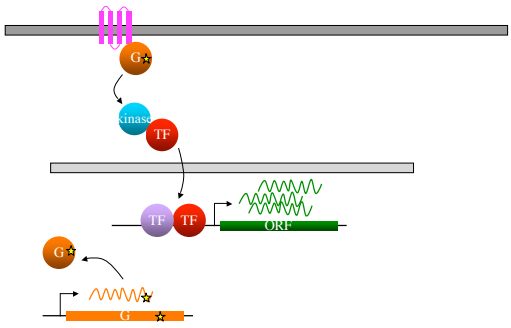
Office hours
3-4pm Wednesday, Dec. 10
304A Stanley Hall

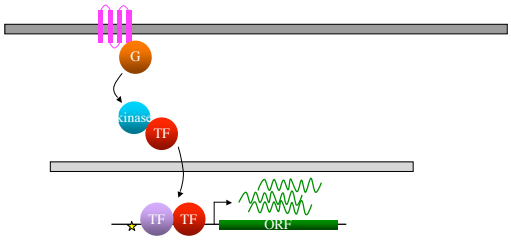
Review session
5pm Thursday, Dec. 11
GPB100

Final exam
12:30pm Saturday, Dec. 13
277 Cory Hall (NE campus)

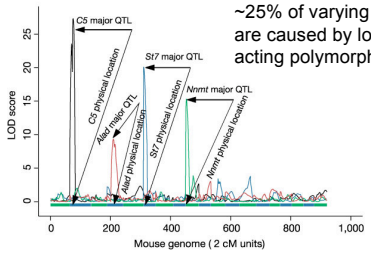
Marker is linked to polymorphism in expression regulation cascade



Locally acting regulatory variant



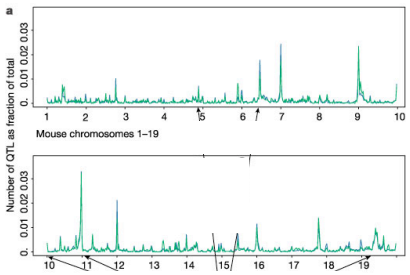
Locally acting polymorphisms



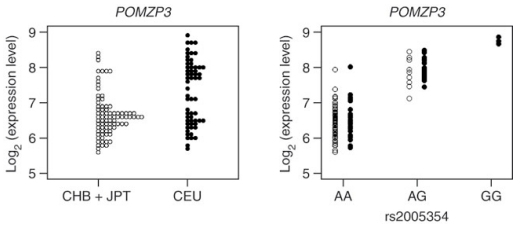
~25% of varying mRNAs are caused by locally acting polymorphism

Polymorphism responsible for mRNA difference is at the locus of the gene itself

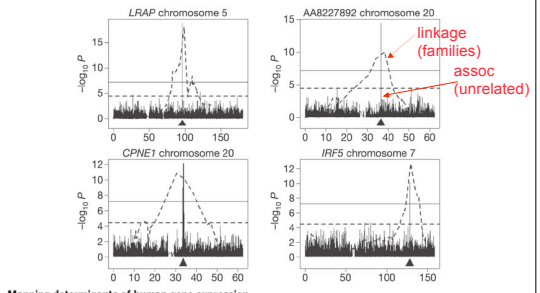
Nonlocal polymorphisms



Association in multiple populations



Association of human transcripts



Mapping determinants of human gene expression by regional and genome-wide association

Vivian G. Cheung[1,2], Richard S. Spielman[1], Kathryn G. Ewens[1], Teresa M. Weber[1,2], Michael Morley[1] & Joshua T. Burdick[1]

A new brand of genetic variation

Translation

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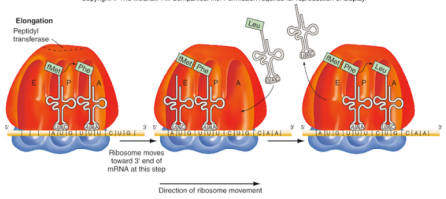

Fig. 8.25

Translation

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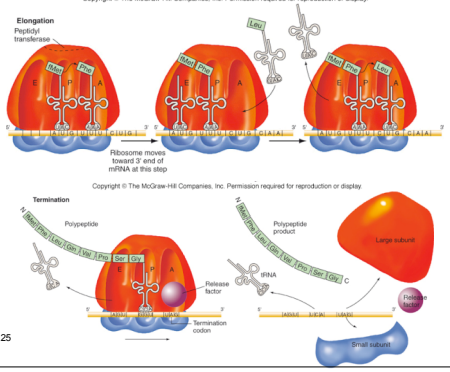

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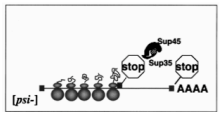
Fig. 8.25

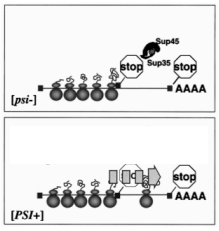
PSI+ yeast read through STOPs



[*PSI*+], *SUP35*, AND CHAPERONES

TRICIA R. SERIO* AND SUSAN L. LINDQUIST†

PSI+ yeast read through STOPs



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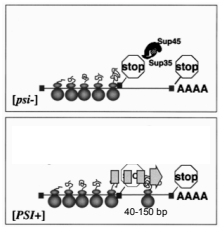

[*PSI*$^+$], *SUP35*, AND CHAPERONES

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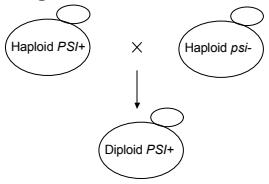
Weird genetics of read-through



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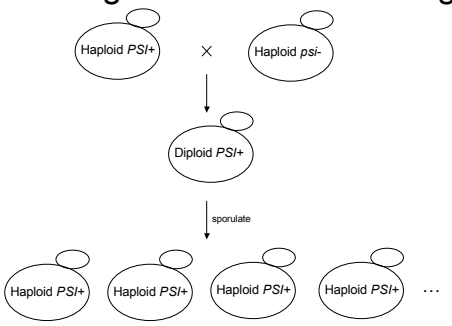
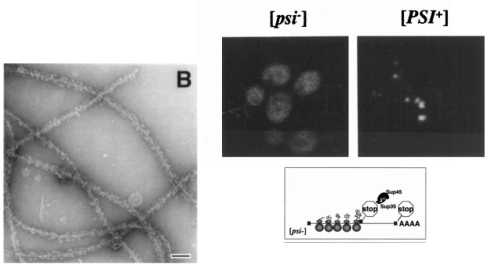


Cytoplasmic aggregates of Sup35



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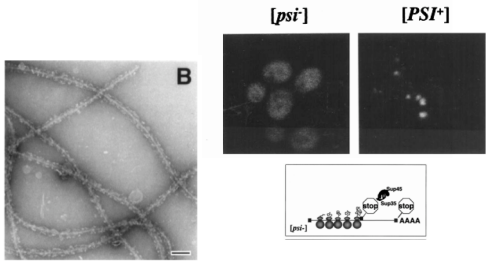
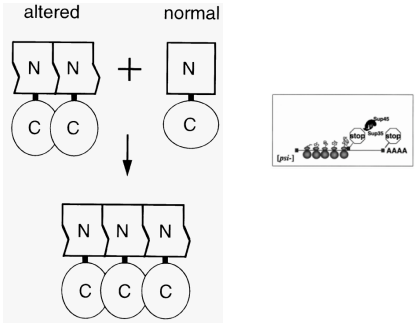


How would this explain the results?

Hard to make aggregate, easy to join



Protein inheritance

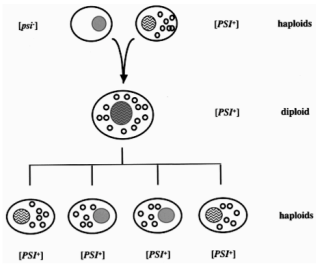
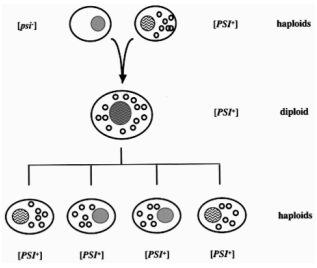


FIG. 1. [*PSI*$^+$] is cytoplasmically inherited. Black circles: [*PSI*$^+$] determinant. Yeast cells can grow either as haploids (one copy of each chromosome) or diploids (two copies of each chromosome). When a [*PSI*$^+$] haploid is mated to a [*psi*$^-$] haploid, the resulting diploid is [*PSI*$^+$], indicating that [*PSI*$^+$] is dominant. On sporulation, each nuclear determinant (gray fill and wavy lines) segregates to half the haploid progeny (2:2), and the cytoplasmic [*PSI*$^+$] determinant segregates to all progeny (4:0).

Protein inheritance



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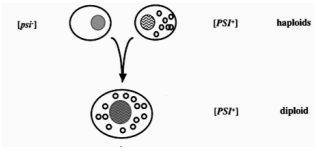
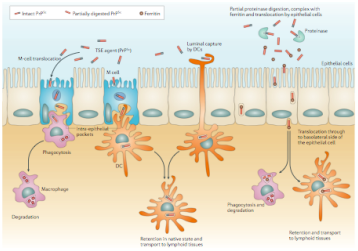
Original from *PSI+* nucleates in all progeny

PSI+ begets more *PSI+*



Not due to dominant genetics in the usual way.

Nucleating prions in mad cow disease

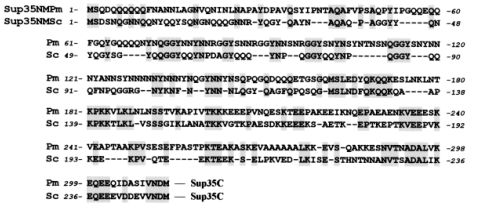


Prions and their lethal journey to the brain

Neil A. Mabbott* and G. Gordon MacPherson†

Is *PSI+* the yeast analog of mad cow or Alzheimer's?

If bad, would be lost



Evolutionary conservation of prion-forming abilities of the yeast Sup35 protein

Yury O. Chernoff,* Alexey P. Galkin,† Eugene Lewitin, Tatiana A. Chernova,† Gary P. Newnam and Slava M. Belenkiy

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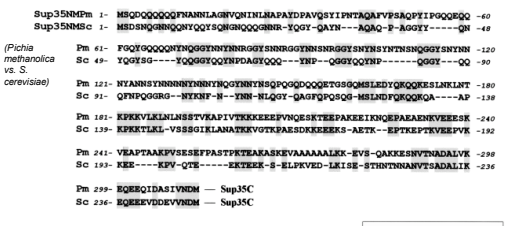

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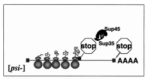
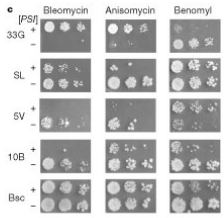


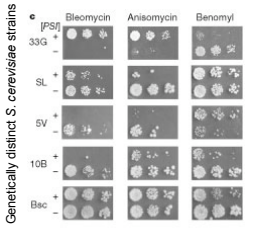
PSI+ phenotypes



A yeast prion provides a mechanism for genetic variation and phenotypic diversity

Heather L. True & Susan L. Lindquist

PSI+ phenotypes



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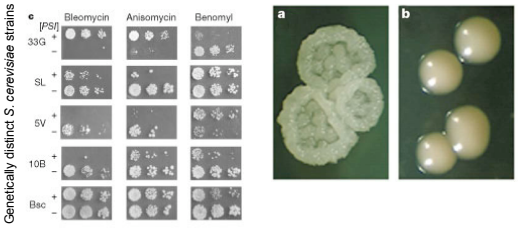

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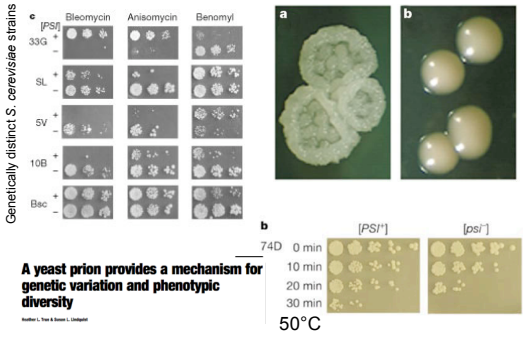

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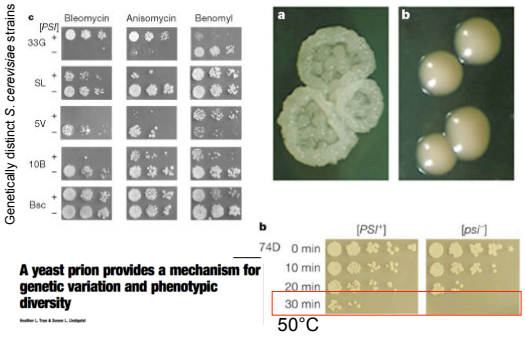
PSI+ phenotypes



A yeast prion provides a mechanism for genetic variation and phenotypic diversity

Heather L. True & Susan L. Lindquist

PSI+ phenotypes

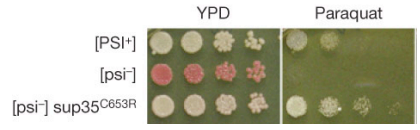
Why would aggregates result in so many novel abilities and traits??

PSI+ phenotypes

Why would aggregates result in so many novel abilities and traits??

Apparently does not happen in Alzheimer's…

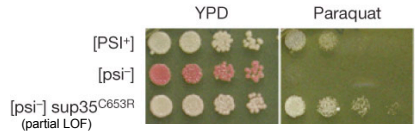
The clincher



Epigenetic regulation of translation reveals hidden genetic variation to produce complex traits

Heather L. True*, Rana Berlin & Susan L. Lindquist

The clincher



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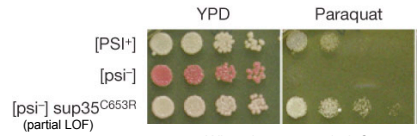


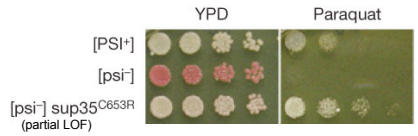
What do you conclude?

A. Sup35 does not cause resistance to paraquat.
B. Prions do not cause resistance to paraquat.
C. Aggregation is not necessary to cause resistance to paraquat.
D. Aggregation is not sufficient to cause resistance to paraquat.

Epigenetic regulation of translation reveals hidden genetic variation to produce complex traits

Heather L. True*, Rana Berlin & Susan L. Lindquist

The clincher

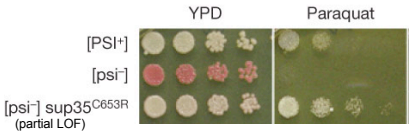


Aggregates per se don't cause resistance.

Epigenetic regulation of translation reveals hidden genetic variation to produce complex traits

Heather L. True*, Rana Berlin & Susan L. Lindquist

The clincher



Aggregates per se don't cause resistance.
Losing function of sup35 does.

Epigenetic regulation of translation reveals hidden genetic variation to produce complex traits

Heather L. True*, Rana Berlin & Susan L. Lindquist

Aggregation = more read-through

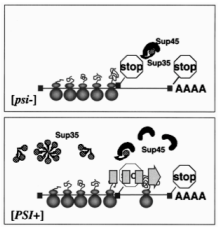


FIG. 3. Model for the [*PSI*+] phenotype. The black line denotes a messenger RNA with a stop codon mutation in the coding sequence. In [*psi*-] cells (top), Sup35 (hatched spheres with black, crescent tails) is soluble and binds to Sup45 (black crescent). The Sup35/Sup45 complex promotes translation termination at all nonsense codons (stop). In [*PSI*+] cells (bottom), Sup35 forms aggregates in the cytoplasm through interaction of the N-terminal domain (black crescent). The level of soluble Sup35 available for binding to Sup45 is greatly reduced. Consequently, ribosomes (gray spheres) are able to read through nonsense codons at a low frequency (dashed arrow), leading to the production of full-length protein, which suppresses the effects of the mutation.

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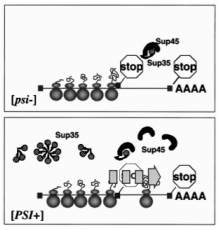

New extra-long forms of proteins cause new traits.

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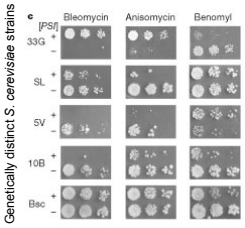
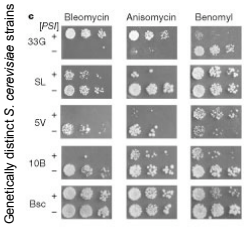
PSI+ allows epigenetic change in protein sequence.

Genetic effects?



Phenotypes varied between genetically diverse *PSI*+ strains.

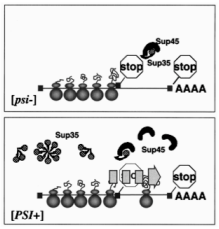
Genetic effects?



Phenotypes varied between genetically diverse *PSI*+ strains.

How can the cause be genetic and non-genetic (protein aggregates) at the same time?

Aggregation = more read-through



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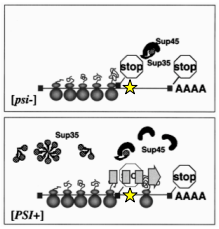
Aggregation = more read-through



UTR mutations usually occur and have no effect

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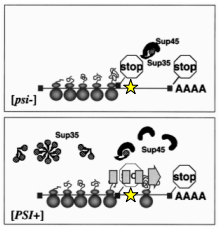
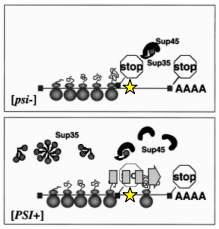
Aggregation = more read-through



UTR mutations usually occur and have no effect, so organism doesn't die and allele is maintained.

FIG. 3. Model for the [*PSI*+] phenotype. The black line denotes a messenger RNA with a stop codon mutation in the coding sequence. In [*psi*-] cells (top), Sup35 (hatched spheres with black, crescent tails) is soluble and binds to Sup45 (black crescent). The Sup35/Sup45 complex promotes translation termination at all nonsense codons (stop). In [*PSI*+] cells (bottom), Sup35 forms aggregates in the cytoplasm through interaction of the N-terminal domain (black crescent). The level of soluble Sup35 available for binding to Sup45 is greatly reduced. Consequently, ribosomes (gray spheres) are able to read through nonsense codons at a low frequency (dashed arrow), leading to the production of full-length protein, which suppresses the effects of the mutation.

Aggregation = more read-through



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Now in *PSI+*, they manifest!

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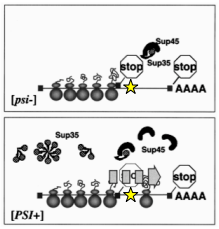

Sequence differences in read-through region cause phenotypic differences between *PSI+* strains.

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Cryptic variation: DNA sequence differences between individuals that are usually not expressed