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Comparative Rates of Spontaneous Mutation

RATES of spontaneous mutation suitable for making comparisons between different species should consist of averages of rates at many sites, and should reflect all changes in DNA sequence in the tested regions. Average rates can be obtained by measurements of forward mutation, preferably within several different cistrons which should be totally dispensable for growth in permissive conditions, but sensitive even to missense mutations under restrictive or selective conditions. There are very few systems which fulfil most or all of these conditions (Table 1).

Table 1. COMPARATIVE FORWARD MUTATION RATES

Organism	Base pairs per genome	Mutation rate per base pair replication	Total mutation rate
Bacteriophage λ	4.8×10^4	2.4×10^{-8}	1.2×10^{-3}
Bacteriophage T4	1.8×10^5	1.7×10^{-8}	3.0×10^{-3}
<i>Salmonella typhimurium</i>	4.5×10^6	2.0×10^{-10}	0.9×10^{-3}
<i>Escherichia coli</i>	4.5×10^6	2.0×10^{-10}	0.9×10^{-3}
<i>Neurospora crassa</i>	4.5×10^7	0.7×10^{-11}	2.9×10^{-4}
<i>Drosophila melanogaster</i>	2.0×10^8	7.0×10^{-11}	0.8
Man	2.0×10^9	?	?

For all entries up to and including *N. crassa*, mutations arise predominantly during chromosomal replication², and the mutation rate was calculated from the formula²

$$m = 0.4343 (f - f_0) / \log (N/N_0)$$

where m is the mutation rate per chromosomal or nuclear replication, f is the mutant frequency and N is the population size. Where necessary, an average amino-acid was assumed to weigh 110 daltons, as calculated from average amino-acid frequencies among *E. coli* proteins³; and a gene was assumed to contain 1,000 base pairs, corresponding to a polypeptide weighing 36,700 daltons. The data for bacteriophage λ are collected in ref. 4; the mutation rate was calculated for the *cI* cistron, the protein of which weighs about 30,000 daltons. The data for bacteriophage T4 are collected in ref. 2; the mutation rate was calculated for the *rII* cistrons (0.6 of the *r* mutants), which are estimated to contain about 1,770 base pairs^{5,6}. The bacterial data are collected in refs. 2 and 7; the *E. coli* mutation rate was calculated for 5 *ara* cistrons, and the *S. typhimurium* mutation rate was calculated for 10 *his* cistrons. The mutation rate for the *ad3* locus of *N. crassa* was calculated from the mutant frequency⁸ in a growth experiment encompassing about 60 generations (de Serres, personal communication; and ref. 9).

Mutations in *Drosophila* arise both during and independently of cell division¹⁰. An estimate of the total mutation rate per sexual generation per haploid set of chromosomes¹¹ is 0.4, and an approximate mutation rate per base pair¹² was calculated by assuming that all mutations arise during cell replication, and that an average of forty cell generations separate the fertilized egg from the progeny gametes. The human genome¹³ contains about 40 per cent of redundant species of nucleotide sequences¹⁴, the contribution of which to the mutational target size is unclear. Redundancy is not observed in the prokaryotes, and is not yet reported in *Drosophila*.

Spontaneous mutation, expressed per base pair per replication, clearly proceeds at strikingly different rates in different organisms. This is also illustrated by the observation⁴ that the temperate bacteriophage λ assumes a mutation rate 20–100 times lower when multiplying as prophage (a set of bacterial genes) than when multiplying lytically (under autonomous control). Among the prokaryotes, however, species differences in mutation rates largely disappear when rates are expressed per genome per replication: the mutation rate per base pair is inversely related to the size of the genome. Among the eucaryotes, very few data exist which can be transformed into average mutation rates, and it is not yet clear how these rates will vary with genome size.

If the constant mutation rate per genome suggested for prokaryotes by Table 1 is general, then very small genomes should show very high mutation rates per cistron or per base pair. Comparisons should be sought in organisms which encode their own DNA polymerases and which are insulated from any but their own repair systems. Two likely candidates are *Bacillus subtilis* bacteriophage $\phi 29$ (ref. 15) and animal cell mitochondria¹⁶, the chromosomes of both of which are composed of double stranded DNA and are less than one tenth of the size of the chromosome of bacteriophage T4.

Observed mutation rates depend on several factors: the primary rate of damage or error insertion, the efficacy

of repair, and the probability of detection of an altered phenotype. Decreased local mutation rates associated with increased genome size could be achieved by reducing the error rate, and also by increasing the sophistication of repair systems. (It is less clear whether mutations will tend to produce less drastically altered phenotypes in more complex organisms.) The spontaneous mutation rates listed in Table 1 are chiefly the result of point mutations, which may be divided into base pair substitutions and frameshift mutations. About 80 per cent of T4rII mutants contain frameshifts (although the leaky nature of many rII base pair substitution mutants prevents their recovery)². The frequencies of frameshift mutants are about 20–40 per cent among *S. typhimurium his* mutants, about 15 per cent among *N. crassa ad3* mutants (where missense mutants are efficiently detected), and an indeterminate but significant percentage among *E. coli lac* mutants (see refs. in preceding article). Species specific differences in average mutation rates therefore reflect changes in both of the elementary types of point mutations. Because these clearly arise by a number of very different mechanisms², alterations in average mutation rates must reflect changes in many enzymatic systems.

The frequent appearance of heritable changes in spontaneous mutation rates within a species emphasizes the extent to which mutation rates are genetically determined. Most of these heritable changes consist of mutator genes. In prokaryotes, however, and particularly in those with small genomes, there exists the possibility of antimutator genes. These have now been described in bacteriophage T4 (preceding article).

The reasons for the approximately constant mutation rate per genome in the prokaryotes are not yet clear. Mutation rates may be adjusted by natural selection to achieve a balance among the mostly deleterious effects of mutation, the need for variation, and the cost of suppressing mutation (for example, by slowing DNA synthesis, by introducing energy-consuming repair processes or by adopting informational redundancy). It can be imagined that prokaryotic genomes are all so small that the intrinsic difficulties of achieving a sufficiently low total mutation rate are minor, and that more general factors (such as the ability to adapt rapidly versus the mutational load) are sufficient to fix the rate. At the other end of the scale, however, genome sizes may have expanded to the point where the cost of achieving the necessarily very small mutation rates per base pair becomes very large. It is therefore possible that the human total mutation rate is even larger than the very large *Drosophila* rate. Were this the case, the modern species, with its generally low numbers of offspring, might be particularly sensitive to increases in its mutation rate, such as may result from chemical modifications of the environment.

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