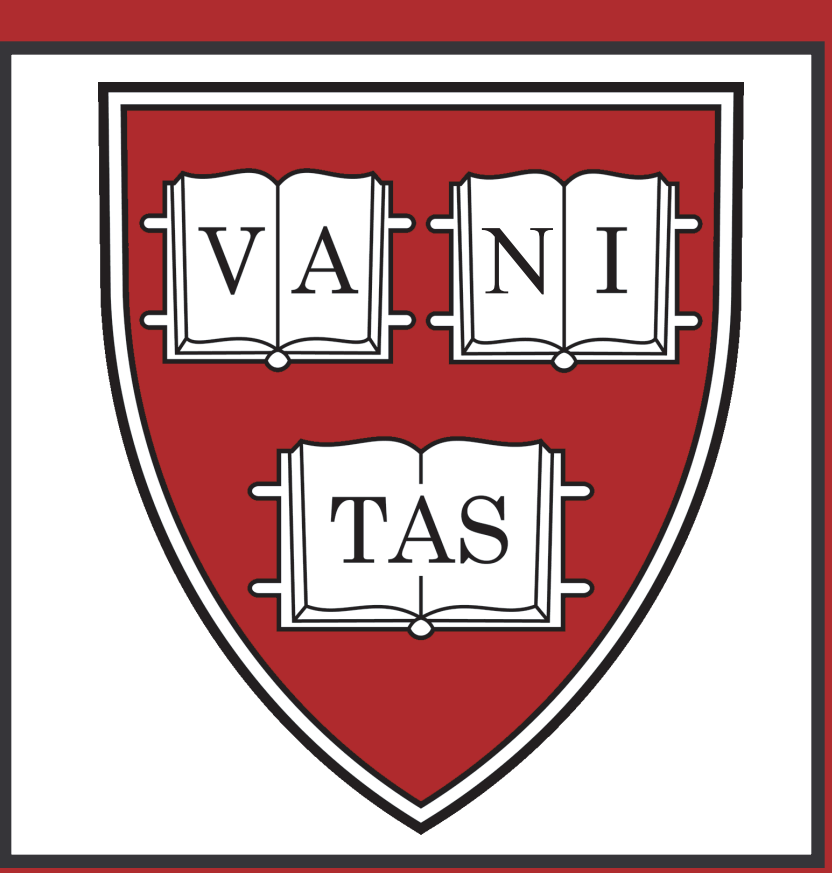


# Variation in Mutation Rate along Yeast Chromosome VI

Greg I. Lang and Andrew W. Murray

Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA



## BACKGROUND

### ABSTRACT

Recent growth in the field of experimental evolution has renewed interest in determining the degree of variation in basic parameters of evolution such as mutation rate.

We tested the hypothesis that mutation rate is uniform across the genome by measuring the mutation rate at the *URA3* reporter integrated approximately every 4 kb across Chromosome VI of *Saccharomyces cerevisiae*.

Our results indicate that mutation rate is not uniform across the genome and that there are regions where the mutation rate is significantly different from the median mutation rate of Chromosome VI.

### WHY MUTATION RATE VARIATION?

Mutation rate is an important parameter in evolution. *The rate of adaptation and the equilibrium fitness of a population depend upon the mutation rate.*

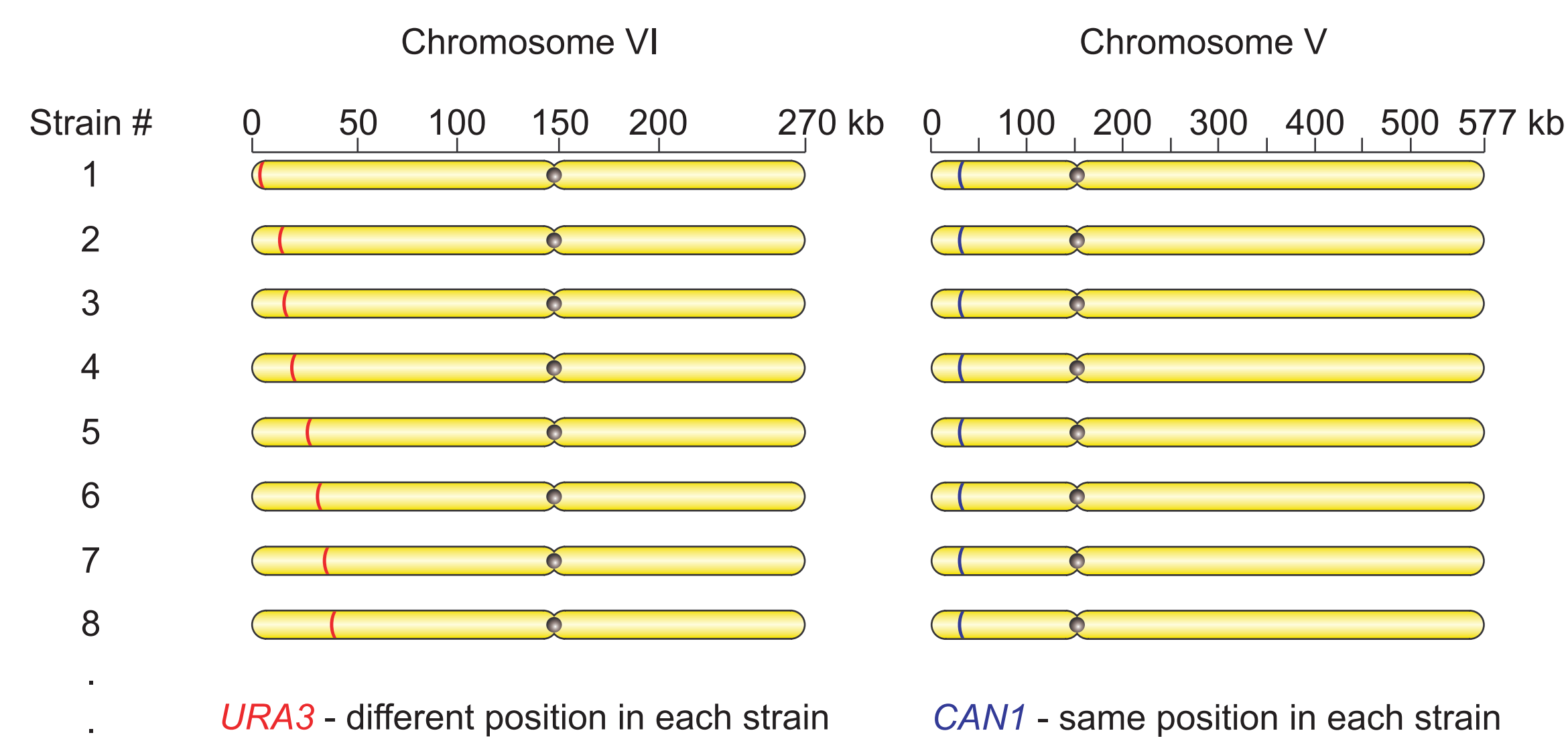
Strains with an elevated mutation rate have a selective advantage in laboratory competitions.

Mutation rate is under selection. *Mutator strains often fix during long term evolution experiments.*

We do not know the degree to which mutation rate varies between different strains, environments, and locations within the genome. *This information is necessary in order to interpret results from laboratory evolution experiments.*

## METHODS

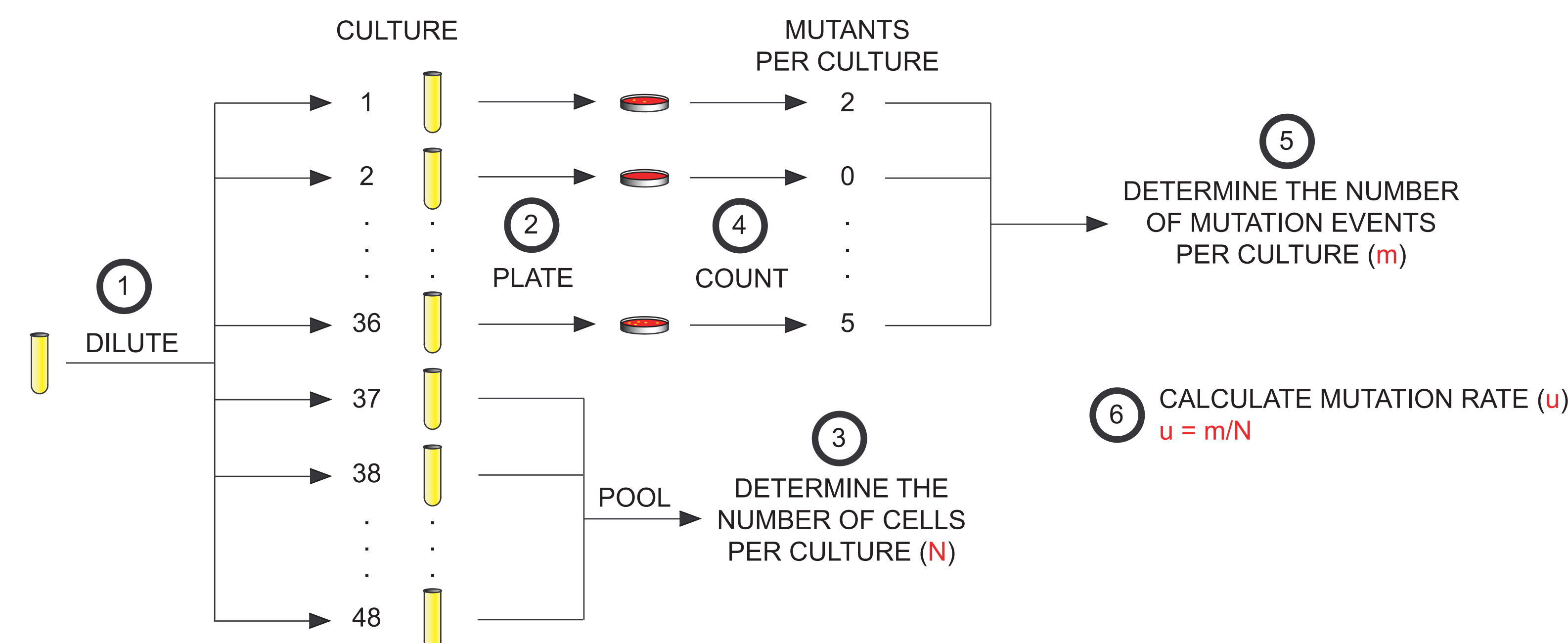
### INTEGRATE *URA3* AT 48 POSITIONS ACROSS CHROMOSOME VI



### MEASURE MUTATION RATES USING THE FLUCTUATION ASSAY

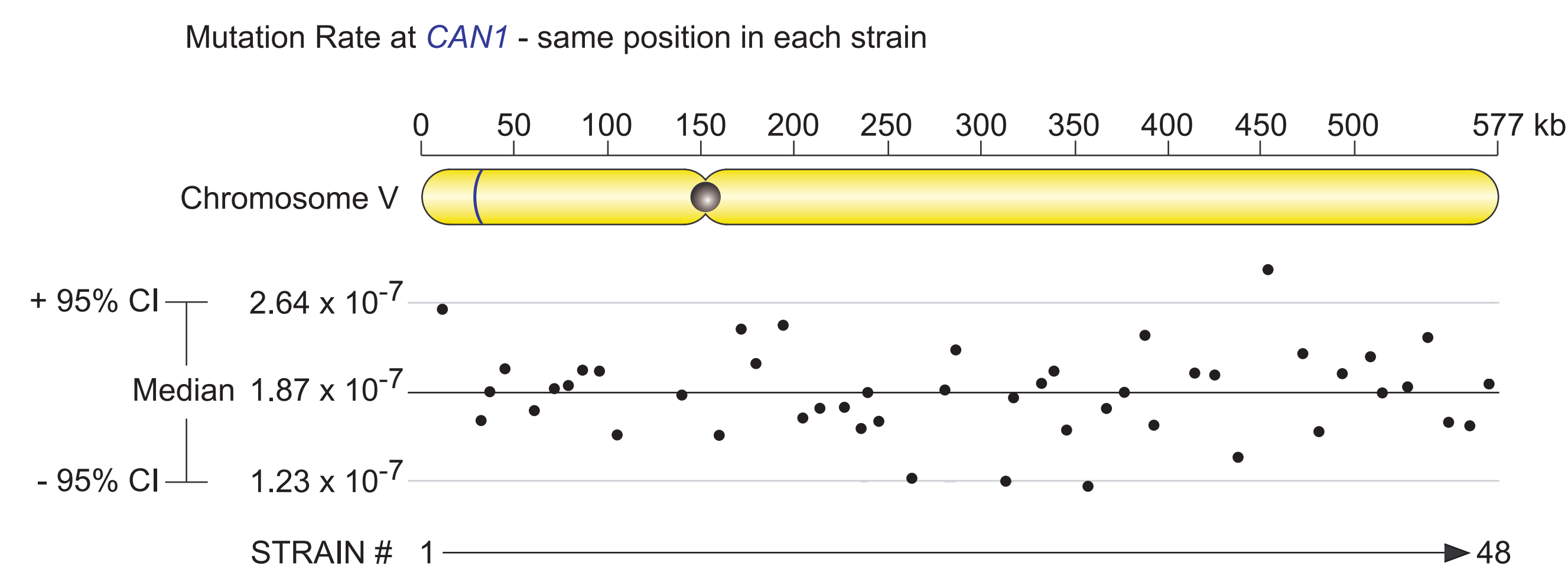
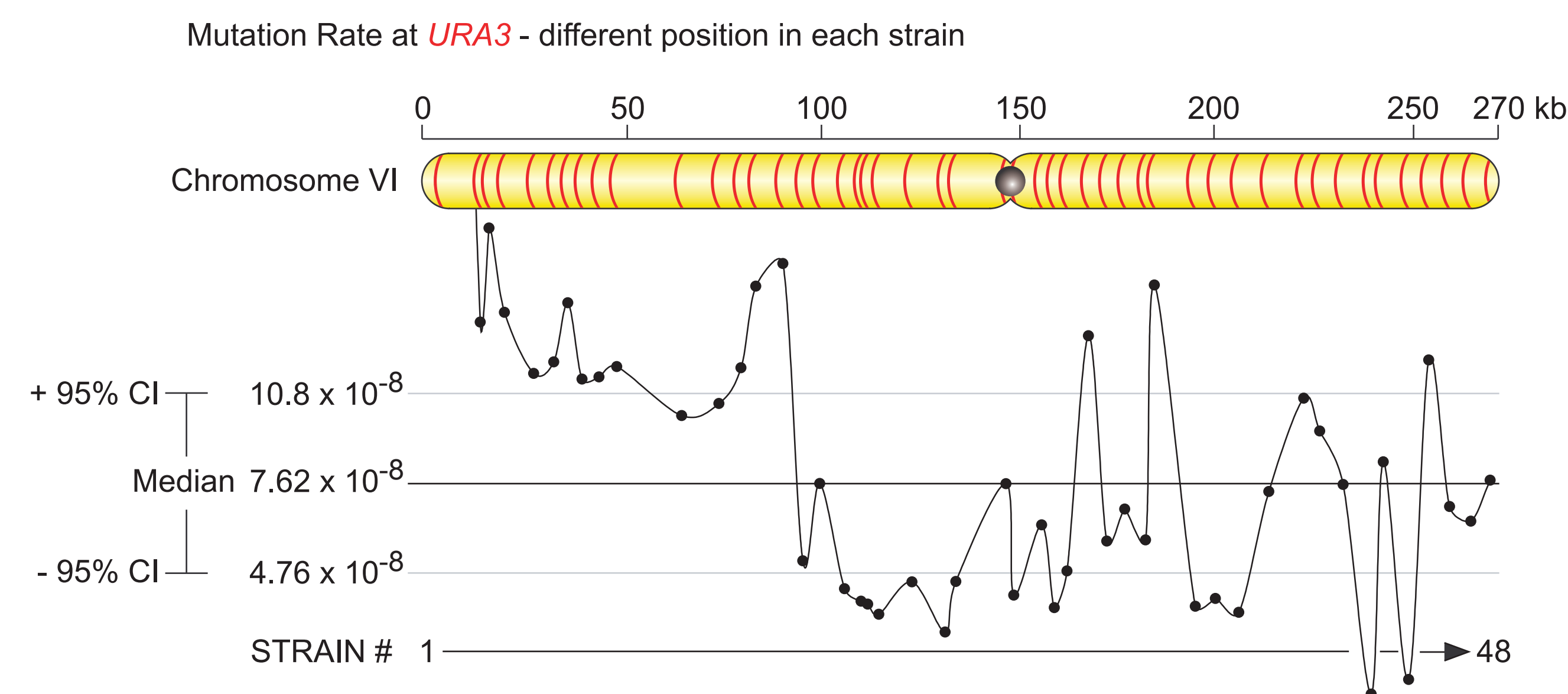
For each of the 48 strains, the rate of loss of function was measured at *URA3* and *CAN1*

- Dilute 1:10,000 into 48 parallel cultures
- Plate 36 cultures onto selective media (5FOA for *URA3*; Canavanine for *CAN1*)
- Pool 12 cultures and Coulter count to determine the number of cells per culture (*N*)
- Count the number of mutants per culture. *Although the number of mutation events follows the Poisson, the number of mutants per culture varies depending upon when during the growth of a culture the mutation(s) occurred.*
- Using a maximum likelihood method determine the expected number of mutation events per culture (*m*) from the distribution of the number of mutants per culture. *95% confidence intervals can be determined for *m*.*
- Calculate the mutation rate (*u*).  $u = m/N$

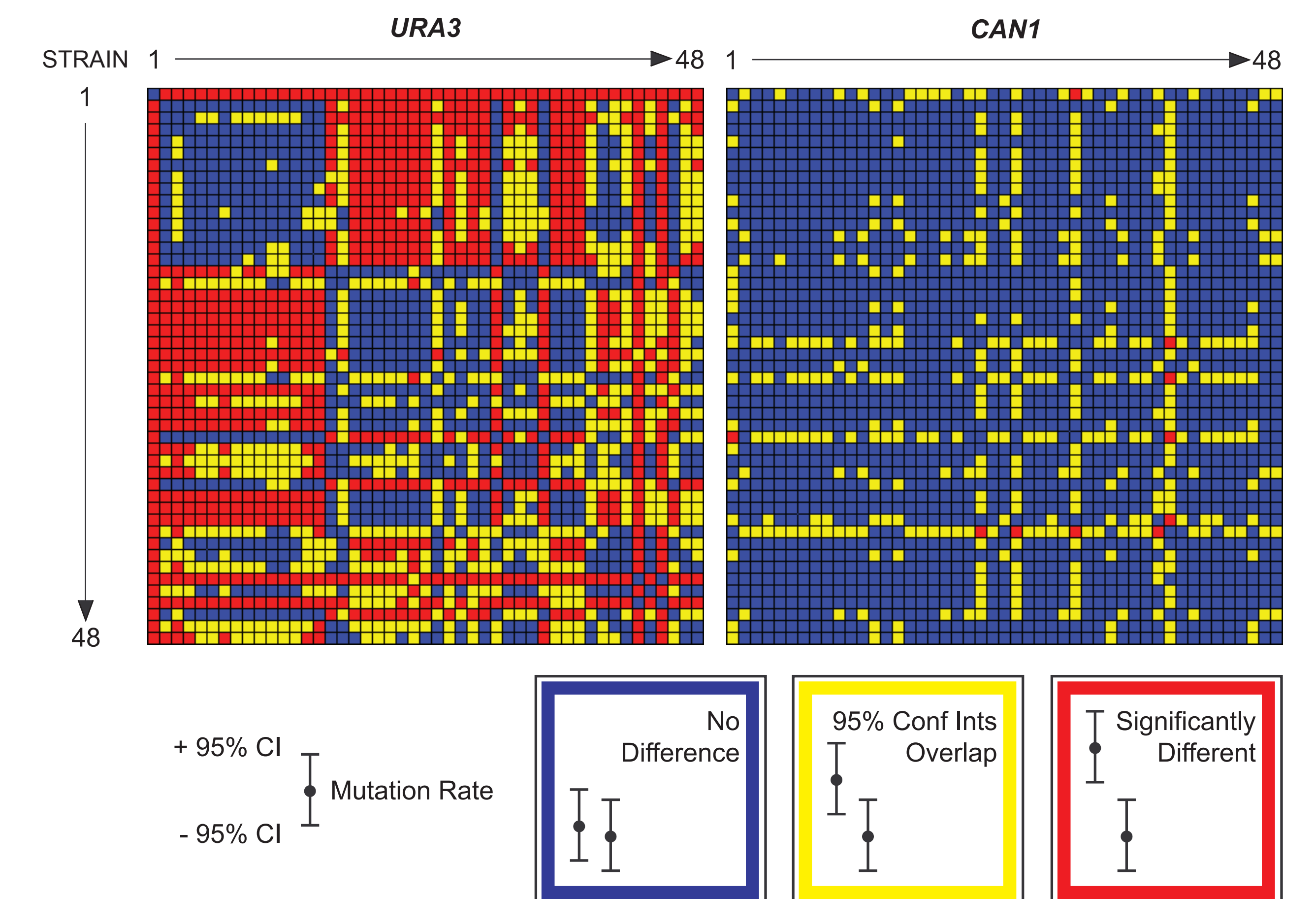


## RESULTS

### MUTATION RATE VARIES ACROSS CHROMOSOME VI



### PAIRWISE COMPARISON OF MUTATION RATES



## SUMMARY

### CONCLUSIONS

- Mutation rate is non-uniform across the yeast genome.
- Mutation rate varies over an order of magnitude across the length of Chromosome VI.
- A portion of the left arm of Chromosome VI (1-94000 bp) has a significantly higher mutation rate than the rest of the chromosome.
- In the 48 strains tested there is no correlation between the mutation rate at *URA3* and at *CAN1*. *data not shown*
- There is no significant correlation between gene dispensability and its location within high or low mutation rate regions of Chromosome VI. *data not shown*

### RESULTS FROM RELATED PROJECTS

- GROWTH RATE INDEPENDENCE OF MUTATION RATE:
  - Mutation rate does not vary with the length of the cell cycle. *Mutations occur at a constant rate per cell division, not per unit time.*
- ENVIRONMENTAL VARIATION IN MUTATION RATE:
  - Mutation rate is elevated under osmotic stress. *The mutation spectrum in high salt is similar to that of gamma irradiation, indicative of double strand breaks*
- GENETIC VARIATION IN MUTATION RATE:
  - Two common laboratory strains (S288c and W303) differ in mutation rate by an order of magnitude. *Genetic analysis suggests that this difference is due to two major effect loci.*
- QUALITY OF DATA:
  - We have developed methods for assessing the quality of data from fluctuation tests.