Why is the house mouse karyotype so variable?

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Rates of robertsonian chromosomal evolution in the Western European house mouse are about two orders of magnitude greater than for most other mammals. This has resulted in a remarkable diversity of karyotypic races in a very short period of time. Recent studies are beginning to shed light on the relative contributions of mutation, drift, selection and meiotic drive in producing this pattern.

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The Western European house mouse (*Mus domesticus*) has an exceptionally variable complement of chromosomes. In addition to the standard 2n = 40 all-acrocentric karyotype, there are numerous populations characterized by metacentric chromosomes resulting from robertsonian (Rb) fusion mutations (Box 1). Such variability in karyotype is of great interest to biologists, in part because chromosomal rearrangements have the potential to act as simple genetic changes that promote speciation[1,2]. The first wild house mice with Rb chromosomes were discovered 25 years ago in Switzerland[3]. Since then, it has become increasingly clear that the study of Rb variation in the house mouse can contribute to a basic understanding of chromosomal evolution for several reasons.

First, there are many karyotypic races and many combinations of metacentrics. Eighty-nine different metacentrics have been described in wild mice (Table 1) involving all autosomes except number 19. These define over 40 distinct chromosomal races (Fig. 1), many of which are limited to small geographic areas (up to a few hundred square kilometers). Often these Rb races form hybrid zones either with each other or with the standard all-acrocentric race[4].

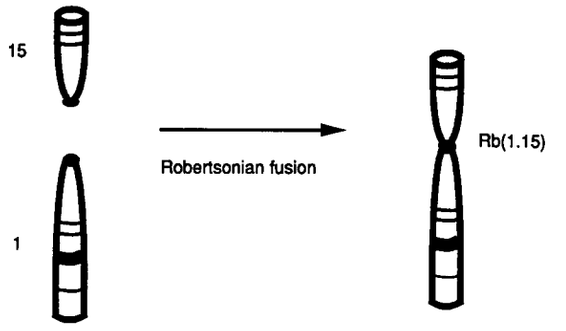
Second, chromosomal evolution appears to have been extremely rapid. Recent molecular data support the idea that the massive accumulation of Rb chromosomes has occurred within the past 10000 years[5,6]. During this time, Rb races have evolved independently in many different geographic regions and a number of these races have become fixed for nine pairs of metacentrics (i.e. fusions involving all chromosomes except the sex chromosomes and one pair of autosomes, resulting in 2n = 22). Because the Rb races are of recent origin, it is possible to make comparisons between mice that differ in karyotype but that are otherwise very similar. In fact, genetic and morphological differences between mice with different karyotypes are small or non-existent.

Third, an interesting contrast is provided by *M. musculus* and *M. domesticus*. These sister taxa (considered subspecies by some) both have the same standard karyotype, occupy similar ecological niches (both are commensal with humans), have similar life history traits, and hybridize both in nature and in the laboratory. Although Rb fusions are widespread in *M. domesticus*, they are virtually absent from *M. musculus*. An understanding of this difference may provide profound insight into the factors involved in chromosomal evolution.

Finally, the house mouse is an excellent biomedical model. We have enormous background knowledge about the genetics of the house mouse as well as a broad range of laboratory-generated Rb fusions available for study (28 in total; Table 1).

Box 1. The robertsonian fusion

The ancestral karyotype of the house mouse consists of 40 acrocentric chromosomes, that is, chromosomes with the centromere adjacent to one of the telomeres (chromosome ends). The autosome pairs are labeled 1–19 according to size (with 1 the largest). The sex chromosomes are labeled X and Y. Pairs of these chromosomes may undergo robertsonian fusion: the joining together of acrocentrics at their centromeres to form a single metacentric chromosome, that is, a chromosome with a distinctly internal centromere. The accumulation of robertsonian fusions reduces the number of chromosomes in the karyotype; there are mouse chromosomal races characterized by as few as 22 chromosomes. Among wild mice, only robertsonian fusions involving the autosomes have been found. Among laboratory strains, robertsonian fusions involving the autosomes as well as the X chromosome have been found (Table 1). The Y chromosome has important genes between the centromere and nearby telomere that would presumably be lost during robertsonian fusion. Here, we illustrate the robertsonian fusion of autosomes 1 and 15 to form a metacentric, described as Rb(1.15) according to the standard nomenclature, where chromosomes 1 and 15 have become arms of the new metacentric.



Once an Rb fusion has occurred, there are potentially two types of chromosomal rearrangement that can alter the disposition of the arms of the metacentric without affecting their integrity: robertsonian fissions (where the arms dissociate to generate acrocentrics again) and whole-arm reciprocal translocations (where the metacentric swaps arms with another metacentric or an acrocentric). Both may have occurred in wild house mice but are difficult to demonstrate and, in general, we have disregarded them in this article.

Table 1. The robertsonian metacentrics that have been described in wild house mice or in their laboratory equivalent[a]

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	X
1		Δo	Δo		Δ	Δ	Δ			Δ	Δ				*			Δ		
2				Δ	Δ	o		Δ						Δ	Δ	Δ	Δo	Δ		o
3				Δ	*	Δ		Δo	Δ	Δ		Δ	Δ	Δ	*		Δ			
4					Δ	Δ				Δ	Δ	Δ	Δ	Δ*	Δo		Δ	*		
5						Δo	Δ			Δ		Δ	Δ	Δ	Δ		Δ		o	
6							Δ		Δ	Δ	Δ	Δ	Δo	Δ	Δo	Δ	Δ	o	*	
7								Δ					o		Δ			Δ		
8									Δ	Δ		Δ	Δ	Δ	Δ	Δ	Δo		*	
9										Δ	Δ	Δ	Δ	Δ		Δ			o	*
10											Δ	Δ	Δ	Δo	Δ		Δ			
11													Δ	Δo	Δ	Δ*	Δ	Δ		
12													Δ*	Δ						*
13														Δ	Δ	Δ				
14																	Δ			
15																	Δ			
16																	Δ			

[a]Numbers correspond to autosome acrocentric arms. The metacentrics listed arose in either wild mice (Δ), laboratory stocks (o) or laboratory stocks that already carry one or more metacentrics (*). Note that the Y chromosome has never been found as part of a Rb metacentric.

Research on Rb chromosome variation in the house mouse over the last quarter-century has focused on topics such as the fitness of hybrids[4,7–11], the structure of hybrid zones[4,12–15], the role of Rb chromosomes in speciation[1,16], the evolutionary history of Rb races[5,6,17], and the evolutionary consequences of Rb variation[2,18,19]. Here, we concentrate on the underlying causes of the variation. Why exactly are so many different karyotypes present in this species? In this review, we call attention to recent empirical and theoretical studies that are beginning to answer this question.

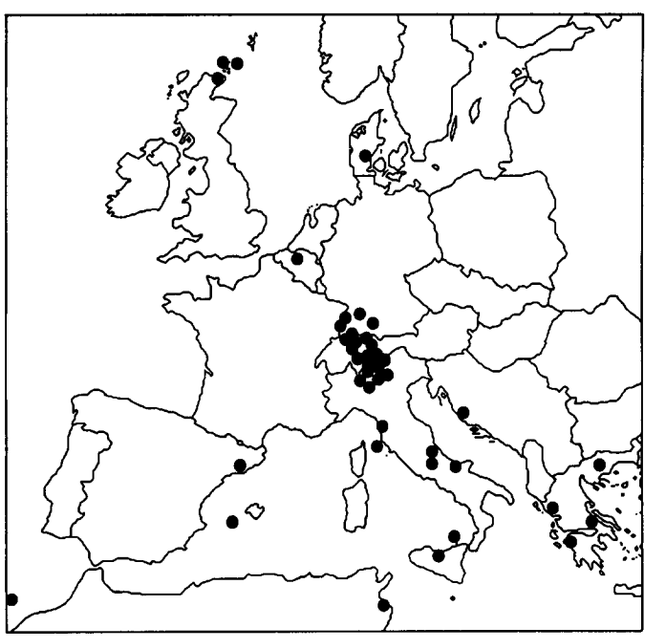


Fig. 1. Map showing the location of robertsonian (Rb) races in the house mouse (*Mus domesticus*). Despite the worldwide distribution of *M. domesticus*, Rb races have only been found in Europe and North Africa. The Rb races, either singly or in groups, appear to constitute islands in a sea composed of the standard all-acrocentric race. Typically, Rb races form narrow hybrid zones on contact with the all-acrocentric race. Rb races in different geographic areas sometimes share identical Rb chromosomes; however, many races also have Rb chromosomes not found elsewhere.

Rapid evolution in spite of underdominance

To appreciate the rapid rate of chromosomal evolution in *M. domesticus*, it is useful to compare it to rates in other mammalian taxa. For many species of mammals, fixation rates (k) of Rb mutations (estimated from phylogenetic comparisons of known age and summarized by Lande[20]) are approximately such that $k = 10^{-6}$–10^{-7} fixations per generation. In house mice, up to nine metacentrics have become fixed within each Rb race, and this has occurred independently in many different Rb races. Assuming that these fixations occurred since mice moved into Europe within the past 10000 years[21], and assuming that mice have four generations a year, then the fixation rate for each of these Rb lineages is k = (9 mutations)/[(4 generations/yr)(10000 yr)] = 2.25×10^{-4} fixations per generation. These are conservatively high estimates of the age of Rb lineages and the number of generations per year. Nonetheless, the fixation rate in these lineages is at least two orders of magnitude higher than the fixation rate in other species of mammals, and approximately equal to the mutation rate for Rb fusions estimated in humans (10^{-4} per gamete per generation[20]).

Explaining this high fixation rate is complicated by underdominance, the lower fitness of heterozygotes relative to either homozygote. Theoretical work shows that the probability of fixation of new mutations under such circumstances can be very low[20,22]. Underdominant mutations have a single unstable equilibrium frequency that depends on the relative fitness of the alternative homozygous forms. When alternative homozygotes have equal fitness, underdominant mutations are selected against when they are in the minority but selected for when they are in the majority, leading to the expectation that new underdominant mutations will very rarely become fixed.

Mice that are heterozygous for Rb fusions are expected to have reduced fitness relative to homozygotes because of aberrant pairing and segregation during meiosis and consequent lowered fertility (Box 2). The extent of the reduction in fertility depends on the number of heterozygous Rb fusions, the genetic background in which they are tested, and the particular chromosomes involved[4,7,10]. When wild mice homozygous for Rb chromosomes are crossed with standard-karyotype laboratory mice, the resultant Rb heterozygotes have non-disjunction frequencies (per heterozygous chromosome) as high as 30% in males and 60% in females[7,10]. However, wild mice that are simple heterozygotes for 1–3 metacentrics have much lower levels of non-disjunction (<10% in males) and may have nearly normal fertility[4,8,9]. These rates of non-disjunction in wild mice suggest that selection against Rb heterozygotes is probably weak to moderate (that is, $s \leq 0.1$).

Some combinations of chromosomes may be substantially more deleterious than others. For example, although fusions involving the X chromosome or autosome 19 have

arisen in laboratory mice, they have not been found in natural populations (Table 1). Certain aneuploids involving these chromosomes (XO, XXY and Trisomy 19) are the only aneuploids in the mouse that may survive beyond birth (Box 2)[23]. By producing these long-lived yet unproductive aneuploids, heterozygotes for Rb fusions involving the X chromosome or autosome 19 may have particularly low fitness (because of wasted parental investment) compared with heterozygotes that only produce short-lived aneuploids. Consistent with this hypothesis is the observation that, after XXY and Trisomy 19, the next longest surviving trisomy is Trisomy 18, and chromosome 18 is the least well-represented of the autosomes found in wild metacentrics (Table 1).

Additional evidence for underdominance comes from hybrid zone studies. The fact that Rb heterozygotes are not broadly distributed within *M. domesticus* but are restricted primarily to hybrid zones corroborates the view that naturally occurring Rb heterozygotes have lowered fitness. However, the width of clines for single metacentrics in hybrid zones can be wide (ca. 10 km) relative to average dispersal distances (<100 m)[4], suggesting that selection against some heterozygotes may be quite low (e.g. $s = 0.001$) (Ref. 24).

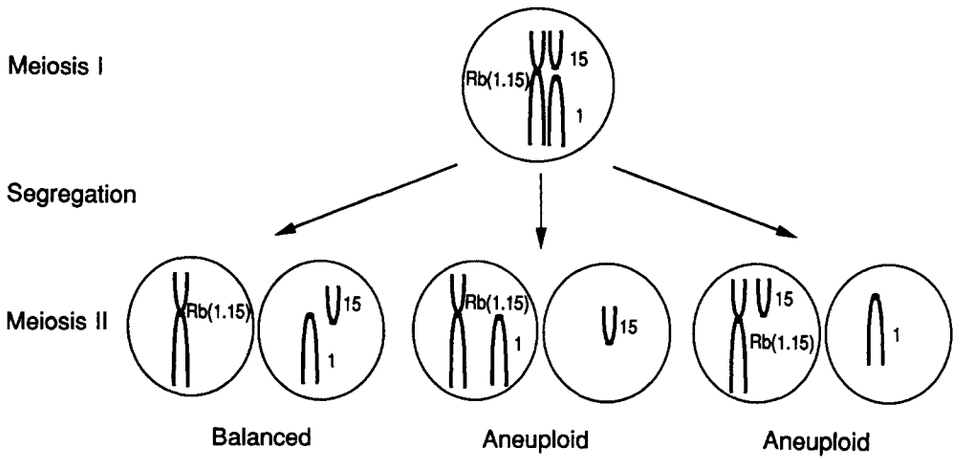
Although the underdominance associated with Rb fusions in the house mouse may not be as high as once thought[7], even weak underdominance will present an obstacle to fixation. A realistic range of selection coefficients (s) for most single, wild Rb heterozygotes is likely to be from $s = 0.001$ (estimated from hybrid zones) to $s = 0.1$ (estimated from rates of non-disjunction).

How can we explain the high fixation rate in light of this selection against new Rb fusions? The fixation rate depends on the rate of occurrence of new mutations (i.e. the mutation rate) and on the probability of fixation for each new mutation. Theoretical studies[20,22,25,26] have identified three main forces that separately or in combination may increase the probability of fixation for underdominant rearrangements: drift (and/or inbreeding), selection for new homozygous Rb fusions, and meiotic drive. Here, we consider each of these, as well as the mutation rate, with the aim of understanding which factors are sufficiently different between *M. domesticus* and other mammals (particularly *M. musculus*) that they could account for the high rate of chromosomal evolution.

Are drift and inbreeding common in mice?

It is clear that drift and/or inbreeding may be sufficient to counteract selection against heterozygotes and allow the fixation of new fusions. This can be seen in Fig. 2 for a range of realistic values of selection coefficients for wild Rb heterozygotes. For all values of s, the rate of fixation increases as the population size decreases. If underdominance is extremely weak ($s = 0.001$), then drift may fix rearrangements even in population sizes as large as 1000. When $s = 0.1$, however, we see that except in very small populations (e.g. <10), drift alone will never allow metacentrics to become fixed.

Box 2. Fertility of heterozygotes



Simple robertsonian heterozygotes contain a metacentric chromosome and homologous acrocentric chromosomes, as shown here for Rb(1.15). They are produced in hybrid zones (e.g. where the standard all-acrocentric race meets a metacentric race) and are present when a Rb fusion first arises within a population. In meiosis I, it is apparently essential for the chromosomes to be completely paired; otherwise the meiocyte will die. In the case of Rb heterozygotes in the mouse, the centromeric regions of the acrocentrics sometimes remain unpaired (not shown). In males, this may reduce sperm counts (and cause sterility in extreme cases) and in females, this can shorten the reproductive lifespan. Meiocytes that survive to anaphase I may undergo proper segregation (left arrow) or non-disjunction (right two arrows). Non-disjunction produces aneuploid gametes, which survive to fertilization but generate monosomic and trisomic embryos. All autosomal monosomies die at the time of implantation, while autosomal trisomies live for a variable length of time. The longest surviving trisomy is Ts 19, which may live up to four weeks beyond birth, while the shortest surviving trisomies (e.g. Ts 15) only live until mid-gestation. Non-disjunction in heterozygotes for X-autosome Rb fusions may produce XO and XXY offspring, which can develop into subfertile and sterile adults, respectively.

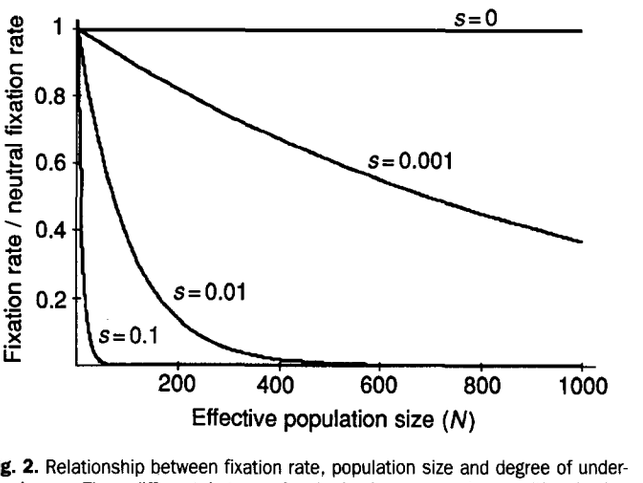


Fig. 2. Relationship between fixation rate, population size and degree of underdominance. Three different degrees of underdominance are shown, with selection against heterozygotes (s) ranging from mild (0.001) to moderate (0.1). This represents a realistic range of values for single Rb heterozygotes. For strictly neutral mutations ($s = 0$), the fixation rate is independent of population size and is exactly equal to the mutation rate. This is because as population size increases, the probability of fixation for any one mutation decreases, but this is exactly offset by the increase in the number of individuals contributing new mutations to the population. For underdominant mutations, in contrast, the rate of fixation decreases as population size increases. If $s = 0.01$ and $N > 500$, or if $s = 0.1$ and $N > 100$, the fixation rate becomes zero unless some other force (like meiotic drive) is operating to promote fixations. The fixation rate for underdominant mutations relative to the neutral fixation rate (i.e. the y-axis in the figure) is given by the approximation $y = e^{-s(N-2)}$, from equation (13.56) in Nei[47].

The view that arose from early biochemical studies was that house mouse populations are highly subdivided, that individual demes are small, and that gene flow is very low[27,28]. This was thought to arise in part because mice are commensal with humans and live in structured, locally isolated environments. More recent studies have challenged this view somewhat. First, molecular markers suggest that both short- and long-distance gene flow can be quite common[29–31]. Second, Potts and colleagues have demonstrated that house mice discriminate among mates on the basis of MHC alleles, choosing to breed with mates that are different from themselves[32]. Such mate choice avoids inbreeding. Third, both allozyme[5] and mitochondrial[6] data show that Rb and non-Rb populations have similar levels of genetic variability, providing no evidence for bottlenecks in the founding of Rb races.

Understanding the structure of mouse populations from genetic data is complicated and depends in part on the scale of investigation. Genetic variation can provide estimates of long-term effective population size but may be less informative about the frequency of short-term, isolated demes that may nonetheless be important for the establishment of chromosomal variants. While it is not typical for island populations to show low allozyme variability[33], there are a few examples where this is the case[30], suggesting that severe bottlenecks can occur.

Although *M. domesticus* populations may occasionally be reduced to a very small size, it is not clear that small populations are more common in *M. domesticus* than in other, less chromosomally variable species of small mammal, such as *M. musculus*. Levels of genetic variability within populations, and amount of differentiation between populations, are similar for *M. musculus* and *M. domesticus*[27], as expected of species with similar population structures. Thus, drift alone is probably not a sufficient explanation for the rapid fixation rate of Rb fusions in *M. domesticus*.

Are Rb chromosomes selectively favored?

If Rb homozygotes are adaptive, selection can facilitate the fixation of new, weakly underdominant rearrangements. In the absence of direct evidence for metacentric superiority, researchers have looked for indirect evidence of selection. Are Rb mice preferentially found in certain habitats? Are phenotypic differences (that may be under selection) associated with Rb mice? Does the movement and spread of Rb mice fit the expectations of models invoking selection?

One study in Tunisia found that standard and Rb mice appear to segregate by habitat where a 2n = 40 and a 2n = 22 population meet and form a mosaic hybrid zone[13]. The 2n = 40 animals are found in rural situations and the 2n = 22 mice are found in more urban areas. However, in other situations, such as in northern Italy, standard and Rb mice are found in identical habitats[15]. While the observations in Tunisia are interesting, they do not appear to characterize Rb populations in general. Attempts to document behavioral or morphological differences between standard and Rb mice have been inconclusive. Although differences in levels of aggression and differences in mate choice have been described between standard and Rb mice[19,34], these studies involved small sample sizes and need to be replicated to see if general patterns emerge. In the Tunisian hybrid zone[13], and in a hybrid zone from central Italy[12], multivariate morphological measurements discriminate standard and Rb mice to some extent, although there is overlap in measurements from the two groups in both cases.

The movement and spread of Rb chromosomes may also provide indirect evidence of selection. In 1982, Berry and co-workers released a sample of 77 mice on the Isle of May, a 60 ha island off the coast of Scotland already inhabited by approximately 1000 standard 2n = 40 mice[30]. The released mice were monomorphic for three Rb chromosomes and also possessed distinct allozyme, Y chromosome, and mtDNA markers. Within three years, the mtDNA had moved little from the point of introduction, but the Y chromosome, introduced allozymes, and Rb chromosomes had spread across the small island, remaining at intermediate frequencies. Berry *et al.* interpreted this rapid spread in terms of the lower fitness of the resident island population owing to inbreeding. Sage *et al.* pointed out that the rapid spread is also consistent with a hypothesis of metacentric superiority[19]. This latter interpretation, however, does not explain why the Rb chromosomes have not gone to fixation. Indeed, one general difficulty with the hypothesis that Rb mice are selectively favored is that they have only replaced 2n = 40 mice over a small part of the range of *M. domesticus* (Fig. 1), although it is also possible that the narrow ranges of Rb mice simply reflect their recent origin. It should be noted that if underdominance is extremely weak (as may be true for single Rb heterozygotes), then an advantageous mutation is expected to spread rapidly within a species, even with low levels of gene flow among populations.

An additional difficulty with metacentric superiority is that potential mechanisms for selection remain unclear. Because a wide variety of metacentric arm combinations occur in nature, it is unlikely that they are all favored because they induce some common physiological or behavioral feature, such as aggressiveness[19]. Rb fusions do create new linkage groups and there may be significant suppression of recombination around the fusion point in heterozygotes[35]; it is possible that the association of advantageous alleles from centromeric loci on different acrocentrics may play a role in local adaptation. If selection is the primary force promoting the local fixation of metacentric chromosomes, it remains unclear what differences between *M. domesticus* and *M. musculus* favor metacentrics in one species but not in the other.

Is meiotic drive important in Rb evolution?

Meiotic drive, broadly defined, is the biased transmission of one of the allelic forms in the gametes of a heterozygous parent. This may result from uneven segregation during meiosis, particularly in females where three out of four meiotic products are lost. It may also result from equal meiotic segregation followed by haploid selection favoring some gametes over others. If mice heterozygous for a Rb chromosome preferentially transmit the metacentric to their offspring (instead of the two acrocentrics), then the likelihood of fixation of the Rb chromosome in the population is greatly increased.

This possibility is attractive from a theoretical point of view for several reasons. First, it is a powerful force that can counteract underdominance, even in the absence of drift[22]. Second, both chromosomal and genic meiotic drive[36] may be possible in Rb heterozygotes. Chromosomal drive occurs when a rearrangement is favored because of a replication or orientation advantage on the spindle during female meiosis, allowing it to be preferentially retained in the oocyte. Genic drive typically involves the interaction of two loci that are in strong linkage disequilibrium and results in a post-meiotic advantage for one haplotype over another. The region of suppressed recombination around the centromere of Rb chromosomes[35] provides a possible location for such drive loci. Third, an increase in frequency of drive alleles is expected to be offset by an increase in frequency of alleles that suppress meiotic drive, so that polymorphisms typically result[37]; this could explain why both Rb and 2n = 40 mice persist within *M. domesticus*.

What is the evidence for drive? Gropp and Winking[7] looked for drive with ten different Rb chromosomes using metacentrics from wild mice that were introduced into a laboratory-mouse genetic background. In male heterozygotes, they found no evidence for transmission distortion. In female heterozygotes, their data provide strong statistical support for drive favoring acrocentrics with two rearrangements [Rb(1.3) and Rb(6.13)] and weaker evidence for drive favoring acrocentrics with another three rearrangements [Rb(16.17), Rb(10.11), Rb(4.15)]. They found no evidence for drive favoring metacentrics. Another study[38] involving a wild Rb chromosome [Rb(6.16)] in a laboratory mouse background found evidence for drive favoring acrocentrics in males.

Using wild mice, Britton-Davidian *et al.*[39] did not detect drive in Rb(16.17) heterozygotes (in contrast to the results of Gropp and Winking, above). Likewise, Viroux and Bauchau[8] found no evidence of distortion for wild Rb(4.12) heterozygotes. It is important to note that even with large sample sizes, a small level of drive (e.g. <10%) can go undetected, though this rate may be an important force for the fixation of new mutations. In addition, absence of drive in wild Rb heterozygotes could reflect a balance between drive and suppressor alleles in the individuals tested. Harris *et al.*[40] did find evidence of drive favoring metacentrics in Rb(9.12) heterozygotes, and this Rb chromosome was newly arisen in a captive population of wild mice.

Thus, in both wild mice and mice with mixed wild/laboratory genomes, some studies have revealed meiotic drive and others have not. In all cases of drive in mice with mixed wild/laboratory genomes, acrocentrics were favored over metacentrics. This may reflect the poor performance of wild metacentrics when introduced into well-established laboratory-stock acrocentric genomes. In the only case of meiotic drive in wild mice, metacentrics were favored over acrocentrics. It is clear that results obtained with artificial hybrids may bear little relation with the situation in the wild[39]. More work is needed on meiotic drive in wild mice to assess adequately the importance of this force in Rb evolution.

A high mutation rate?

In addition to the forces that increase the probability of fixation of Rb fusions in the house mouse, the rate of fixation will depend critically on the mutation rate. For strictly neutral mutations, the fixation rate is equal to the mutation rate[41]. Since Rb mutations are underdominant, the fixation rate will be lower than the mutation rate (Fig. 2). For example, if $s = 0.01$ and population size is $N = 250$, then the fixation rate will be about one tenth the mutation rate. If $s = 0.01$ and population size is $N = 500$, then the fixation rate will be about one hundredth the mutation rate. The fixation rate in mice is about $k = 2.25 \times 10^{-4}$ fixations per generation. This high fixation rate can be explained, in theory, by a high mutation rate alone. Under the two scenarios above ($s = 0.01$, $N = 250$ and $s = 0.01$, $N = 500$), the necessary mutation rates are 2.25×10^{-2} and 2.25×10^{-3}, respectively. These values are both much higher than the mutation rates measured in humans for Rb mutations ($\mu = 10^{-4}$ per gamete per generation[20]).

Direct estimates of the mutation rate in mice have not been made. However, the appearance of metacentrics in laboratory stocks may provide some feel for the range of realistic values. Altogether, 28 Rb chromosomes have appeared in laboratory strains (Table 1). Interestingly, many of these have appeared in mice that already contained a metacentric (Table 1), suggesting that some lineages may be more likely than others to mutate. At one of the large mouse laboratories (MRC Radiobiology Unit, Didcot, UK) eight new Rb fusions have been detected in Rb-containing stocks with under 4000 mice scored (E.P. Evans, pers. commun.). In contrast, no Rb fusions were detected in over 5500 mice screened by Ford[42] at the MRC Unit between 1954 and 1969, and none was detected in 5900 standard-karyotype mice scored in a German laboratory[43]. As very rough estimates, it may be reasonable to say that μ for Rb stocks is 10^{-2}–10^{-3}, while μ for non-Rb stocks is 10^{-4} or less. These observations are consistent with the hypothesis that certain lineages may contain novel DNA sequences that predispose the mice to Rb fusion[19]. These observations also suggest that in some lineages mutation rates may be exceptionally high and sufficient to explain the high fixation rates in this species. In contrast, fission is probably a very rare event because of the difficulty of acquiring functional centromeres[44].

If a high mutation rate is the primary cause of the high fixation rate for Rb chromosomes in *M. domesticus*, then *M. musculus* must have a different mutational mechanism. To consider the molecular basis for a high Rb mutation rate in *M. domesticus*, studies have been made of the centromeric region, where chromosome breakage and fusion occurs (Box 1). The major satellite DNA near the centromere is known to be rather similar among the different chromosomes in *M. domesticus*[45]. This suggests that non-homologous chromosomes are readily exchanging DNA and that other breakage–reunion events in the pericentromeric region, including Rb fusions, are possible. In contrast, the major satellite DNA of *M. musculus* is more heterogeneous among different chromosomes[46], which may indicate less movement of sequences among autosomal centromeres and less possibility for Rb fusion.

Conclusions and prospects for the future

Assessing the relative importance of drift, selection, drive and mutation in Rb evolution presents a daunting but exciting challenge for mouse geneticists. Fortunately, predictions can be made to test the role of each of these factors, and the next decade of research will bring us a more-detailed picture of their relative contributions.

Several important conclusions are already clear. Underdominance of single Rb fusions is probably low, and certainly lower than originally believed, but may still be an obstacle to fixation. The possibility that certain lineages within *M. domesticus* may have an exceptionally high mutation rate is consistent with available data and certainly merits further study. On the other hand, there is no compelling evidence that metacentric superiority plays a primary role in the fixation of new Rb fusions. Drift occurs in all populations to some extent and has probably facilitated the fixation of fusions in some, though not necessarily all, populations. Meiotic drive may be an important force in Rb evolution, but further work is needed on mice with a natural genetic background to test this hypothesis.

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The advantages of being evergreen

Rien Aerts

Recent research shows that the dominance of evergreen species in nutrient-poor environments can be explained by their low nutrient loss rates. From this work it appears that the plant traits that are associated with low nutrient loss rates lead to low maximum-dry-matter production and to low rates of litter decomposition. This suggests a positive feedback between the evergreen habit and low nutrient availability. The growth characteristics of evergreens lead to a low responsiveness to environmental changes. As a result, global warming may lead to changes in the distribution of evergreens.

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Evergreens occur in all parts of the world: from the tropics to polar regions, from lowland to subalpine altitudes. Monk[1] postulated that the evergreen habit is an adaptation to habitats with low nutrient availability. Since that seminal paper, a considerable amount of papers has been published about the adaptive significance of evergreenness in nutrient-poor habitats. Most of these papers emphasized that evergreens, because of their long leaf-lifespans, have a higher nutrient-use efficiency (NUE: productivity per unit nutrient uptake or loss) than deciduous species[2–4]. However, these papers considered only the level of the individual leaf, thus ignoring the fact that the large mass of stems, roots and rhizomes might modify the observed patterns considerably[5]. In recent years, the adaptive significance of evergreenness at the whole-plant level and the benefits and costs of the evergreen habit have been studied. This review emphasizes the importance of the low nutrient loss rates of sclerophyllous evergreens and the consequences for leaf physiology, dry matter production, leaf construction costs, litter decomposition and responsiveness to environmental change.

The advantage of the low nutrient loss rates of evergreens

A generally accepted explanation for the dominance of evergreens in low-nutrient habitats is that they have a higher NUE than deciduous species[2]. The problem with the current indices of NUE is that they are ratios and as such do not directly show why a high NUE is beneficial in low-nutrient habitats[6]. Comparisons of the NUE of evergreen and deciduous species at the whole-plant level even show that there are no differences[6] or that the deciduous species have a higher NUE[7].

Two recently developed models show that the dominance of evergreens in low-nutrient habitats can be explained by their low nutrient loss rates[8,9], without considering the

