resorption not only in male rats, but also in females in which bone resorption is stimulated by oestrogen withdrawal.

Food intake in the rat is associated with a large and rapid increase in bone resorption that occurs in a diurnal rhythm[8,9], which is affected differentially by inhibitors of bone resorption, such as calcitonin and the bisphosphonate alendronate, because of their different mechanisms of action[9]. The effect of alendronate is maximal after about three days, whereas calcitonin works within a few hours to inhibit the height of the peak only during the diurnal rhythm; oestrogen treatment works only after two days. Peak height is inhibited similarly by calcitonin and onion, the maximal effect being attained 6 to 12 hours after ingestion. The effect of onion on the acute regulation of bone resorption therefore resembles that of calcitonin.

Our results indicate that several common vegetables in the human diet alter bone metabolism in the rat. If this also happens in humans, then including an appropriate amount of these vegetables in the daily diet could be an effective and inexpensive way to decrease the incidence of osteoporosis.

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Genetic recombination

Intron size and natural selection

Intron sizes vary widely among different genes and among homologous genes of different species. The distribution of intron sizes may be maintained in a steady state, reflecting the processes of insertion and deletion of gene sequences, or it may be that the distribution is constrained by natural selection[1–3]. If intron size is governed by natural selection, there should be a statistical association between this size and the rate of recombination per map unit of the genome, assuming that natural selection is less effective in genomic regions of low recombination[4–6]. Here we show that larger introns of *Drosophila melanogaster* occur preferentially in regions of low recombination, which is consistent with large introns having a deleterious effect. The association is significant ($P = 0.001$, linear regression), despite the fact that no effort was made to stratify the data by other factors that affect intron size, such as the size of the associated coding region[7] or the presence of regulatory sequences inside the intron.

The mechanisms by which splice sites are selected and the evolutionary patterns are different in 'small' (up to 80 base pairs) and 'large' (more than 80 base pairs) introns in *Drosophila*[3,8–10]. Size-class transitions in homologous introns are frequent (about 20%) between *D. melanogaster* and *D. virilis* or *D. pseudoobscura* but rare among most closely related species[3,11]. We investigated the relation between intron size and recombination rate by analysing each intron type separately (Fig. 1a), and found that recombination occurs in small introns on average at 2.45 ± 0.04 centimorgans per million base pairs (cM Mb^{-1}), whereas the value for large introns is 2.20 ± 0.05 cM Mb^{-1}, a difference that is significant at the 0.001 level (by analysis of variance).

Within large introns, there is no significant association between recombination rate and intron size ($b = -0.012$, $P > 0.2$), so whatever causes this relation must act equally against all large introns, irrespective of their absolute size. In small introns, there is a significant, positive association between recombination rate and intron size ($b = +0.002$, $P = 0.02$), indicating that very small introns are also deleterious: they tend to occur in regions of low recombination, where natural selection is less efficient.

The average rate of recombination for introns of less than 60 base pairs is 2.26 ± 0.07 cM Mb^{-1}, whereas the rate for introns of 60 to 80 base pairs is 2.56 ± 0.06 cM Mb^{-1}, a difference significant at the 0.001 level (Fig. 1b). These findings are not surprising, as it is known that very small introns do not splice well[8].

Another explanation for these results is that intron size is a neutral trait, with recombination alone generating the association between recombination rate and intron size by its effect on DNA insertion and deletion processes. However, very small and large introns are both associated with regions of low recombination, excluding not only this possibility, but also any other that does not involve the direct action of natural selection on intron size. Fewer than 2% of the large introns in our sample show any sequence similarity to transposable elements, so our results cannot be explained by the accumulation of these elements in regions of low recombination[3,12].

Intron size usually changes through small deletions and insertions of DNA[2,3,13].

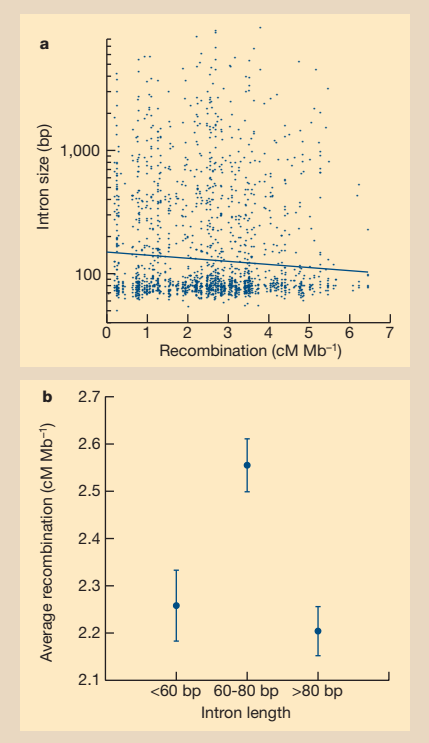

Figure 1 Association between intron size and recombination rate. **a,** Relation between local recombination rate and intron size over 1,817 introns (from 590 GenBank accessions) in expressed genes of *Drosophila melanogaster* (linear regression on log-transformed size: $b = -0.026$, $P = 0.001$, $r^2 = 0.006$). Recombination rates were estimated as described[5]. **b,** Average rates of recombination (± one standard error) for introns of less than 60, 60–80, and more than 80 base pairs (bp); *n* is 370, 665 and 782, respectively.

Our results suggest that natural selection in *Drosophila* acts on the variants generated by these processes, selecting against large introns and very short introns, as both tend to occur in regions of low recombination where selection is less effective.

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