Meiosis and speciation: a study in a speciating *Mus terricolor* complex

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Abstract

The three chromosomal species of the *Mus terricolor* complex possess $2n = 40$ chromosomes. We show that their karyotypes differ in stable heterochromatin variations fixed in homozygous condition as prominent short arms in autosomes 1, 3 and 6. The three chromosomal species exhibit a high incidence of polymorphisms for Robertsonian fusions and pericentric inversions. Breeding experiments and histological analysis of testis show that heterozygosity for pericentric inversions and Robertsonian fusions had no effect on fertility. Meiotic analysis shows normal overall progression of meiosis in the heterozygotes, which is consistent with their normal gametogenesis. Nevertheless, both the inversion and fusion heterozygotes had undergone some alterations in the regular process of homologous synapsis, and it appeared that certain features of the meiotic system circumvented the potential negative effects of these polymorphic chromosomal rearrangements. The results indicate that the attributes of the meiotic system in a given organism could modulate the potential of a chromosomal rearrangement as reproductive barrier. The meiotic modulation hypothesis offers an explanation for the contradictory effects of the similar kinds of chromosomal mutations reported in different species.

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Introduction

Models of chromosomal speciation postulate that a chromosomal rearrangement (CR) facilitates speciation when it is negatively heterotic and gets fixed in homozygous condition in a population (White 1978, 1982; King 1981; Shaw 1981). Heterozygosity for the negatively heterotic rearrangement in F_1 hybrids between populations that differ owing to CR would result in their reduced fertility (see reviews by White 1978; King 1981) or would lead to reduced viability of subsequent generations (Shaw 1981). An explanation for the apparent paradox of the homozygous-fixation of a negatively heterotic CR in a population has been sought in the population structure of a given organism, and could further be favoured by drift, selection, a specialized phenomenon like meiotic drive, etc. (reviewed by King 1993). The basic tenet of the chromosomal speciation models, namely negative heterosis, has however been criticized, since many CRs do not reduce heterozygote fitness (for example Porter and Sites 1985; Davis *et al*. 1986; Nachman and Myers 1989). The reason for such a criticism, however, might be a lack of appreciation of the critical difference between CRs that get fixed but reduce fitness when heterozygous and CRs that exist as chromosomal polymorphisms without conferring any selective disadvantage (see King 1993).

To examine whether the CRs that get fixed in a population and CRs that exist as polymorphisms could have different implications in cladogenesis, it is crucial to analyse their effect on heterozygote fitness in the same given organism. Such an analysis may address two basic tenets of chromosomal speciation: first, the relative contribution of these CRs in reducing heterozygote fitness and thus in promoting species barrier; and second, the factor(s) contributing to the species-specific nature of the impact of CRs.

Here we report high incidence of polymorphisms for pericentric inversions and Robertsonian fusions in the

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Indian pygmy field mice *Mus terricolor*, vis-à-vis the fixation of autosomal heterochromatin variations in stable homozygous condition among the three chromosomal species. Histological analysis and breeding experiments demonstrated that the inversions and fusions did not impair fertility in heterozygous condition, while meiotic analysis showed that the heterozygosity did not affect normal meiotic progression. Conversely, the experimental male hybrids among the chromosomal species of *terricolor* had spermatogenic impairment, due mainly to abnormalities in meiotic synapsis (A. Bardhan, M. Bahadur and T. Sharma, submitted). The heterochromatin heterozygosity (in the hybrids) adversely influenced synaptic progression, as revealed by the higher frequency of synaptic abnormalities in the heterozygous backcross hybrids compared to the backcross hybrids with homozygous karyotypes. This implied that the heterochromatin variations were negatively heterotic (A. Bardhan, M. Bahadur and T. Sharma, submitted).

We discuss the possible ways by which potential negative influences of the polymorphic chromosomal rearrangements could have been circumvented during meiosis. This could be important in modulating their speciation potential.

Materials and methods

Mus terricolor I were collected from Varanasi in north India, *M. terricolor* II from Mysore in south India, and *M. terricolor* III from Chennai and Tirupati in south India. Wild-caught animals were kept for breeding in the laboratory, but inbreeding was strictly avoided. Hybridizations among *terricolor* I, II and III were set up using the first-generation pups born in the laboratory, when they were about one month old. To analyse the effect of pericentric inversions on fertility, wild-caught animals were bred for more than a year, and after that mitotic chromosomes from all the male parents were analysed. Litter sizes of crosses with males devoid of the inversions, males heterozygous for either of the inversions, and males heterozygous for both the inversions were compared. A Robertsonian fusion was found in one laboratory hybrid (see results), the parents of which died before they were analysed. With the expectation that the same fusion might be present in some of the littermates if it was inherited from one of the parents, and the optimism that we could get a male heterozygote for the fusion to investigate its meiotic behaviour, we backcrossed the two female hybrid littermates to *terricolor* II males. All the backcross hybrids ($n = 17$) were examined for the presence of the Robertsonian fusion.

Mitotic chromosomes were prepared from bone marrow of colchicine-injected mice by conventional method. G-banding (Seabright 1971) was done to identify chromosomes, and karyotypes were arranged according to the Committee on Standardized Genetic Nomenclature for Mice (1972). Sumner's method was followed for C-banding (Sumner 1972). Meiotic chromosomes were prepared following Evans *et al*. (1964). For analysis of pachytene synapsis, surface-spread synaptonemal complexes (SCs) were prepared and stained with silver nitrate (Fletcher 1979), or stained immunocytologically (Dobson *et al.* 1994) using rabbit 'B' serum raised against Chinese hamster SCs (kindly provided by P. Moens). Frequencies of metaphase II aneuploidy was determined as double the frequency of hyperhaploid cells. Testes were fixed in Bouin's fixative, dehydrated and paraffin embedded, and 5–6 µm sections were cut; sections were stained with haematoxylin and eosin. Always the right testis was taken for histological analysis and the left one for cytological study.

Results

The *M. terricolor* chromosomal species *terricolor* I, II and III are apparently parapatrically distributed and exhibit both premating and postzygotic isolations (Sharma 1996). All the three chromosomal species have $2n = 40$, but their karyotypes differ in the presence or absence of large heterochromatic p arms on the autosome pairs 1, 3 and 6. While the karyotype of *terricolor* I is characterized by all-acrocentric autosomes, *terricolor* II and III possess two and three pairs of submetacentric autosomes with large heterochromatic p arms, respectively (figure 1). All three have identical sex chromosomes. Two autosomal pairs, 2 and 5, exhibit a high frequency of pericentric inversion polymorphisms (figure 1); they are present in heterozygous or homozygous conditions in *terricolor* II and III, but are absent in *terricolor* I.

In about 850 karyologically investigated mice, eight different Robertsonian (centric) fusions, all in heterozygous condition ($2n = 39$), were observed (table 1; figure 2, for example). A trivalent was consistently present whenever meiotic diakinesis/metaphase I stages were observed. All the fusions were found from wild populations, except Rb (1;2) which was first found in a laboratory F_1 hybrid (table 1). The same fusion was also identified in one male and two female backcross hybrids (see Materials and methods), implying that it was inherited from one of the parents of the F_1 hybrid.

Two each of *terricolor* II and *terricolor* III males heterozygous for the inversions in autosome pairs 2 and 5 were analysed for reproductive and meiotic performance. Testis histology showed normal spermatogenesis with peripheral mitotic spermatogonia, adluminal meiotic spermatocytes and postmeiotic round spermatids, and elongated spermatozoa in the lumen. Laboratory breeding revealed that the inversions did not reduce fertility (data shown in table 2). Litter size of males devoid of the inversions did not significantly differ from that of males

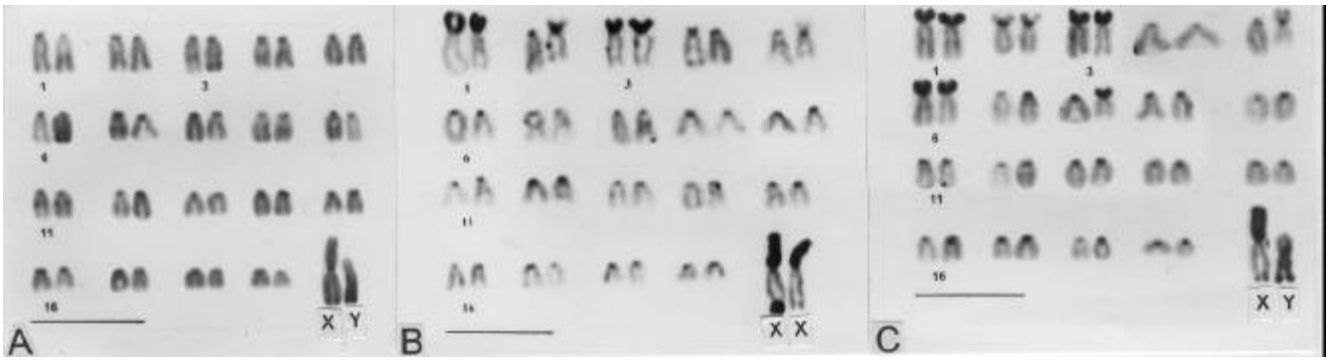

Figure 1. C-banded karyotypes of (A) *Mus terricolor* I: all autosomes are acrocentric; (B) *M. terricolor* II: autosome pairs 1 and 3 are submetacentric with large C-positive heterochromatic p arms; and (C) *M. terricolor* III: autosome pairs 1, 3 and 6 are submetacentric with large C-positive heterochromatic p arms. Autosome pairs 2 and 5 are heterozygous for pericentric inversions in B, while pair 2 is homozygous and 5 is heterozygous for the inversions in C. Autosome pair 8 is heterozygous for heterochromatic short arm in C, which is a very rare polymorphism. The X chromosome is submetacentric with C-positive large p arm and the Y is large C-positive acrocentric in all the three chromosomal species. The distal ends of the long arms of both the X and Y are also C-positive. Bar = 10 µm.

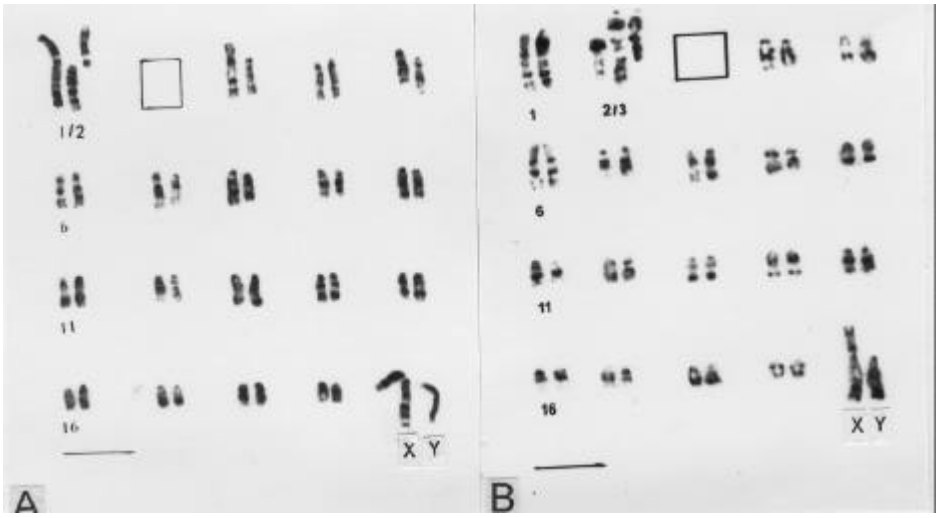

Figure 2. G-banded karyotypes of (A) Rb(1;2) and (B) Rb(2;3) heterozygotes. Bar = 10 µm.

Table 1. Robertsonian fusions recorded in *M. terricolor* I, II and III.

Fusion	Means of identification	Recorded from
Rb(1;8)	G-banding	*terricolor* I
Rb(4;6)	G-banding	*terricolor* I
Rb(13;16)	G-banding	*terricolor* I
Rb(2;6)	Length of euchromatic arms	*terricolor* II
Rb(2;3)	G-banding	*terricolor* III
Rb(2;4)	Length of euchromatic arms	*terricolor* III
Rb(2;5)	G-banding	*terricolor* III
Rb(1;2)	G-banding	Hybrid between *terricolor* I and II

Table 2. Summarized data of laboratory breeding with males with or without pericentric inversion on autosome pairs 2 and 5.

	Karyotype	No. of Progeny	No. of litters	Mean litter size (± SD)
M. terricolor II	2/2, 5/5	154	35	4.4 ± 1.3
	$2/2^{inv}$, 5/5; or 2/2, $5/5^{inv}$	154	33	4.7 ± 1.1
	$2/2^{inv}$, $5/5^{inv}$	162	39	4.1 ± 1.6

heterozygous for inversion on either chromosome 2 or 5 (t = 0.9, P > 0.2, df = 66), and of males heterozygous for both the inversions (t = 0.7, P > 0.2, df = 72). Also, the litter size did not differ between the single and double heterozygotes (t = 1.6, P > 0.05, df = 70).

To examine whether selection operates against the inversions, their frequency distribution in the natural population was calculated from a total of 46 wild-caught *terricolor* III collected at one time from one locality in

Chennai in the year 1998. The total number of individuals devoid of the inversions, individuals heterozygous for the inversions, and individuals homozygous for the inversions were obtained by karyotypic analysis. The data are summarized in tables 3 and 4. Comparison between the observed and the expected frequencies showed no significant disagreement in a chi-square test. The results suggest that the population was in Hardy–Weinberg equilibrium and there was no strong selection against the inversions.

Analysis of meiotic synapsis in 200 pachytene spreads showed that all the autosomal bivalents had linear, fully synapsed SCs, suggesting that the inversion heterobivalents underwent nonhomologous synapsis. Similar nonhomologous synapsis of the heterobivalents was observed at late zygotene/early pachytene in an earlier study of progression of meiotic synapsis in pubertal *terricolor* II (Bardhan and Sharma 2000). This nonhomologous synapsis could hinder formation of chiasma within the inverted segment and thus prevent deletion/duplication of chromosomal segments (White 1973). Segregation analysis of 137 metaphase II cells accordingly showed no aneuploidy (data presented in table 5), reflecting normal segregation.

Detailed histological and meiotic analyses of the Rb(1;2) and Rb(2;3) heterozygotes were made. Testis histology showed normal spermatogenesis in both cases. In 48 out of 100 pachytene spreads from the Rb(1;2) heterozygote, the trivalent had large asynapsis around the fused pericentromeric region (figure 3A), while in the remaining cells it was fully synapsed. In the Rb(2;3) heterozygote (number of pachytenes observed = 101), 40 cells had prominent asynapsis (figure 3B), whereas in 15 cells the proximal ends of the two acrocentrics were paired nonhomologously as a distinct side arm (figure 3C). In both cases, in 45 cells where the trivalents were partially synapsed or underwent nonhomologous synapsis between the acrocentrics, the two acrocentric chromosomes were in *cis* configuration with the fused submetacentric (figure 3), and only in two cells they were in *trans*. In the other spreads in which the trivalents were fully synapsed, the light microscope could not resolve the configuration. The trivalents always remained distinctly separate from other SCs implying that the asynapsed segments did not interact with the sex bivalent; this excluded their interference with X-inactivation to disrupt spermatogenesis (reviewed by Forejt 1996). Unfortunately, only three analysable metaphase II cells were

Table 3. Observed frequencies of pericentric inversion polymorphism of autosome 2 in *M. terricolor* III, and the expected frequencies under Hardy–Weinberg equilibrium.

	Genotype				Inversion frequency[1]	
	2/2	$2/2^{inv}$	$2^{inv}/2^{inv}$	Total	2	2^{inv}
No. observed	5	28	13	46	0.413	0.587
No. expected[2]	7.85	22.3	15.85	46		

$\chi^2 = 3.0$ $P > 0.05$ Degree of freedom = 1

[1]The inversion frequency was calculated from the observed numbers of heterozygotes and homozygotes.
[2]The Hardy–Weinberg frequencies were obtained from the calculated inversion frequencies, and each was multiplied by the total number to get the number expected.

Table 4. Observed frequencies of pericentric inversion polymorphism of autosome 5 in *M. terricolor* III, and the expected frequencies under Hardy–Weinberg equilibrium.

	Genotype				Inversion frequency[1]	
	5/5	$5/5^{inv}$	$5^{inv}/5^{inv}$	Total	5	5^{inv}
No. observed	29	16	1	46	0.804	0.196
No. expected[2]	29.73	14.5	1.77	46		

$\chi^2 = 0.5$ $P > 0.3$ Degree of freedom = 1

[1]The inversion frequency was calculated from the observed numbers of heterozygotes and homozygotes.
[2]The Hardy–Weinberg frequencies were obtained from the calculated inversion frequencies, and each was multiplied by the total number to get the number expected.

Table 5. Aneuploidy frequency in *M. terricolor* II and III which were doubly heterozygous for pericentric inversions on autosomes 2 and 5.

	No. of M-II observed	No. of hyperhaploid M-II	No. of hypohaploid M-II	Aneuploidy frequency[1]
terricolor II				
My8-1	31	0	3	Nil
My8-2	51	0	7	Nil
terricolor III				
M5-1	30	0	5	Nil
M9-1	25	0	1	Nil

[1]Aneuploidy frequency was considered to be double the frequency of hyperhaploid cells.

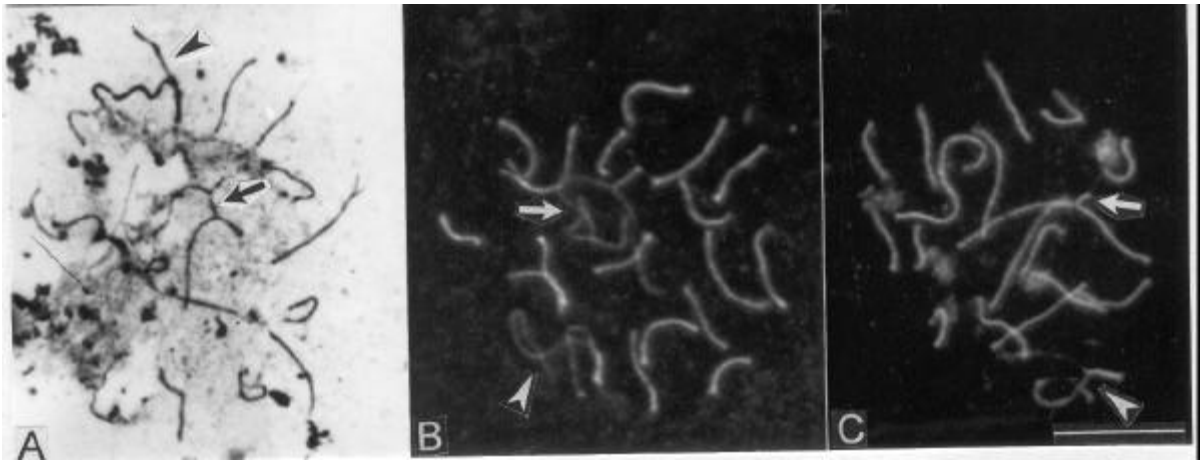

Figure **3.** Surface-spread pachytene spermatocytes from (A) Rb(1;2) and (B, C) Rb(2;3) heterozygotes. In all the cases, the trivalent (arrow) is not associated with the XY bivalent (arrowhead). Large asynapsis around the fused pericentromeric region of the trivalents are seen (in A and B), while the proximal regions of the two acrocentrics are paired heterologously as a side arm (in C). The two acrocentric autosomes in the trivalents are in *cis* configuration with the submetacentrics in A, B and C. Synaptonemal complexes are stained with silver nitrate in A, and immunocytologically with rabbit anti-SC antiserum in B and C. Bar = 10 μm.

obtained, precluding segregation analysis. Nevertheless, the observation that the trivalents were in *cis* configuration in the vast majority of the pachytenes suggests that they would undergo normal disjunction (Moses *et al.* 1979; Davisson *et al.* 1981). The 17 individuals that were born to two Rb(1;2) female heterozygotes had normal ploidy, five with Rb(1;2) ($2n = 39$), and 12 with all-acrocentric autosomal complements ($2n = 40$). Also, the normal litter sizes ruled out foetal loss. Taken together, these data suggested that Rb(1;2) segregated normally in meiosis.

The results demonstrated that heterozygosity for polymorphic CR, namely pericentric inversions and centric fusions Rb(1;2) and Rb(2;3), did not reduce efficiency of the meiotic and gametogenic processes in *terricolor*. Conversely, experimental hybrids among *terricolor* I, II and III (which were heterozygous for the stable variations of the autosomal p-arm heterochromatin, established in homozygous condition in the parental chromosomal species) had partial to complete spermatogenic arrest and general synaptic failure at pachytene. Backcross analysis further revealed that the heterochromatin heterozygosity had a prominent role in the impairment of meiotic synapsis in the hybrid genome (A. Bardhan, M.Bahadur and T. Sharma, submitted).

Discussion

The general observation of low frequency of chromosomal polymorphisms in diverse species has been regarded as the outcome of strong selection against heterozygotes (White 1978; Hall 1983). Contrary to this explanation, it has later been found that a very high rate of chromosomal polymorphisms can be tolerated by some organisms. This questioned the general validity of the chromosomal mechanism of speciation (Porter and Sites 1985; Nachman and Myers 1989). Notwithstanding this, the same kind of CRs were found to reduce heterozygote fitness in some other organisms (the following discussion).

Pericentric and paracentric inversions are known for evolutionary consequences for the disruptive effect on the carrier (Winsor *et al*. 1978; Davisson *et al*. 1981; Fryns *et al*. 1981; Preito *et al.* 1981; Batanian and Hulten 1987). The disruptive effect of inversion heterozygosity is classically regarded as due to formation of chiasma within the inverted segment that produces deletion-duplication chromatids (White 1973). However, if the chiasma distribution is such as to exclude chiasma formation from the inverted segment, evidently the potentially disruptive effect of the inversion would not be exerted. It therefore appears that some features of the meiotic system (in a given species) could modulate the potential negative effects of inversion heterozygosity; for example, shift of chiasma to a terminal position or occurrence of chiasma outside the inversion loop (Hale 1986), reduction of meiotic recombination within the inverted segment (Brown *et al*. 1998), and nonhomologous pairing or reverse pairing of the inverted segment at pachytene (Davisson *et al*. 1981; Tease and Fisher 1988).

Robertsonian or centric fusion could also disrupt normal meiotic and gametogenic processes to different extents. Effect of single Robertsonian heterozygosity on gametogenesis is highly variable; it substantially reduces fertility in humans (Stene and Stengel-Rutowski 1988) and field mice (Saitoh and Obara 1988), but not in wild house mice (Britton-Davidian *et al*. 1990; Wallace *et al.* 1992), common shrew (Searle 1990) and marsh rat (Nachman 1992). Fusion heterozygosity reduces meiotic fitness by interfering with normal segregation, which, however, is largely influenced by the location and number of chiasmata (White 1973). This makes it feasible that the same fusion could have drastically different consequences in different species, owing to the inherent differences in chiasma distribution pattern between species. Furthermore, the synaptic behaviour of the heterobivalents (for example asynapsis and interaction with the X chromosome) could also interfere with meiotic and gametogenic fitness (reviewed by King 1993).

Several features of the meiotic system in *M. terricolor* could have modulated the potential negative influences of the pericentric inversions and Robertsonian fusions. The general chaisma distribution pattern, being interstitial or distal (Sen 1980), reduced the probability of chiasma formation within the proximally inverted segment. The chance of forming a chiasma was rendered further improbable by the lack of homologous synapsis in the inverted segment at zygotene, and the rapid establishment of linear heterologous synapsis at late zygotene/early pachytene (see Bardhan and Sharma, 2000; this study). Though the Robertsonian trivalents underwent variable degrees of asynapsis at early pachytene and mid-pachytene, they were fully synapsed at late pachytene by heterologous synapsis, possibly through a process of 'synaptic adjustment' (Moses *et al*. 1982). Heterologous synapsis also occurred between the asynapsed ends of the nonhomologous acrocentric chromosomes at early pachytene and mid-pachytene. These processes could lead to 'saturation of pairing sites' (Miklos 1974) and nullify the adverse effect of the asynapsis on gametogenesis (Speed 1986). Moreover, the synaptic pattern of the trivalents, i.e. that the two acrocentric chromosomes were predominantly in *cis* configuration, could predispose the chromosomes to normal disjunction (Moses *et al*. 1979; Davisson *et al*. 1981).

Considering the wide interspecies variability of the impact of a chromosomal change on gametogenesis, and on the basis of the above discussion, it is postulated that attributes of the meiotic system in a given species could modulate the potential of a chromosomal change as reproductive barrier. According to this model, a CR can exist as a polymorphism without conferring any selective disadvantage to the heterozygote (and thus without contributing to speciation) when attributes of the meiotic system (for example chiasma distribution pattern, efficiency of the synaptic machinery to undergo nonhomologous synapsis, etc.) in the given organism circumvent the potential negative influence of the chromosomal change. Conversely, the fitness reduction effect of some CR could be due to the consequence of the meiotic system's inability to counteract the negative influence of the CR, and the CR can promote establishment of a species barrier if it is driven to homozygous-fixation. This accounts for the contradictory reports published on the effects of similar kinds of CR on reproductive fitness in different species.

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