III⁸, Kurt Fredrick^{6,7}, Paul Schimmel^{1,11,18*} & Susan L. Ackerman^{2,3,4,5,18*}

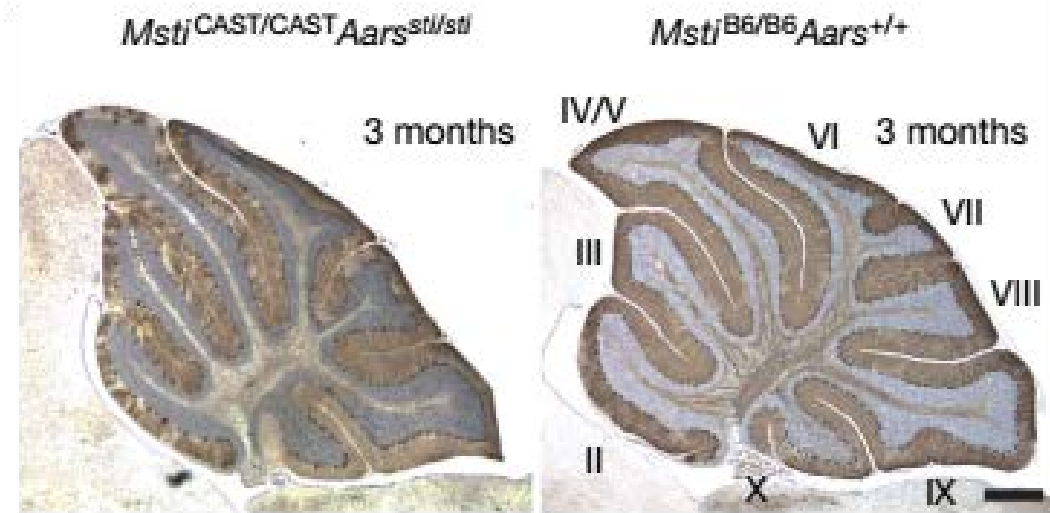
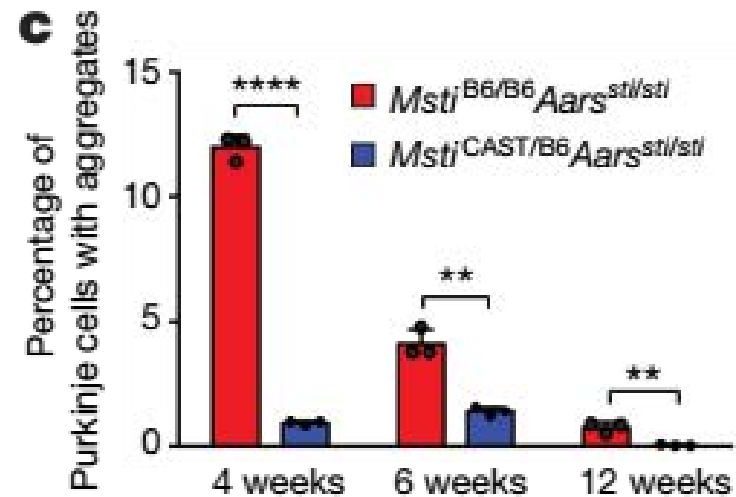
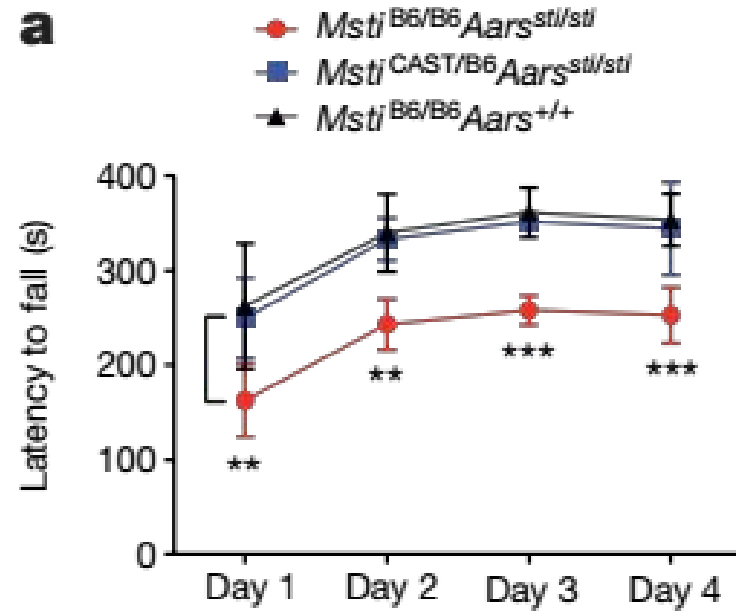
Trait heterogeneity for Purkinje cell degeneration :

B6.*Aars*^{sti/+} (+)

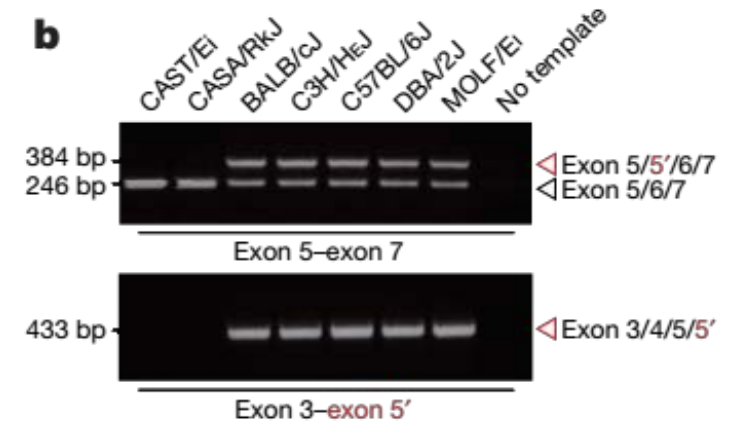
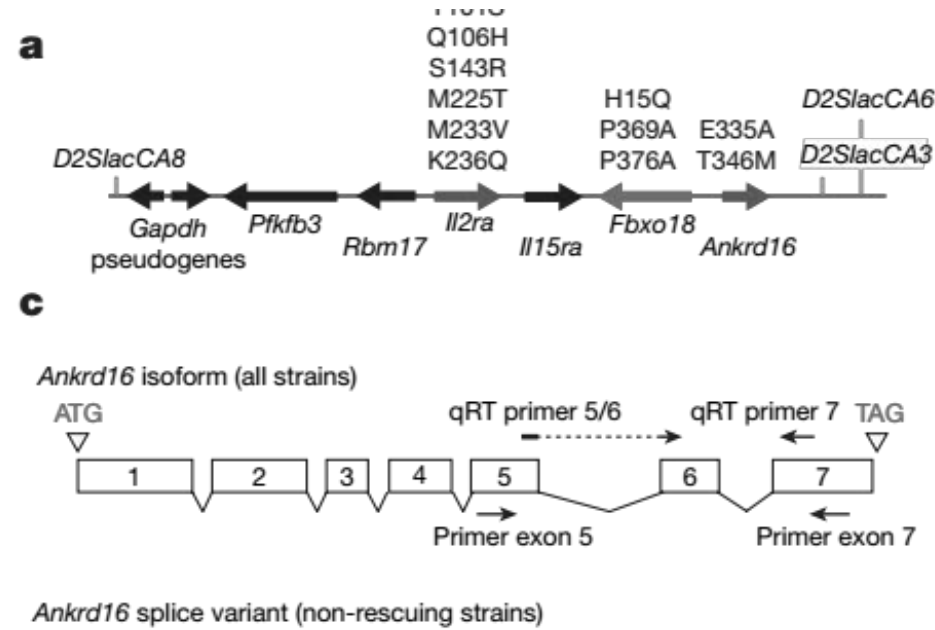
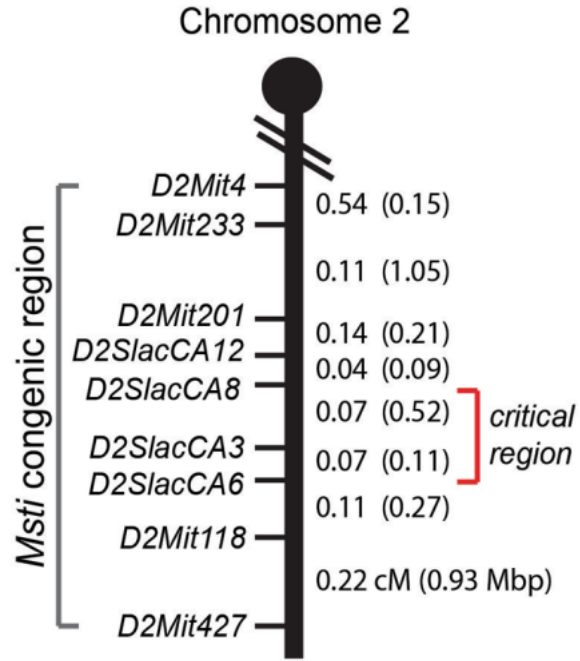
CAST. *Aars*^{sti/+} (-)

What's the causal gene for suppressing neuron loss in CAST background alleles?

Modifier of sticky (*Msti*) suppresses *Aars*^{sti}-mediated neurodegeneration



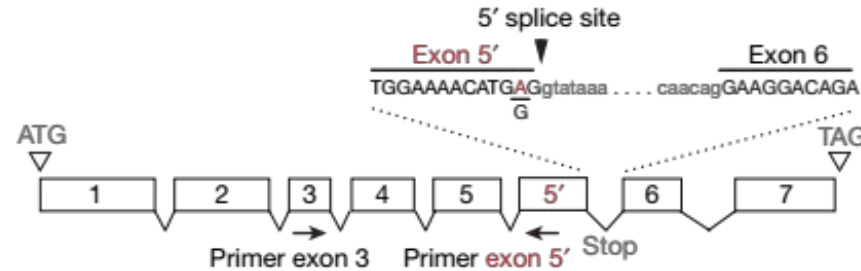
Ankrd16 is the modifier of *Aars^{sti/sti}*



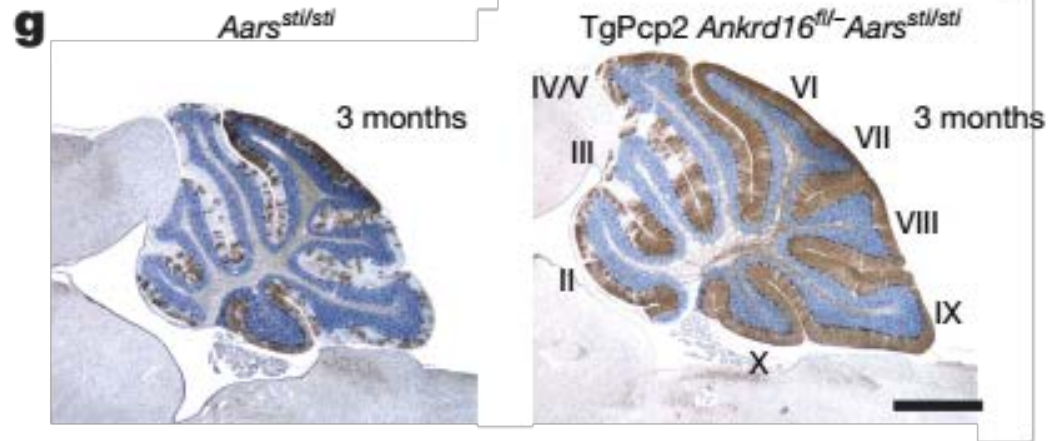
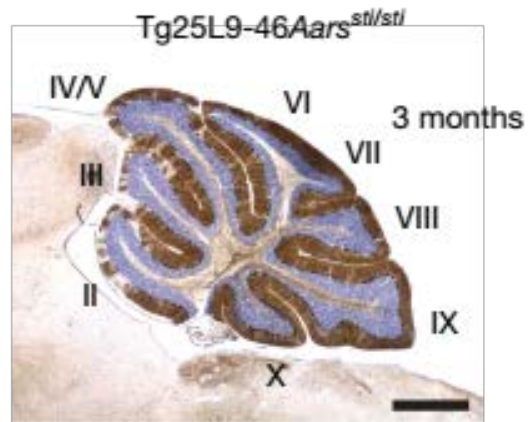
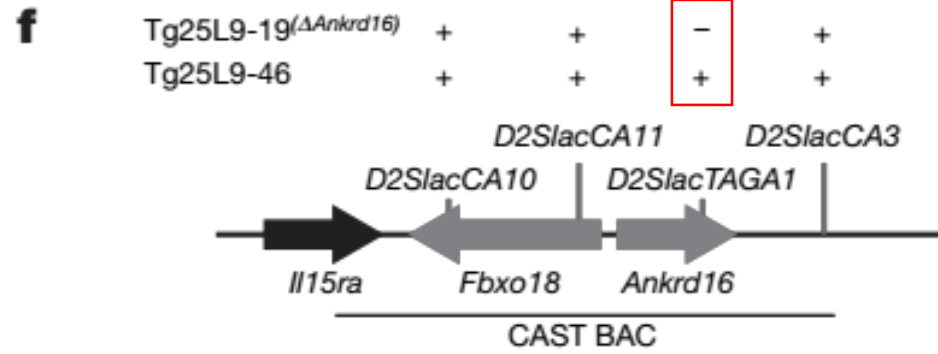
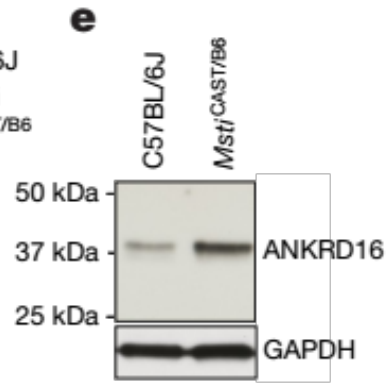
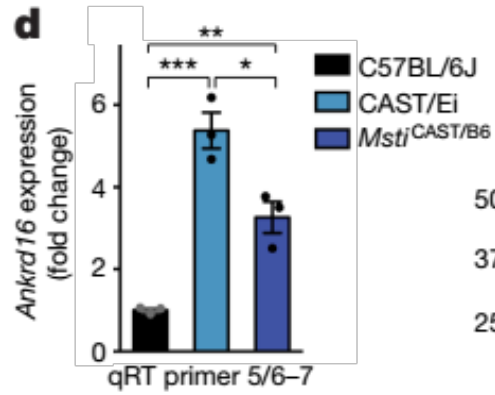
Microsatellite and SNP markers:
0.63-Mb region of critical QTL

RT-PCR and PCR amplification on candidate genes

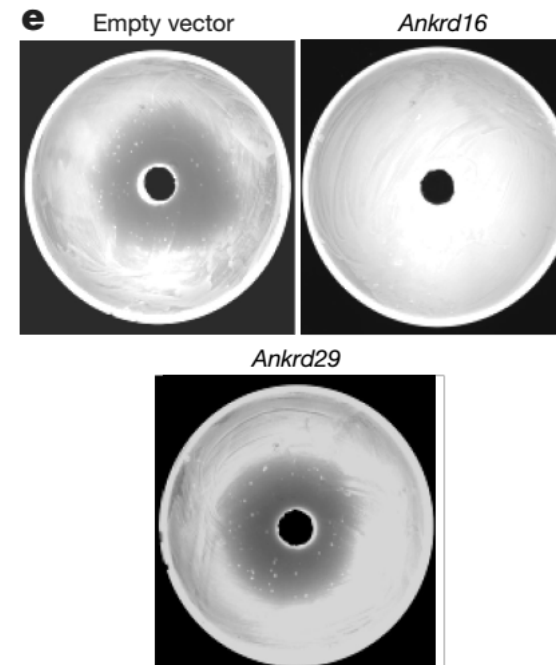
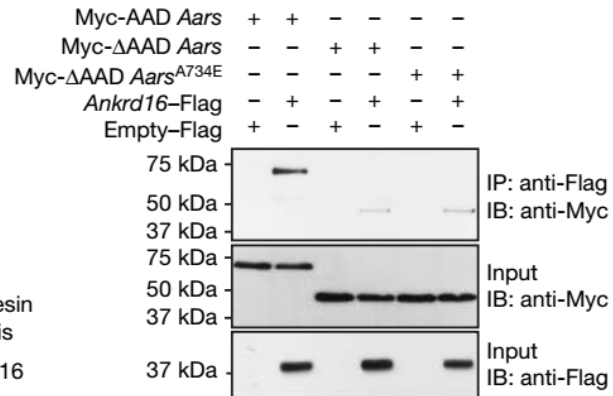
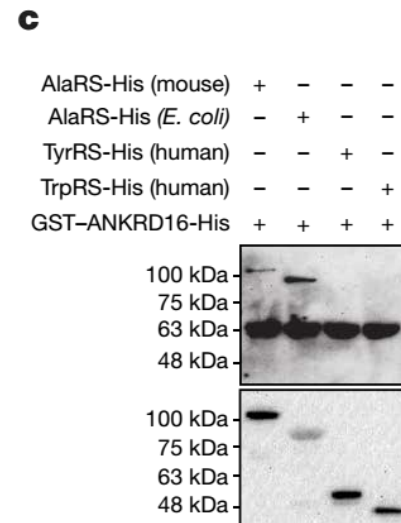
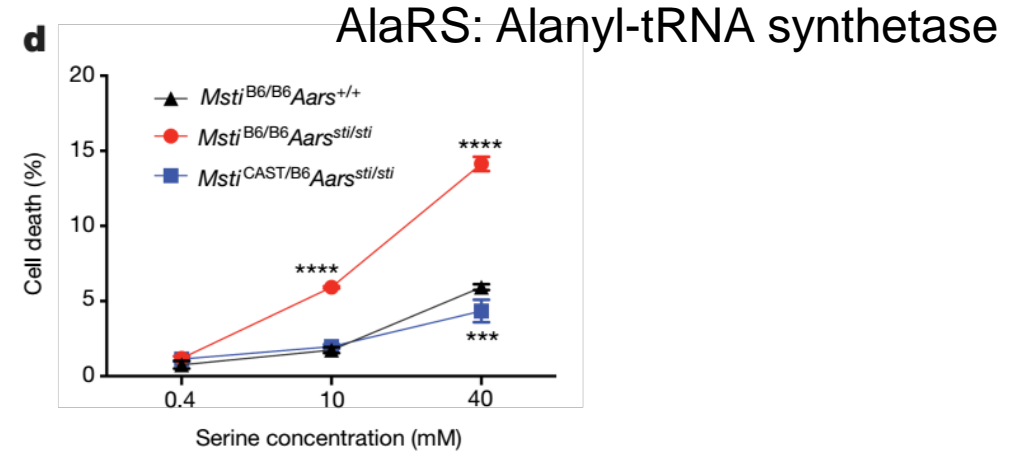
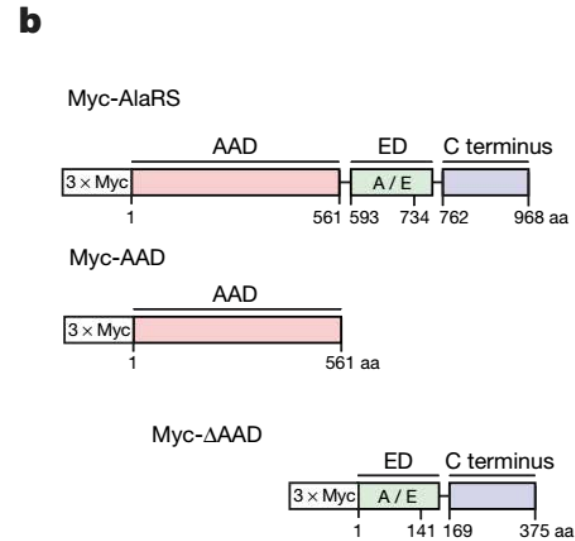
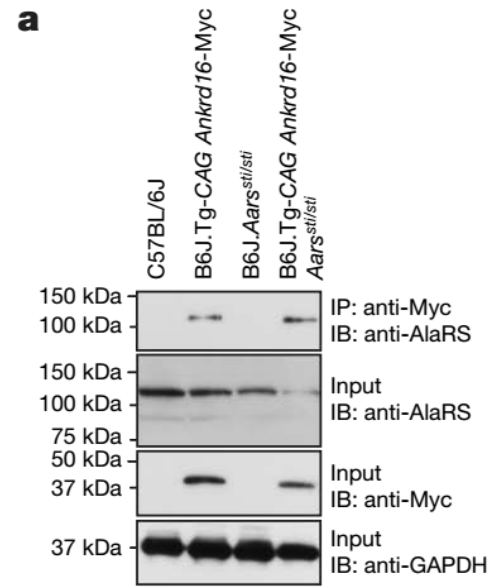
Sequencing for causal genes



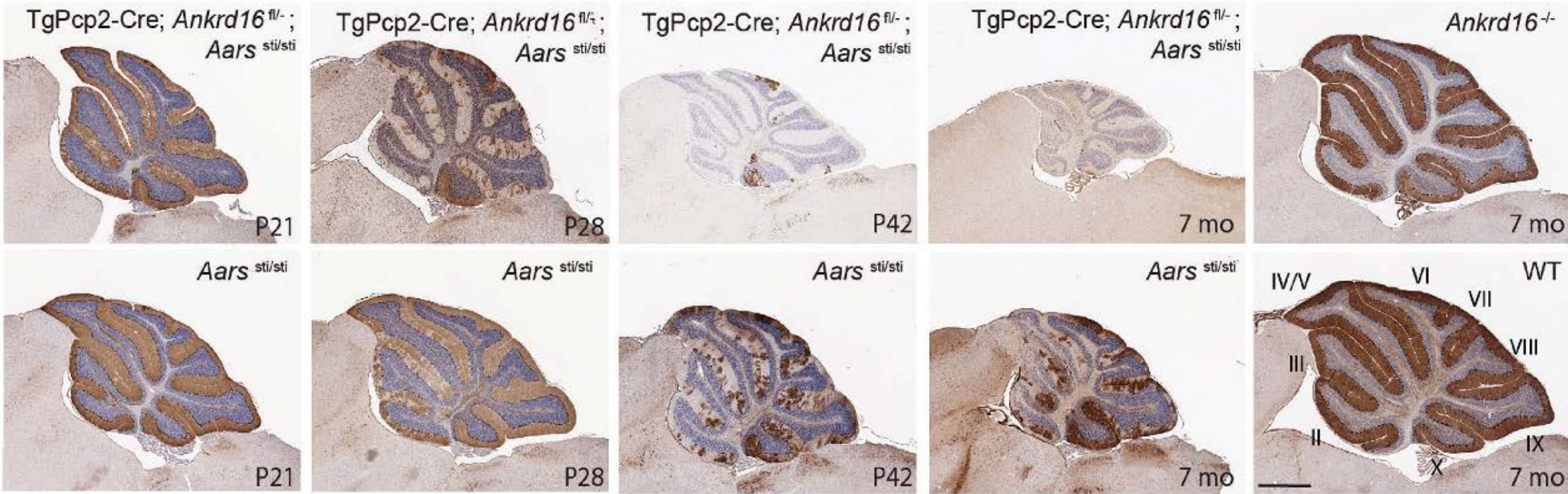
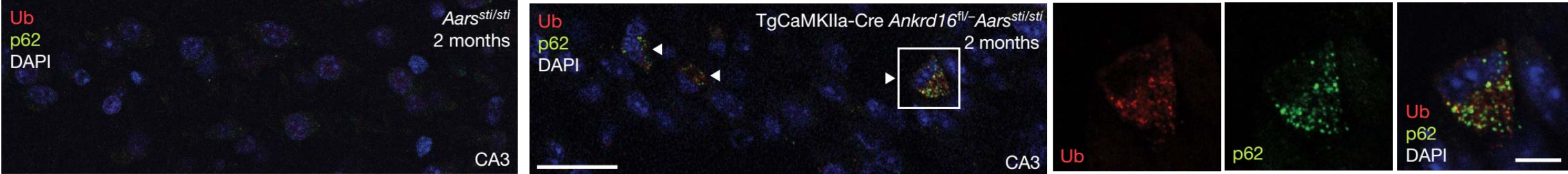
Ankrd16 is the modifier of *Aars^{sti/sti}*



ANKRD16 interacts with AlaRS and prevents mistranslation



Loss of *Ankrd16* in *Aars^{sti/sti}* mice causes protein aggregation and neurodegeneration



Ubiquitin- and p62-positive aggregates were observed both in hippocampal pyramidal cells

Quantitative Mapping of a Digenic Behavioral Trait Implicates Globin Variation in *C. elegans* Sensory Behaviors

Patrick T. McGrath,¹ Matthew V. Rockman,^{2,3} Manuel Zimmer,¹ Heeun Jang,¹ Evan Z. Macosko,¹ Leonid Kruglyak,³ and Cornelia I. Bargmann^{1,*}

Neuron, 2009

Trait: behavioral responses to stimulus changes in environmental O₂/CO₂
Two wild type strains: N2 vs CB4856

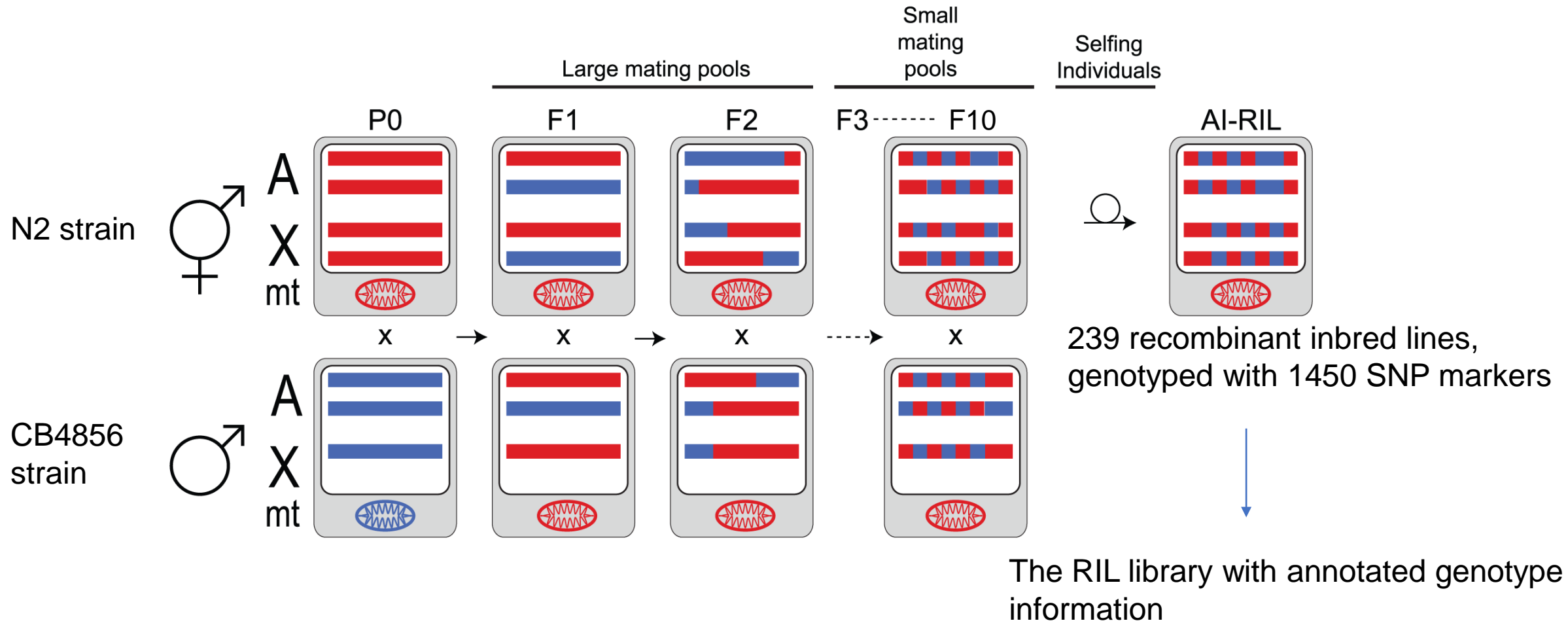


Identifying causal genes using a well-established library for Recombinant Inbred Lines (RILs)

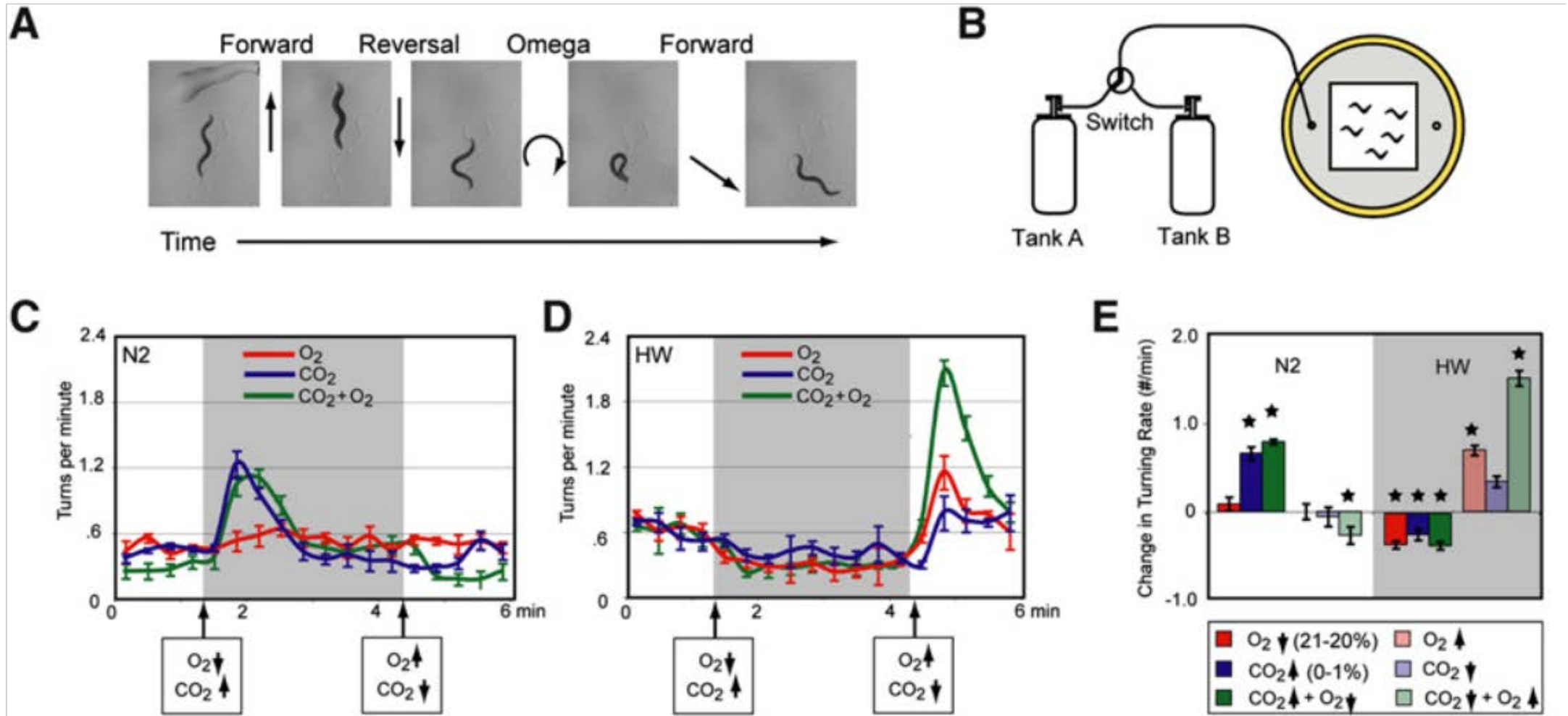


Two QTLs:
Npr-1 for O₂ preference, CO₂ avoidance
Glb-5 for CO₂ preference

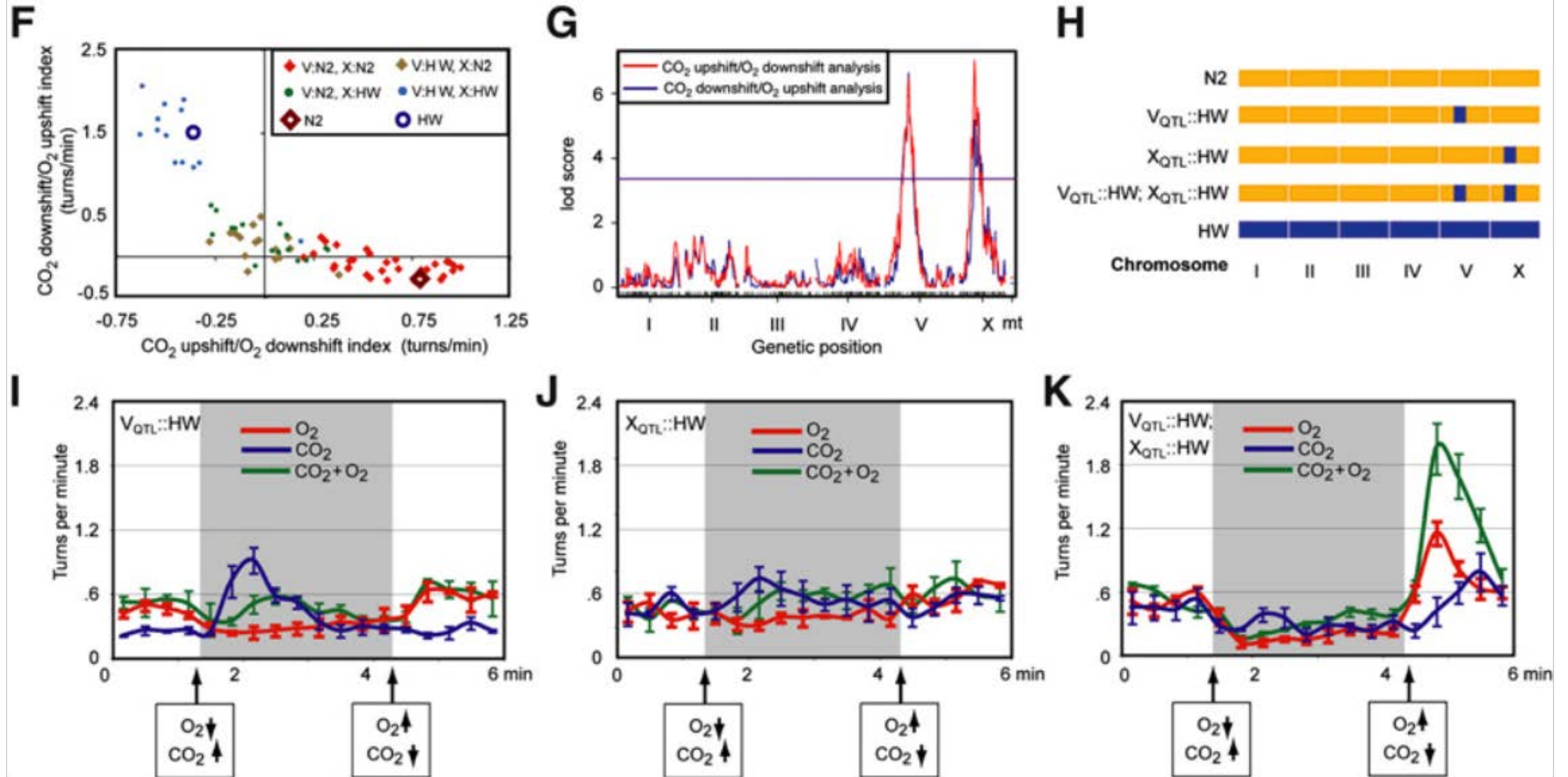
Recombinant Inbred Lines (RILs) developed by Leonid Kruglyak Lab



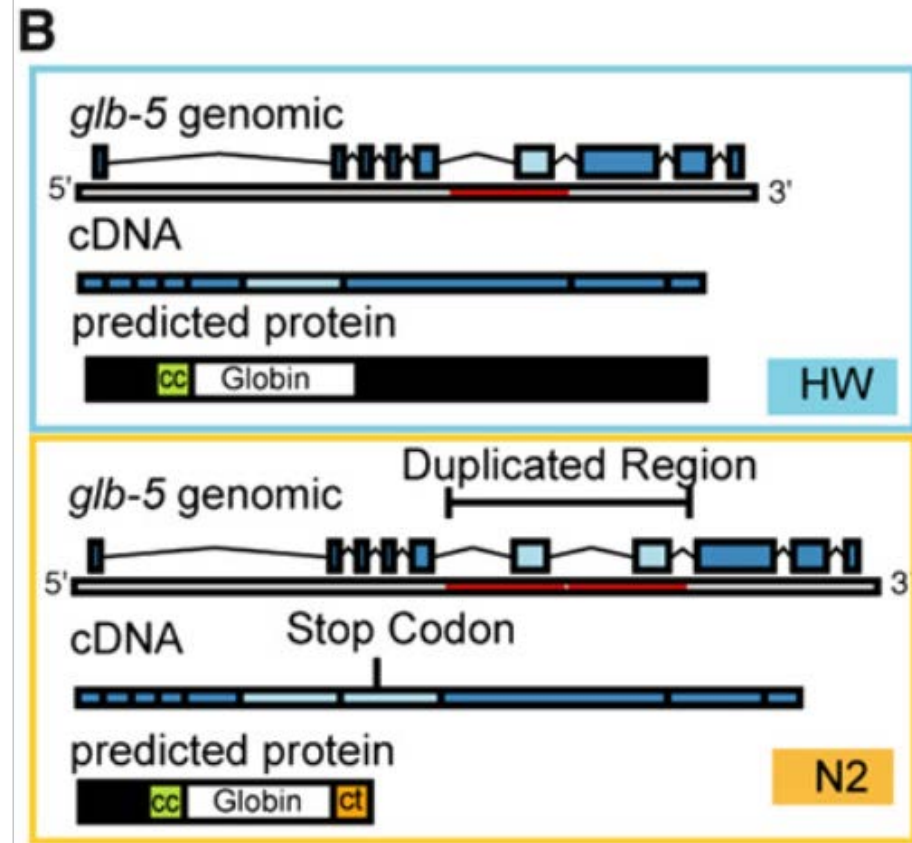
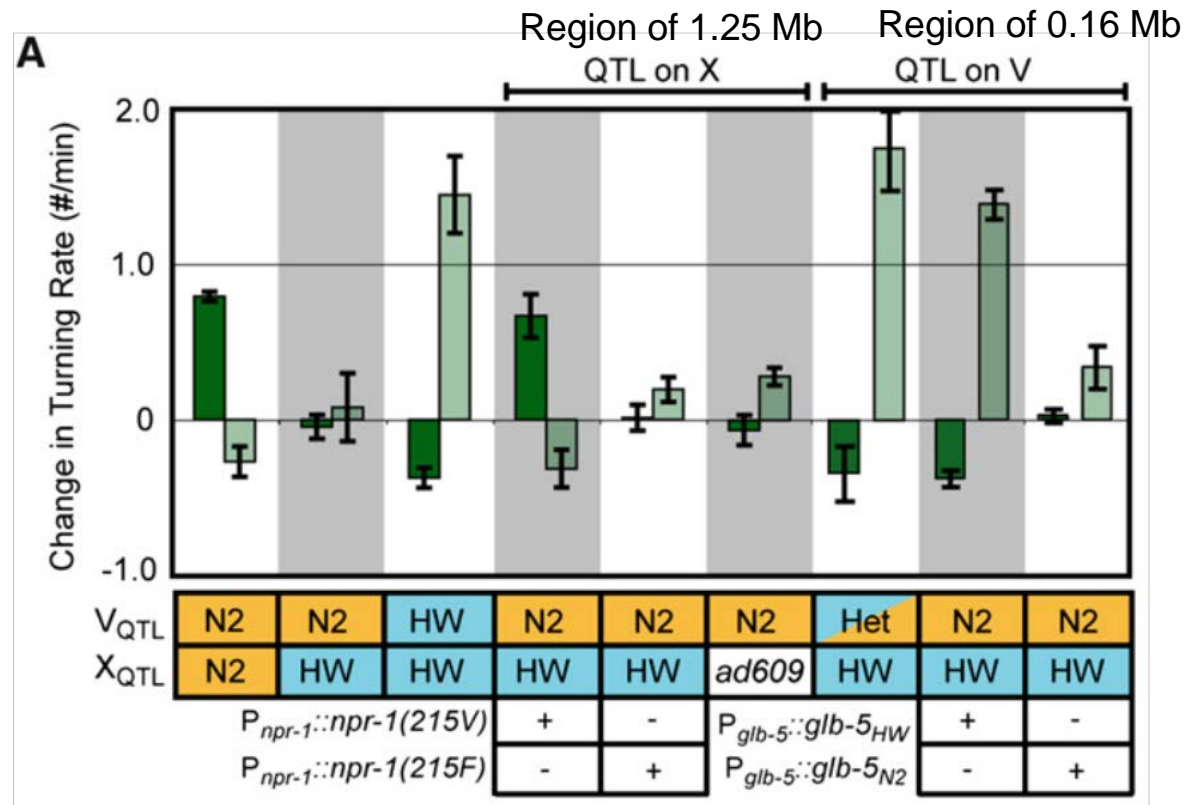
O₂- and CO₂-Evoked Responses of Two *C. elegans* Isolates



QTL analysis of O₂ and CO₂ responses in two strains using RILs

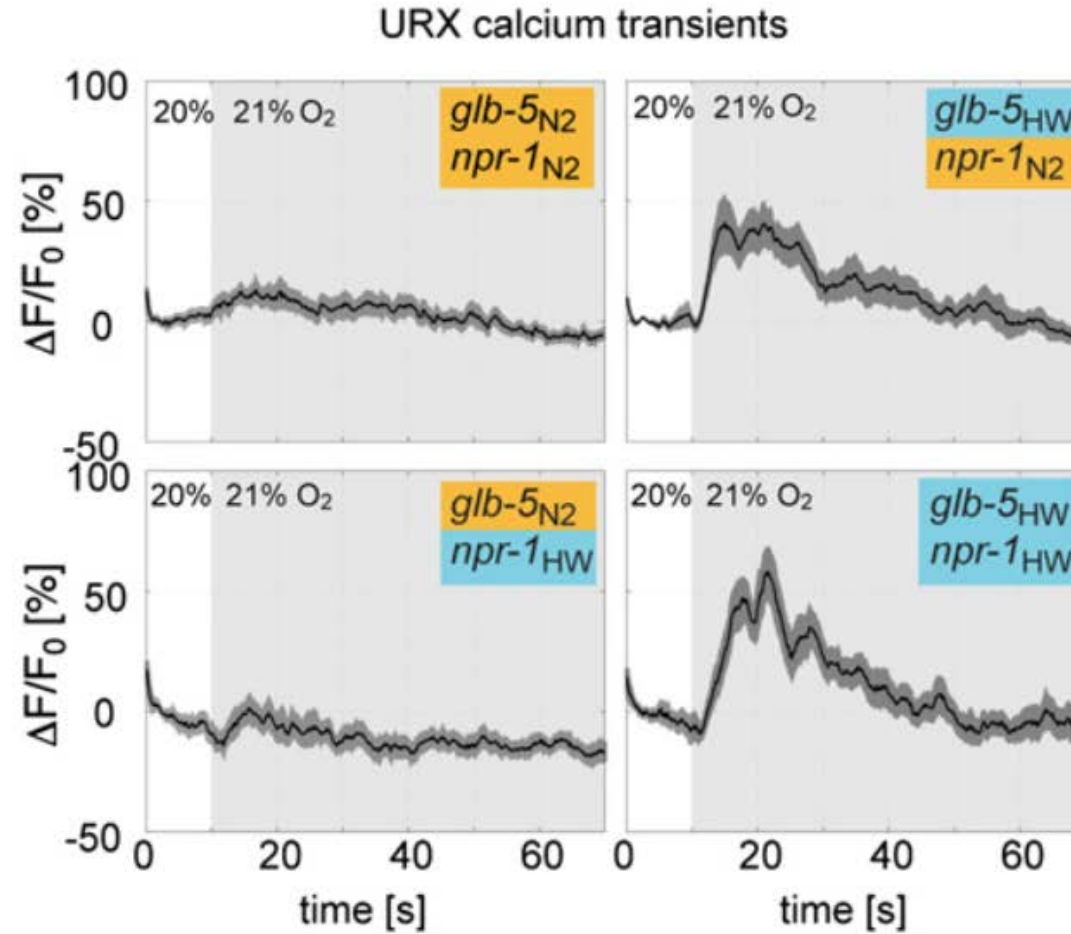
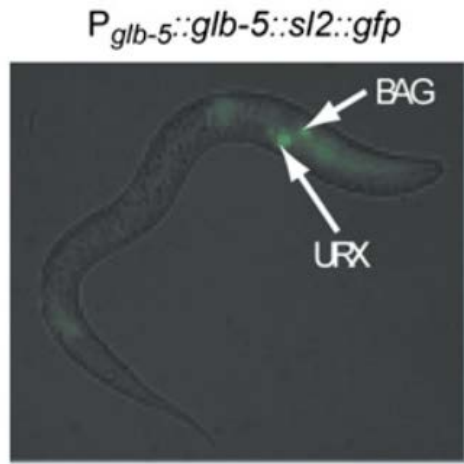


Identification of *npr-1* and *glb-5* for O₂ and CO₂ responses in two strains

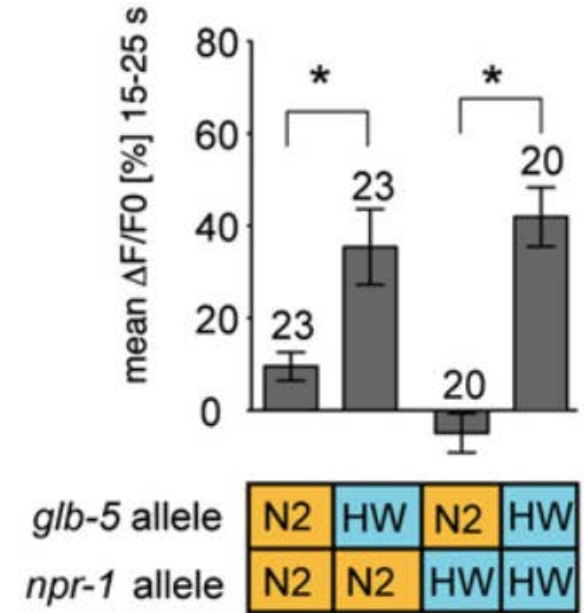


Npr-1: point mutations in 215 from V to F in CB4856, leading to high-activity Npr-1 in N2, low-activity Npr-1 in CB4856;
Glb-5: duplication/insertion of *glb-5* in N2, leading to **truncate of *glb-5* in N2**.

glb-5 Acts in URX, AQR, and PQR O₂-Sensing Neurons



D





ARTICLE

<https://doi.org/10.1038/s41467-019-10636-9>

OPEN

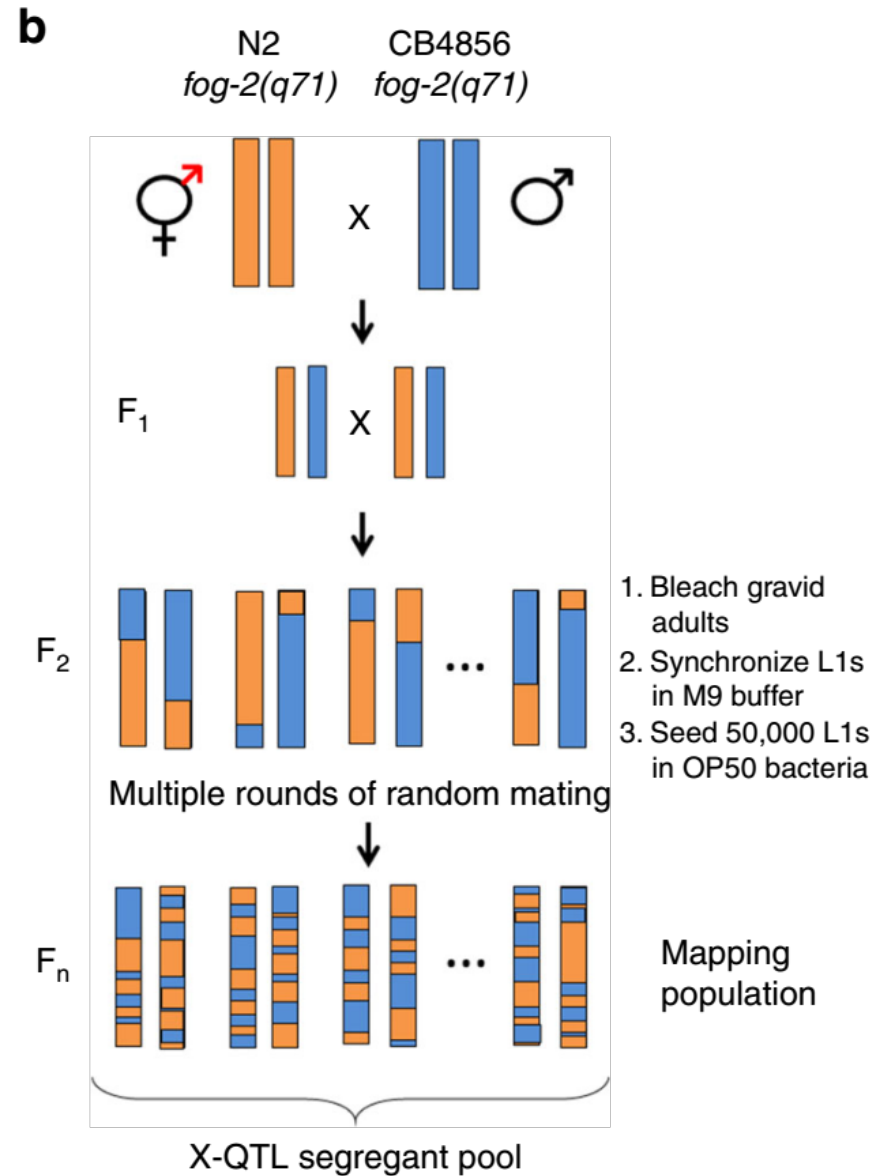
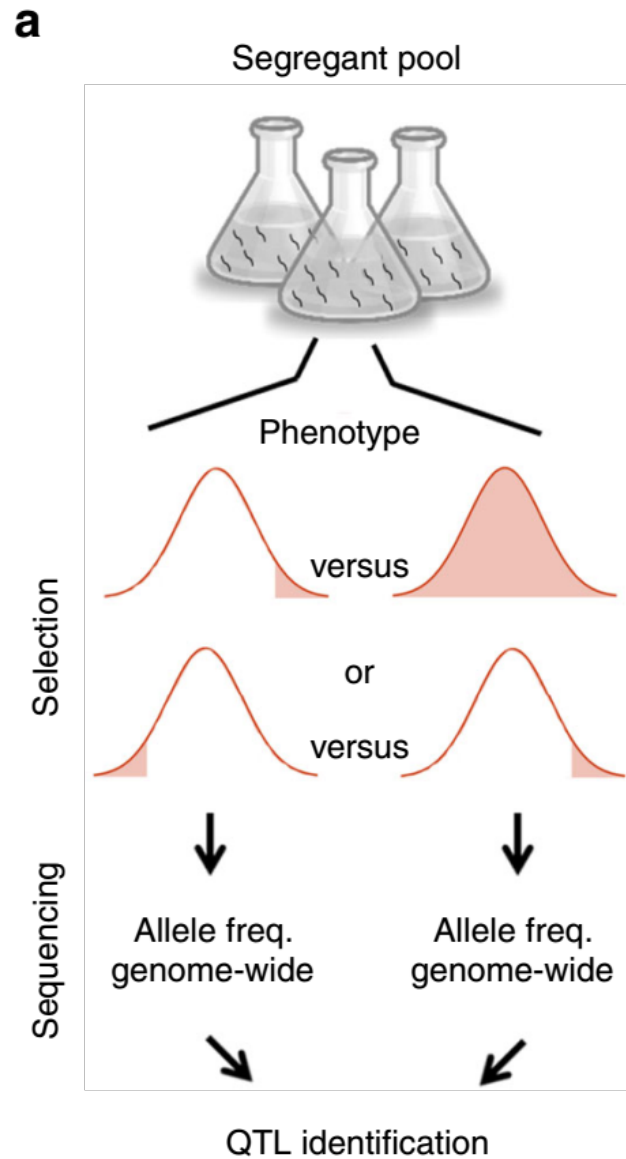
Fast genetic mapping of complex traits in *C. elegans* using millions of individuals in bulk

Alejandro Burga^{1,2,3}, Eyal Ben-David^{1,3}, Tzitziki Lemus Vergara¹, James Boocock ¹ & Leonid Kruglyak ¹

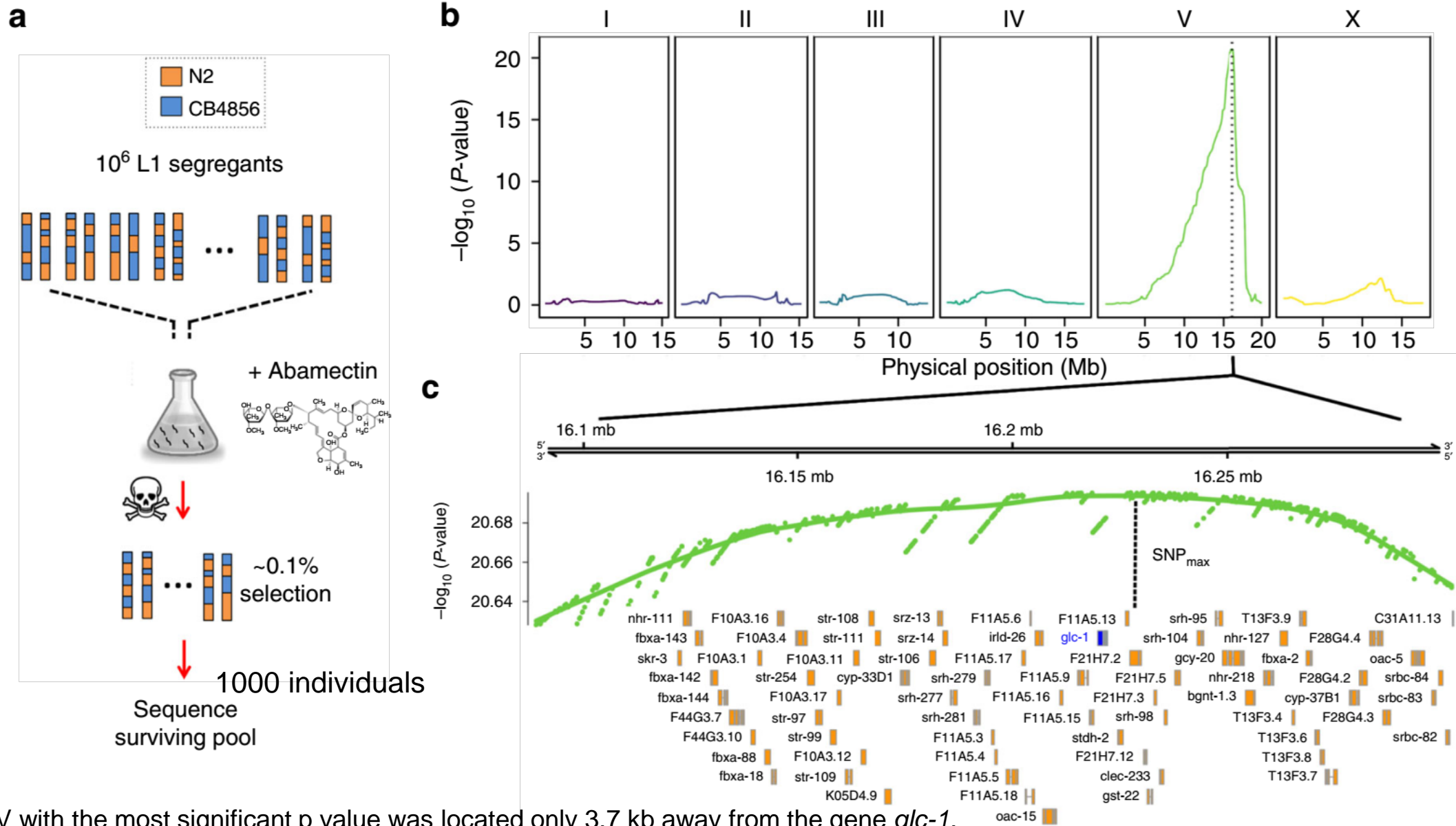
Nature Communications, 2019

C. elegans eXtreme Quantitative Trait Locus mapping (ceX-QTL)

Implementing bulked eXtreme quantitative trait loci (X-QTL) in *C. elegans*

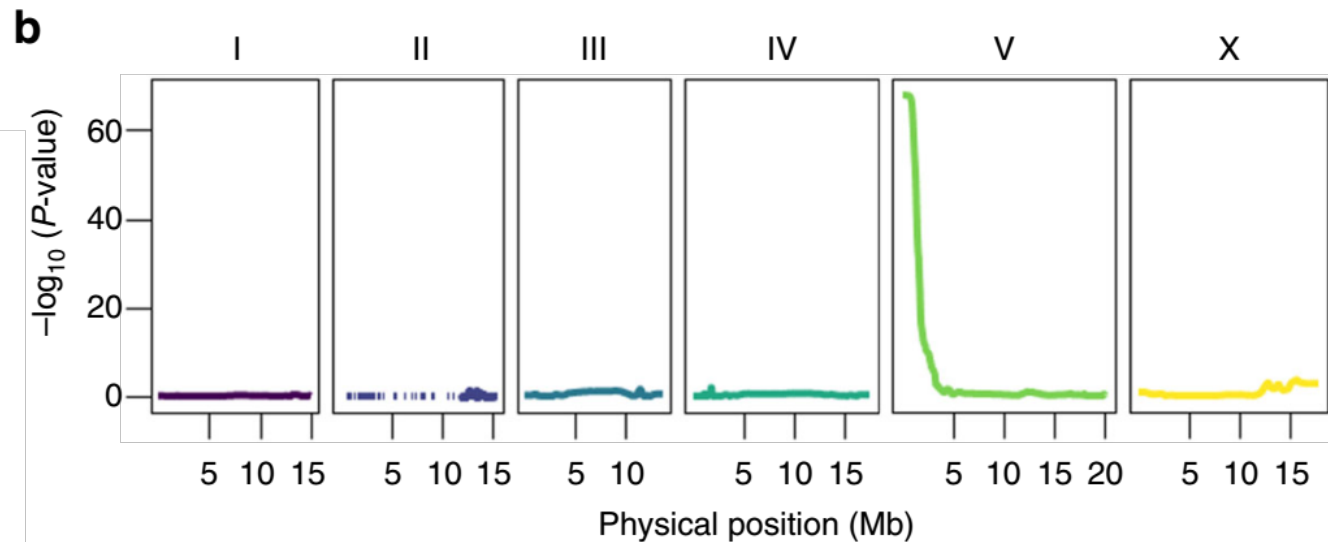
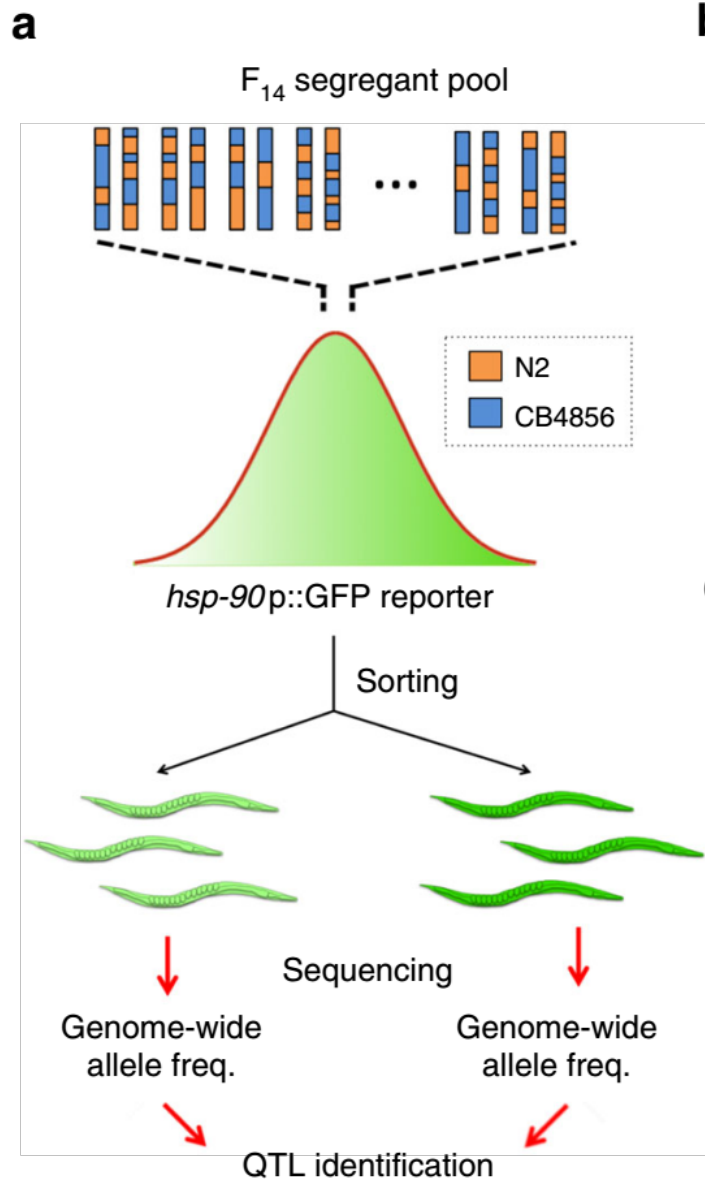


Mapping natural genetic variation in drug resistance



The SNV with the most significant p value was located only 3.7 kb away from the gene *glc-1*. *glc-1* encodes the alpha subunit of a glutamate-gated chloride channel, and has been validated for the causal gene for Abamectin resistance

Coupling X-QTL and worm sorting



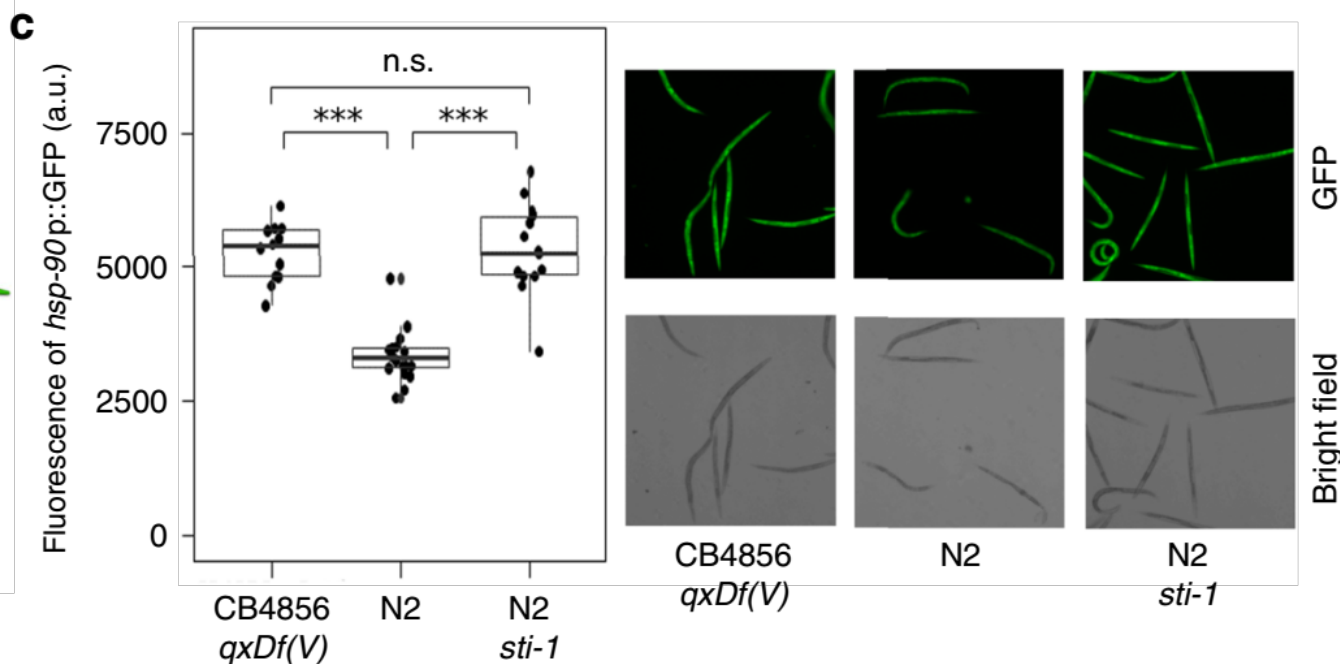
17 candidates

↓

RNAi screening

↓

Sti-1



Summary

1. Classical QTL analysis has associated chromosomal regions with traits like anxiety, aggression, drug preference, and learning, but since a well-defined QTL in *Drosophila* or mouse typically covers 300–500 genes, moving from a QTL to the causative mutation is very difficult.
2. Whole-genome sequences and inexpensive resequencing greatly improved the resolution of QTL mapping and optimizations would speed up the timeline of QTL especially in mice.
3. High-throughput and bulked QTL mapping in small organisms (e.g. *Yeast*, *C. elegans*) greatly improved the efficiency of QTL mapping.

Thanks!