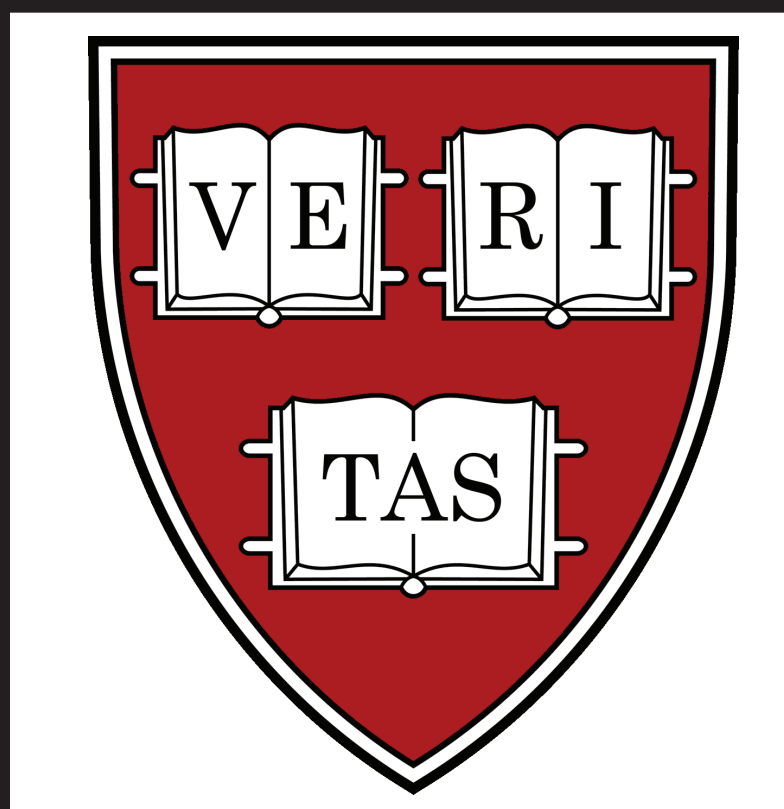


Mutation Rate across Yeast Chromosome VI is Correlated with Replication Timing

Greg I. Lang (lang@fas.harvard.edu) and Andrew W. Murray
 Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA



INTRODUCTION

BACKGROUND

Comparative genomics reveals that mutation rate varies on many levels within the mammalian genome:
 Along a chromosome ~10-100 kb length scales
 Along a chromosome ~1 mb length scales
 Between chromosomes

A similar analysis shows no sign of variation in the yeast genome.

However, several experimental studies suggest that mutation rate in yeast is non-uniform, due in part to variation in mismatch repair.

Ellegren H *et al.* 2003. *Curr Opin Genet Dev.* 13: 562-568. Review.
 Chin CS *et al.* 2005. *Genome Res.* 15: 205-213.
 Ito-Harashima S *et al.* 2002. *Genetics.* 161: 1395-1410.
 Hawk JD *et al.* 2005. *Proc Natl Acad Sci U S A.* 102: 8639-43.

ABSTRACT

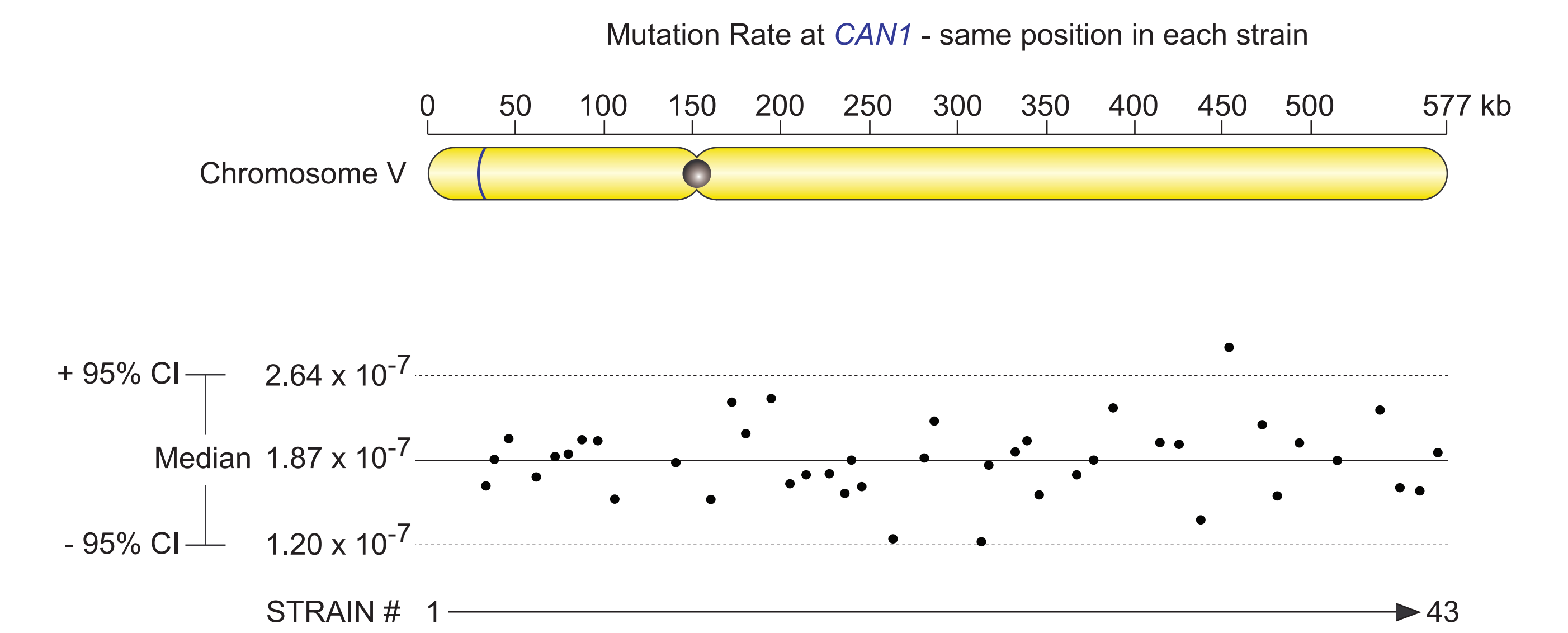
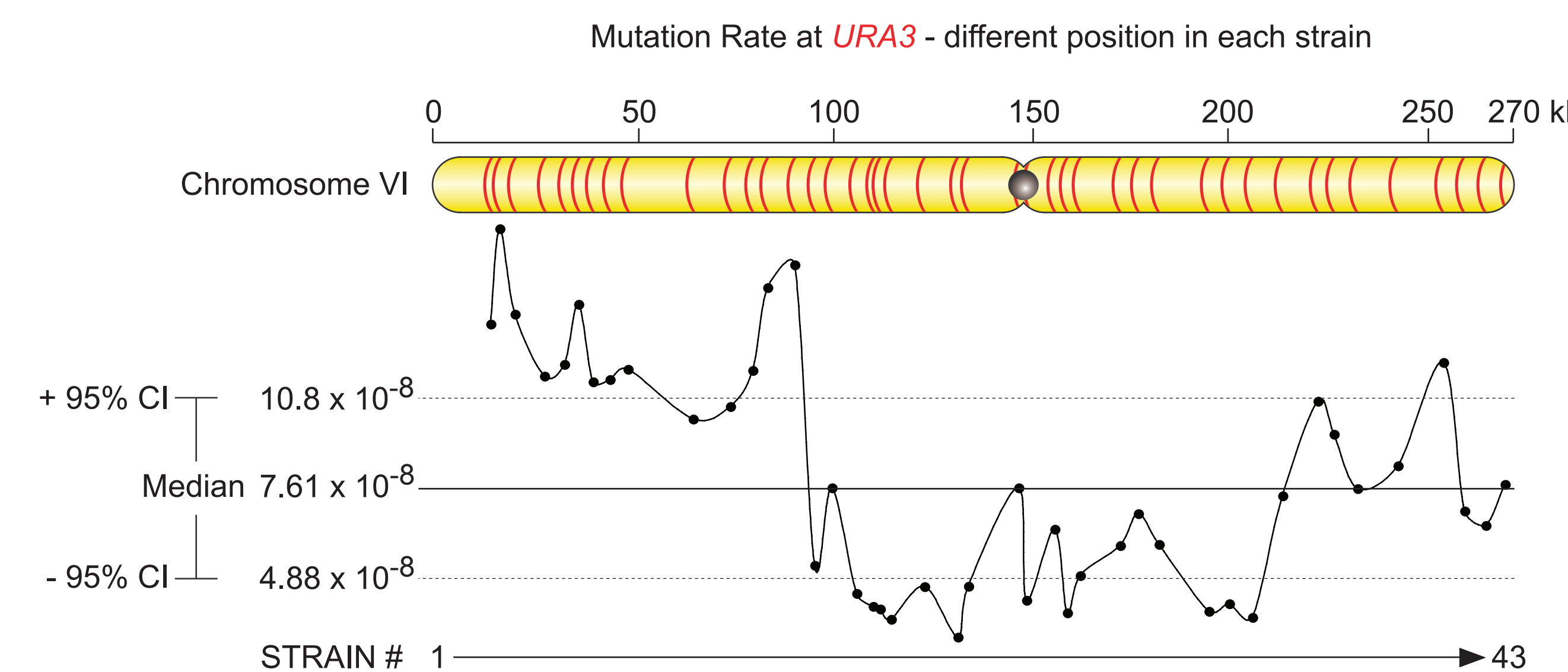
We asked whether mutation rate is uniform across the yeast genome by measuring the mutation rate at the *URA3* reporter integrated approximately every 6 kb across Chromosome VI of *Saccharomyces cerevisiae*.

Our results indicate that mutation rate is non-uniform across Chromosome VI; however, mutation rates cluster such that the chromosome is organized into three regions of similar mutation rate on a length scale of approximately 100 kb.

In addition, we find a significant correlation between mutation rate and replication timing such that regions of the chromosome that are replicated early have a low mutation rate.

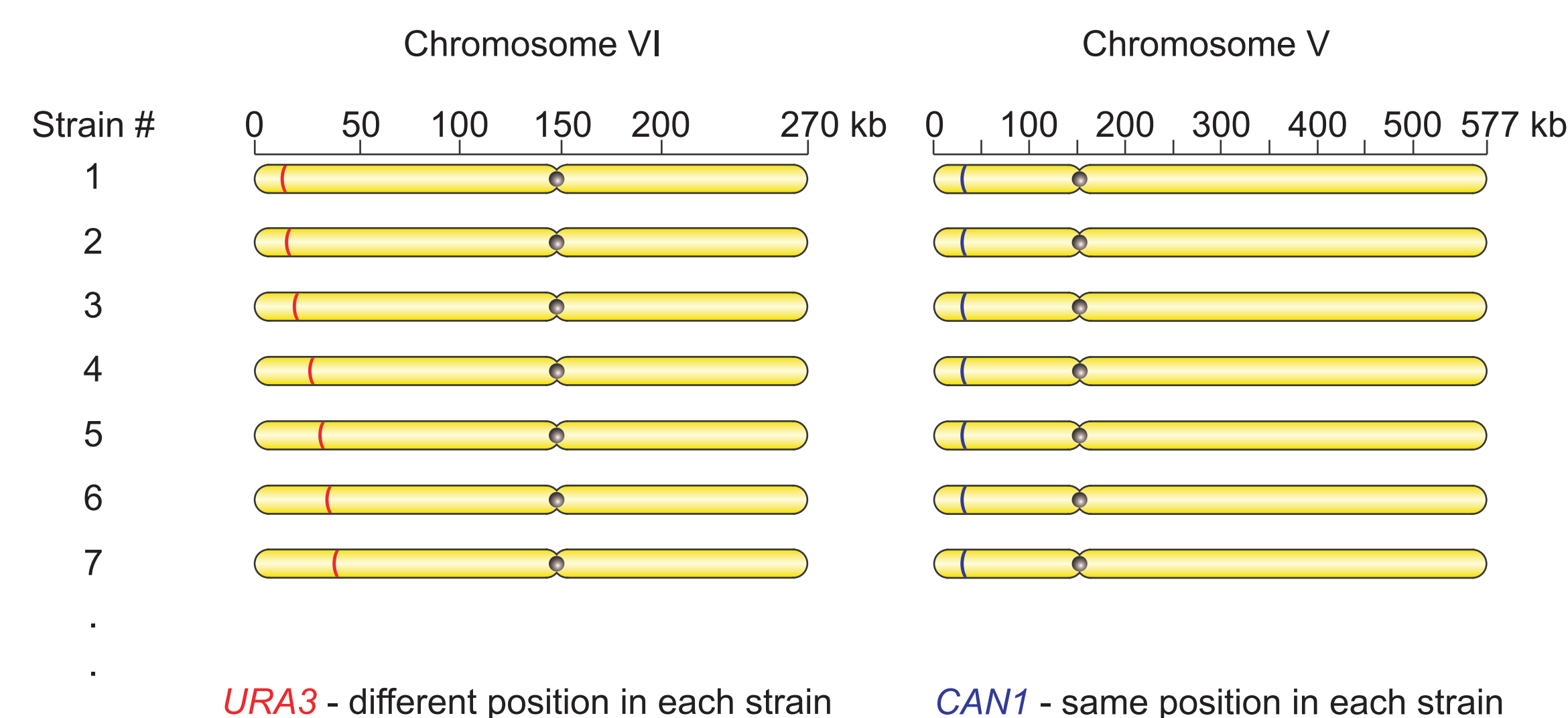
RESULTS

MUTATION RATE VARIES ACROSS CHROMOSOME VI

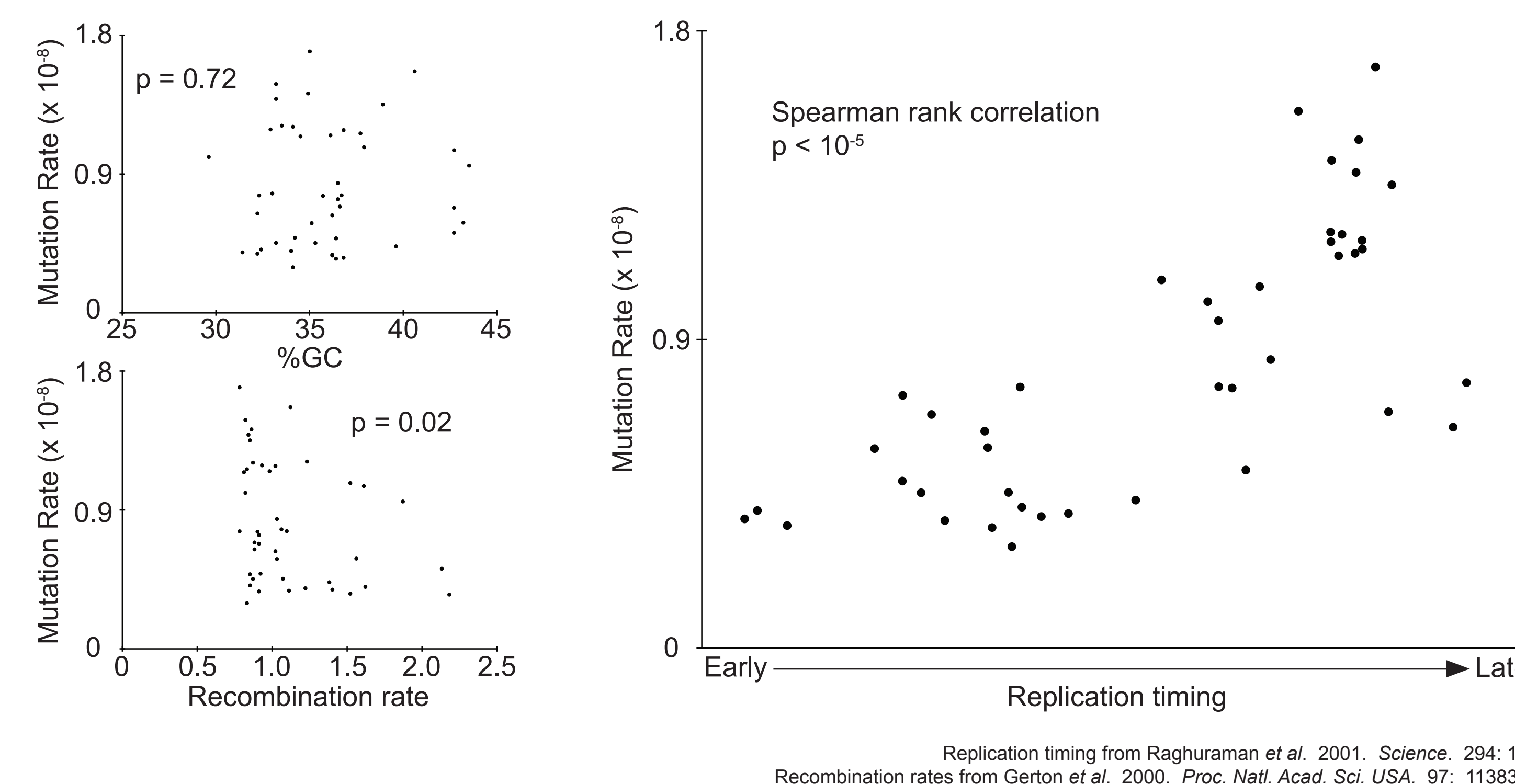


METHODS

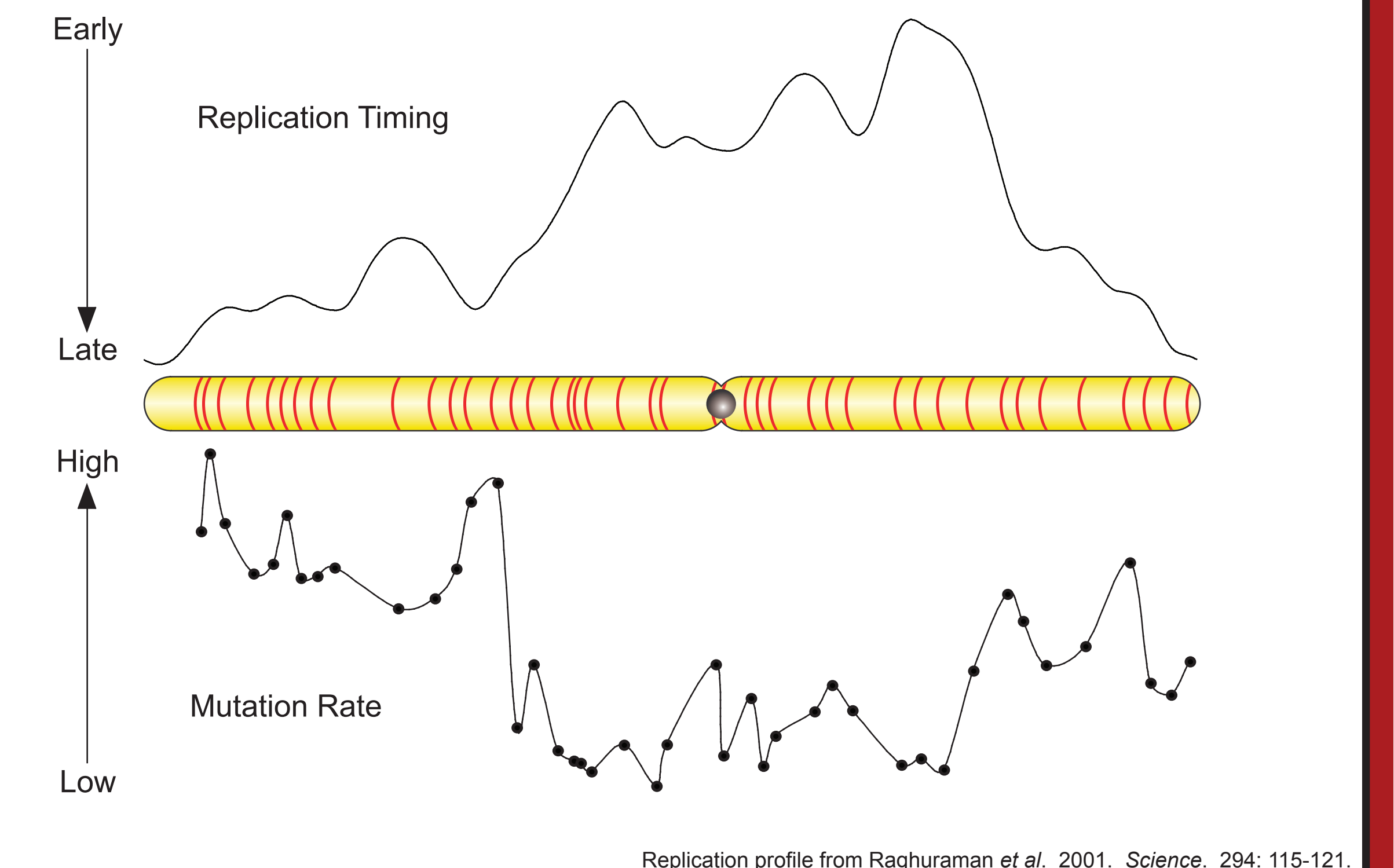
INTEGRATE *URA3* AT 43 POSITIONS ACROSS CHROMOSOME VI



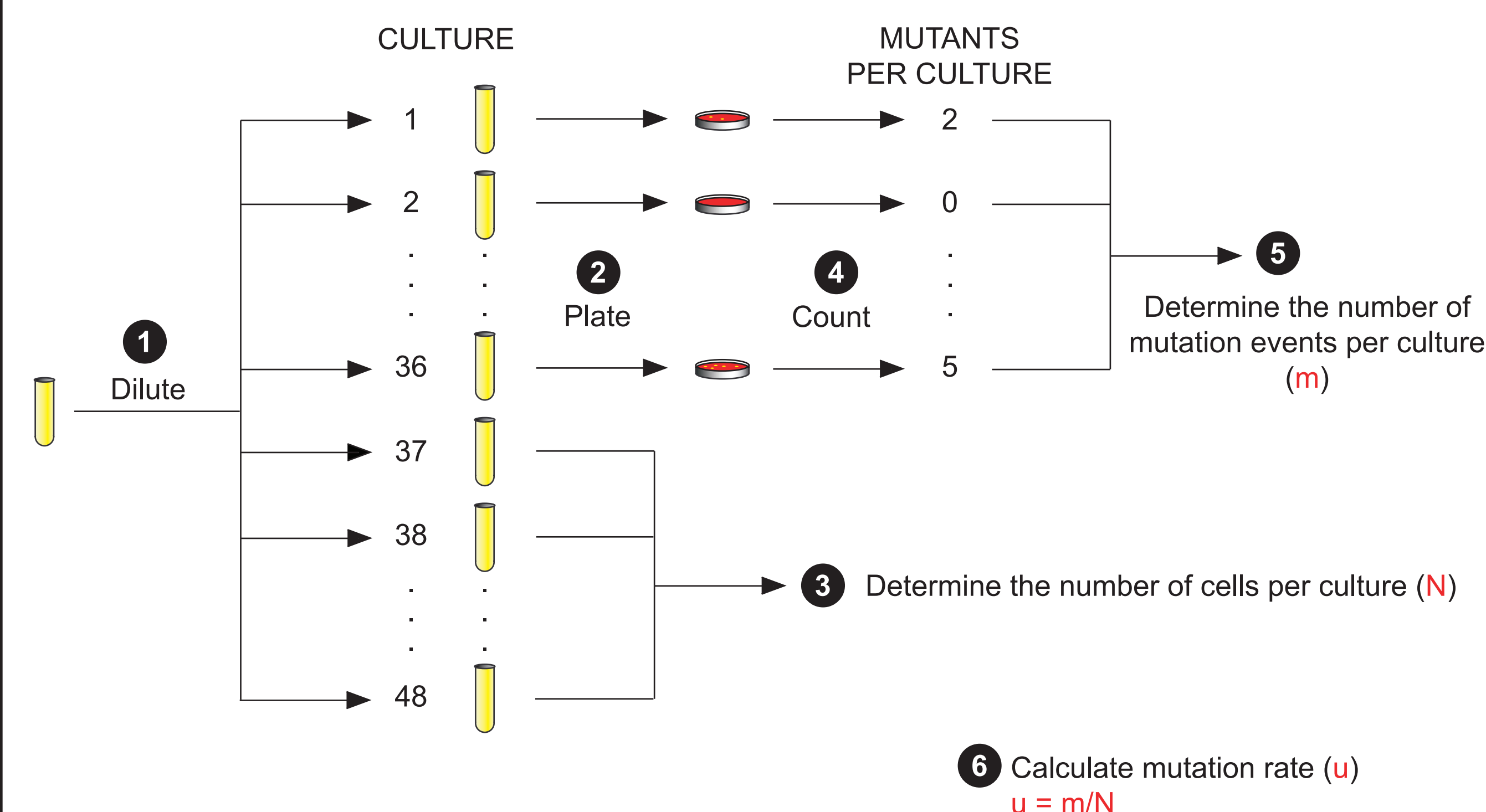
MUTATION RATE IS CORRELATED WITH REPLICATION TIMING



COMPARISON OF THE REPLICATION AND MUTATION PROFILES



MEASURE MUTATION RATES USING THE FLUCTUATION ASSAY



SUMMARY

CONCLUSIONS

Mutation rate varies across Chromosome VI.
 Mutation rate is correlated with replication timing.
 Mutation rate is not correlated with GC content or recombination rate.
 In the 43 strains tested there is no correlation between the mutation rate at *URA3* and at *CAN1* (data not shown).
 Mutation rate is correlated to the synonymous substitution rate between S288c vs. YJM789 and RM11-1a strains (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).

CURRENT WORK

Test the association between replication timing and mutation rate by manipulating replication origins.
 Two explanations for the correlation between mutation and replication:
 (1) Mutations made early in S-phase have more time to be corrected
 (2) Mutation rate is elevated late in S-phase
 Distinguish between these two possibilities, by repeating this experiment in an *msh2* deleted strain.
 Determine the mutational spectra from regions of high/low mutation rate.
 Test for a genome-wide correlation between replication timing and synonymous substitution rate.

RESULTS FROM RELATED PROJECTS

GROWTH RATE INDEPENDENCE OF MUTATION RATE:
 Mutation rate does not vary with the length of the cell cycle.
 Most 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

TARGET SIZE TO PHENOTYPIC MUTATION:
 The effective target size to 5FOA and Canavanine resistance by way of base pair substitutions is 104 and 170 bp respectively.

QUALITY OF DATA:
 We have developed methods for assessing the quality of data from fluctuation tests.