

Hundred years of research on inversion polymorphism in *Drosophila*

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Paracentric inversions are widespread in the genus *Drosophila*. Naturally occurring chromosome inversions were detected very early indirectly as far as genetics history is concerned. Sturtevant in 1917 found that in certain strains of *D. melanogaster* reduced recombination was due to inversions in order of genes in chromosomes, a proposal which was subsequently verified by him in 1926 and 1931 based on the data of genetic mapping. The physical reality of chromosomal inversions was confirmed with the discovery of giant salivary gland chromosomes in *Drosophila* by Painter in 1933. From which the gene order could be known from the banding pattern. Since the initial work of Sturtevant in 1917 on inversions in *Drosophila*, hundred years have lapsed and chromosomal polymorphism due to inversions in a large number of species of the genus *Drosophila* has been extensively studied by using polytene chromosome maps. About one hundred species of *Drosophila* have been found to be chromosomally polymorphic. Hundred years of research on inversion polymorphism in *Drosophila* have revealed that inversions in *Drosophila* are important from view point of population and evolutionary studies. This review briefly summarizes the important findings pertaining to the research of hundred years on inversion polymorphism in different species of *Drosophila*.

Keywords: *Drosophila*, genetic coadaptation, inversion polymorphism, population dynamics.

In chromosomes, structural and numerical changes are known to occur widely in plant and animal species, including humans¹. Chromosome arrangements have significant role in the process of speciation in various types of population². Among different types of numerical alterations in chromosomes, polyploidy which is common in plants has played a significant role in speciation and many species of plants have evolved due to the occurrence of polyploidy³. In structural changes in chromosomes, inversions and translocations are known to occur in many cases, and have been studied with particular reference to genetics, cytogenetics and evolution¹. The occurrence of paracentric inversions in *Drosophila*, pericentric inversions in grasshoppers and crickets, and translocations in *Oenothera* is noteworthy. Translocation heterozygotes in *Oenothera lamarckiana* were used as a

basis of mutation theory of evolution by de Vries⁴. Detailed study on pericentric inversions has been conducted in grasshoppers from Australia and their significance has been discussed from the evolutionary point of view³. Paracentric inversions are of common occurrence in *Drosophila* and have been extensively studied. However, there are reports about translocation and pericentric inversions in *Drosophila*, but these are rare⁵⁻⁷. Inversions in *Drosophila melanogaster* were initially detected quite early in the genetics history⁸. Sturtevant⁹ found that in certain strains of *D. melanogaster*, reduced recombination in chromosomes was due to inversions in the order of genes on a chromosome, a proposal which was experimentally verified by him in 1926 (ref. 10) and 1931 (ref. 11) with the help of genetic mapping data. Dicentric and acentric fragments produced due to crossing-over within the paracentric inversion in a heterozygote are eliminated through polar bodies in females, and the egg receives only a normal non-recombinant chromatid¹². Thus recombinants are not observed. The gametes produced by single crossover event between the breakpoints would never be recovered in progeny. As a consequence, inversions are inherited intact as a single Mendelian unit. In population genetics studies, various gene arrangements are treated as alleles at a single locus. Furthermore, crossing-over may be strongly suppressed within the inversion in heterozygotes. *Drosophila* is characterized by the absence of crossing-over in males. Thus, fertility is not lowered by paracentric inversions. Because of these reasons, paracentric inversions are cytologically neutral. The giant polytene chromosomes in *Drosophila* were detected and chromosome maps were constructed on the basis of banding pattern in *D. melanogaster* for the first time¹³⁻¹⁷. Subsequently, cytological chromosome maps were constructed in a number of species which helped to detect a large number of inversions. From that time, population genetics studies on inversion polymorphism were initiated in various species of *Drosophila*. It has been reported that numerous *Drosophila* species show polymorphism for naturally occurring inversions, but there are monomorphic species also not showing the presence of inversion polymorphism⁸. A large number of species of the genus *Drosophila* have been employed to study population dynamics of inversion polymorphism in detail. These are: *D. pseudoobscura*, *D. persimilis*, *D. willistoni*, *D. robusta*, *D. subobscura*, *D. melanogaster*, *D. ananassae*,

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D. funebris, *D. pavani*, *D. rubida*, *D. nasuta*, *D. flavopilosa*, *D. azteca*, *D. hydei*, *D. buzzatii*, *D. buscki*, *D. immigrans*, *D. mercaturum*, *D. nebulosa*, *D. paulistorm*, *D. bipectinata*, *D. guaramunu*, *D. prosaltans*, *D. athabasca*, *D. algonquin*, *D. virilis*, *D. repleta*, etc. If one surveys the literature in respect of inversion polymorphism in these species of *Drosophila*, one fact is evident that there is much variation in the pattern of inversion polymorphism in different species of the genus. Interestingly, sometimes very closely related species have been found to differ in the degree of inversion polymorphism with respect to both, intra and interspecific variations. At the same time, certain species which were studied for chromosomal variability were found to be almost monomorphic¹⁸. Based on his extensive studies in natural populations of *D. pseudoobscura*, Dobzhansky¹⁹ was the first to demonstrate that inversion polymorphism is subject to natural selection. While extending his work in *D. pseudoobscura*, Dobzhansky showed that inversions play an important role in adaptation of populations to varying environments. Further, he also demonstrated that polymorphism is balanced due to adaptive superiority of inversion heterozygotes, and different gene arrangements of the same chromosome are mutually adjusted or coadapted due to action of natural selection in a population and that inversions show seasonal variation in their frequencies²⁰. Random genetic drift may also cause changes in gene arrangement frequencies in populations. Dobzhansky *et al.*²¹ and Da Cunha and Dobzhansky²² also suggested the ecological niche hypothesis which states that inversion polymorphism in *Drosophila* is a device to cope with the diversity of the environment. Further, Carson²³ has shown the differences between central and marginal populations of *D. robusta* while comparing the degree of chromosomal variability. Inversions also affect crossing-over, which has been studied cytologically and genetically. Recombination may be affected by inversions of the same chromosome and also of different chromosomes. Inversions of the same chromosome often occur in non-random associations^{24,25}. It has also been shown that chromosome inversions may have partial behavioural basis and may affect various fitness traits^{26,27}. Research on inversion polymorphism is still being pursued in different species, and it has also been correlated with molecular data with particular reference to allozyme and DNA polymorphisms^{28,29}. In this article, the research on inversion polymorphism in *Drosophila* conducted during the last 100 years is discussed, which shows that chromosome inversions in the genus are important from the viewpoint of population genetics and evolutionary studies.

Population dynamics of inversion polymorphism in natural populations of different species

Paracentric inversions may be of different types – independent, overlapping and included, which have been

reported in different species. *D. pseudoobscura* and *D. persimilis*, a pair of sibling species are unique in the sense that a large number of overlapping inversions have been detected in them, which have been used for different kinds of studies: population differentiation, seasonal changes, heterosis, balanced polymorphism, genetic coadaptation, role of natural selection, genetic drift and inversion phylogeny. Dobzhansky¹⁹ conducted extensive studies on inversion polymorphism in *D. pseudoobscura*, and found that inversion frequencies showed annual cyclic changes (also inversion clines), thus demonstrating adaptive function of inversion polymorphism. This was the first demonstration of the significant role of selection in maintaining chromosomal polymorphism due to paracentric inversions in *Drosophila* natural populations¹⁹. Inversion polymorphism has been studied in both the sibling species, but data are more extensive in *D. pseudoobscura* than in *D. persimilis*. Further, *D. pseudoobscura* is chromosomally more polymorphic than *D. persimilis*³⁰.

Dobzhansky *et al.*²¹, and Da Cunha and Dobzhansky²² studied inversion polymorphism in four sibling species of the *willistoni* group in Brazil: *D. willistoni*, *D. paulistorum*, *D. tropicalis* and *D. equinoxialis*. There were intra- and interspecific variations in the level of inversion polymorphism. Mean number of heterozygous inversions showed good correspondence with environmental heterogeneity in *Drosophila* populations. Marginal populations showed a lower degree of inversion polymorphism than those in the centre of geographical distribution. On the basis of these results, Dobzhansky and co-workers suggested the ecological niche hypothesis which states that inversion polymorphism is a method to adapt with environmental diversity. The inversion frequencies have also been compared between rural and urban populations in certain species. Interestingly, the inversion frequencies are lower in rural as populations as compared to urban populations in *D. funebris*, which is correlated with ecological opportunities available to the species³¹.

The geographical patterns of inversion frequencies have been studied in detail in *D. robusta*^{23,32,33}. Carson²³ compared the degree of inversion polymorphism between central and marginal populations of *D. robusta* by measuring the amount of chromosomal variability by an index of free recombination (IFR – how much of euchromatin is free to undergo recombination). Polymorphism was lower in marginal populations (high IFR) than the central ones (low IFR). IFR decreased from 99.7% in marginal populations to 67% in geographically central populations. Carson²³ suggested that the amount of crossing-over is an essential adaptive factor and that the low level of chromosomal polymorphism in marginal populations where homoselection (selection favouring homozygotes) predominates, gives a high potential for free recombination from which adaptive novelties are synthesized. However, in geographically central populations, there is a high level of chromosomal variability and

heteroselection (selection favouring heterozygotes) predominates. Thus marginal populations have more adaptability and the central populations have more adaptedness²³. Levitan³² has reviewed the literature, and found the north–south and east–west clines in inversion frequencies in natural populations of *D. robusta*.

Chromosomal polymorphism due to paracentric inversions has been studied in detail in *D. subobscura*, an Old World counterpart in certain ways to *D. pseudoobscura* by European researchers^{6,34–37}. In this species, five acrocentric chromosomes are designated by vowels – A, E, I, O and U; A is the X chromosome and J is often substituted for I. Paracentric inversions are known to occur in all the chromosomes. This species is highly polymorphic; more than 50 paracentric inversions are known in the species and there are interpopulation variations in the inversion frequencies^{6,8,36}. There are clines in the inversion frequencies, but they show variations for different inversions. Most likely selection is related to latitudes. Interestingly, later on this Old World species was found in Chile, Argentina and USA^{36,38–40}. From the data on inversion frequencies, it was suggested that the source of North American invasion was South America. The invasion of New World by a *Drosophila* species of the Old World has been called ‘a grand experiment in evolution’ by Ayala *et al.*³⁹. From the results, it is apparent that latitudinal gradients found in the Old World populations have been established in the populations of South America in the exactly reverse order⁴⁰. Thus these results clearly demonstrate that selection related to latitude is operating to maintain the inversion frequencies in natural populations of *D. subobscura*.

D. melanogaster is a cosmopolitan and domestic species. It was used in genetic studies for the first time in 1909 by Thomas Hunt Morgan, who proposed the theory of linkage and discovered spontaneous *white-eyed* sex-linked recessive mutation in this species for the first time. It has been extensively used as the best biological model for various kinds of studies in genetics, cytogenetics, population genetics, behaviour, ecology, evolution, molecular biology, etc. Inversion polymorphism in this species has been extensively studied by numerous researchers at the global level and has been found to be highly polymorphic chromosomally. Among all the species studied, it shows the highest degree of chromosomal polymorphism as it contains more than 300 paracentric inversions^{41–54}. Naturally occurring inversions in *D. melanogaster* have been classified into four types: common cosmopolitans, rare cosmopolitans, recurrent endemics and unique endemics^{43,49,55}. Inversion polymorphism has also been studied in Indian populations of *D. melanogaster* and 42 inversions have been detected⁴⁹. There is geographic differentiation in the frequencies of four common cosmopolitan inversions at the global level, and inversion frequencies have been correlated with environmental conditions and ecological niches which change

with latitude. Thus latitudinal clines are found in the inversion frequencies in both the northern and southern hemisphere^{43,45–48,50,52–54,56,57}. Thus extensive studies in this cosmopolitan and domestic species have clearly demonstrated that inversion polymorphism is adaptively important, even though species differs from other cosmopolitan and domestic species in this respect^{6,28,53,58}.

D. ananassae is a cosmopolitan and domestic species, but it is mainly circumtropical in distribution. It is of common occurrence in India. It is a genetically unique species characterized by several unusual genetic features^{59–61}. The most unusual genetic feature of this species is the presence of spontaneous male recombination which is meiotic in origin⁶². Chromosomal polymorphism in this species has been studied in detail^{63–73}. Chromosomally, it is highly polymorphic: 78 paracentric inversions, 21 pericentric inversions and 48 translocations have been reported so far⁶⁰. In this species, numerous paracentric inversions are known, but only three paracentric inversions: AL (alpha) in 2L (In(2L)A or subterminal), DE (delta) in 3L (In(3L)A or terminal) and ET (eta) in 3R (In(3R)A or basal) are considered as cosmopolitan inversions and are co-extensive with the species considering the monophyletic origin of these inversions. Singh⁶⁴ detected these three cosmopolitan inversions from different localities in India, including the Andaman and Nicobar Islands and showed the geographic distribution of these inversions at the global level. Population genetics of three cosmopolitan inversions in Indian populations of *D. ananassae* has been extensively studied by Singh and co-workers^{65–67,71}. The results provide evidence that the inversion frequencies vary in Indian natural populations of *D. ananassae*. The level of evolutionary divergence has been quantified by calculating genetic distance (*D*) and genetic identity (*I*), which have demonstrated that Indian populations show considerable degree of genetic divergence at the level of inversion polymorphism. Further, in general, the South Indian populations show greater level of divergence compared to those from the North^{67,70–72,74–76}. Interestingly, the populations from Kerala, and Andaman and Nicobar Islands show greater level of similarity. The level of heterozygosity also varies in different populations. There is a strong genetic differentiation and minimal gene flow in this cosmopolitan and domestic species between populations, which extends evidence that Indian populations of *D. ananassae* show strong sub-structuring associated with inversions⁷⁷. Reddy and Krishnamurthy⁷⁸ reported significant differences in the frequencies of inversion heterozygotes in Nilgiri range in South India; the frequencies were different at different altitudes. Interestingly, an inversion within the subterminal inversion was reported in a laboratory stock of *D. ananassae* obtained from Kuala Lumpur, Malaysia (Figure 1)⁷⁹.

Further, it has also been reported that in *D. ananassae*, body size is controlled by polygenes and inversion

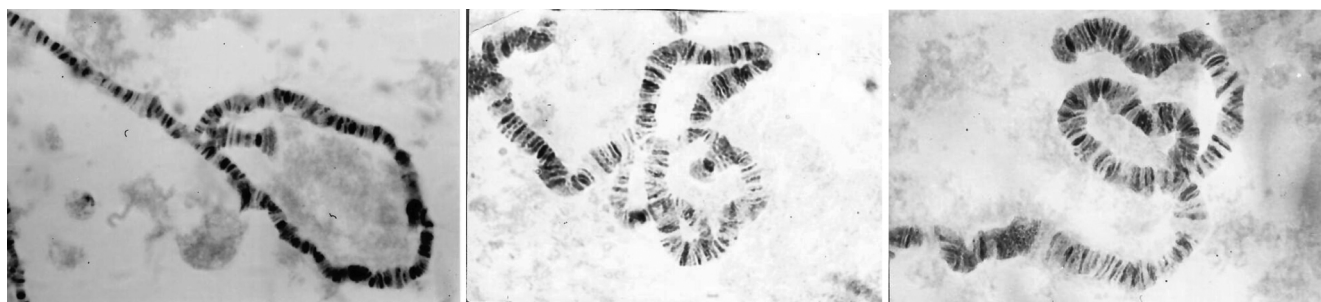


Figure 1. Photomicrographs of heterozygous inversions detected in a laboratory stock of *Drosophila ananassae*⁷⁹.

polymorphism is important in the maintenance of body size which is caused due to modification in the frequency of genotypes under different regimes of selection⁸⁰. The three cosmopolitan inversions in *D. ananassae* could spread and become established in worldwide populations because of heterotic combinations of genes occurring within the inverted segments, and they have become a part of the adaptive machinery in natural populations of this species.

In the *D. bipectinata* species complex, there are four species, viz. *D. bipectinata*, *D. malerkotliana*, *D. parabiptectinata* and *D. pseudoananassae*. Inversion polymorphism has been studied in natural and laboratory populations of all the four species⁸¹⁻⁹³. A large number of paracentric inversions have been reported in these species. Frequencies of inversions do not differ in different geographic populations of *D. bipectinata*, which provides no evidence for geographic differentiation of inversion polymorphism in Indian populations, and suggests that inversion polymorphism is rigid in *D. bipectinata*⁸⁶. In hybridization experiments, inversions have been used to discuss the phylogenetic relationship among the four species of this complex^{81,82,89-92}. In all the studies, one fact is clear that *D. bipectinata*, *D. parabiptectinata* and *D. malerkotliana* are closely related with each other and *D. pseudoananassae* is distantly related to these three species, but other details of their phylogeny do not match with each other⁹². Inversion polymorphism is known to occur in *D. nasuta*, in which there is evidence for geographic differentiation and altitudinal clines in Indian natural populations with respect to inversion polymorphism⁹⁴⁻⁹⁶. Carson⁹⁷ discussed the pattern of chromosomal polymorphism in geographically widespread species of *Drosophila*, and found variation in the pattern of inversion polymorphism in different species. Evidence for rigid inversion polymorphism has been presented in *D. pavani* in which there is homogeneous inversion polymorphism in various natural populations^{98,99}. Seasonal changes in the inversion frequencies have been found in *D. rubida*¹⁰⁰, *D. flavopilosa*¹⁰¹, *D. funebris*¹⁰² and a few other species, which give evidence for flexible inversion polymorphism⁸.

Behaviour of inversions in laboratory populations, heterosis and balanced polymorphism

From the flies collected from nature, laboratory strains are established. In different species, chromosomal analysis of strains was done to identify inversions. These strains were maintained for a large number of generations by transferring the flies to new food bottles in the laboratory. Again they were analysed chromosomally to check the persistence of inversions. Such types of studies have been made in different species. Using homozygous lines for different arrangements, population cage experiments were also conducted in the laboratory. Some examples of such studies are given in this article.

Chromosome inversions persist for many years in laboratory strains in a number of *Drosophila* species. Levene and Dobzhansky¹⁰³ reported that inversions persisted in laboratory populations for many years in *D. pseudoobscura* due to higher Darwinian fitness of inversion heterozygotes. Similar results were also reported by Brncic¹⁰⁴ in *D. pavani*. In *D. pseudoobscura*, population cage experiments were conducted employing various third chromosome gene arrangements, and it was found that polymorphism was balanced due to heterosis, i.e. higher Darwinian fitness of heterozygotes and different gene arrangements were maintained at equilibrium frequencies¹⁰⁵. More or less similar situation was observed in *D. persimilis*¹⁰⁶ and *D. robusta*¹⁰⁷. In *D. pseudoobscura*, random genetic drift and founder effect may cause changes in the frequencies of inversions in laboratory populations¹⁰⁸. In *D. ananassae* also, the adaptive superiority of inversion heterozygotes leads to balanced inversion polymorphism^{109,110}. In *D. ananassae*, three cosmopolitan inversions AL, DE and ET, frequently persist in laboratory stocks due to heterosis exhibited by them¹¹¹. In *D. ananassae*, inversion frequency may change due to random genetic drift¹¹², and laboratory populations established from the naturally impregnated females may diverge to different degrees due to the effect of random genetic drift¹¹³. In *D. melanogaster*, persistence of inversions was observed¹¹⁴. However, when laboratory populations were initiated with naturally impregnated females, a

decline in the frequency of inversions associated with decreasing heterozygosity was observed and some inversions were found to be completely eliminated in certain mass culture populations of *D. melanogaster*¹¹⁵. Different laboratory populations diverged to different degrees due to the effect of genetic drift and founder effect¹¹⁵. Singh and Banerjee¹¹⁶ also found the persistence of inversions in laboratory populations of *D. bipectinata*. When the level of inversion heterozygosity and frequency of inversions in laboratory populations were compared with those in corresponding natural populations, it was found that there was increasing trend in their frequencies and heterozygosity level. This was caused due to adaptive superiority of inversion heterozygotes under strong competition in the laboratory conditions. This clearly demonstrates that in *D. bipectinata*, inversion polymorphism exhibits heterosis¹¹⁶.

Inversions and genetic coadaptation

Using inversion polymorphism in *D. pseudoobscura*, Dobzhansky^{105,117-119} showed that when crosses were made involving strains coming from the same natural populations but having different gene arrangements in chromosomes, heterosis was observed. However, there was breakdown of heterosis in interracial hybridization experiments in *D. pseudoobscura*. A large number of homozygous lines with different chromosome arrangements in the third chromosome of *D. pseudoobscura* were employed by Dobzhansky. The breakdown of heterosis in interstrain crosses was explained by Dobzhansky^{105,117} advocating the hypothesis of genetic coadaptation. According to this concept, 'in each locality the chromosomes with different gene arrangements are coadapted or mutually adjusted to yield highly fit inversion heterozygotes through the process of long continued natural selection. On the other hand, this adaptive superiority of inversion heterozygotes is broken down in interstrain crosses when two different chromosome arrangements are coming from different geographic localities'. Genes are organized in functional gene complexes or supergenes¹²⁰. The supergenes confer higher Darwinian fitness to the genotype. The relative selective values can be assigned to the whole genetic system and evolution depends on gene effects which fit together in a harmonious system¹²¹. Balanced polymorphism and epistatic selection act together to generate polygenic complexes (supergenes), and in this way form a major feature of evolutionary change¹²². Dobzhansky, who suggested genetic coadaptation hypothesis on the basis of experimental results observed in *D. pseudoobscura*, is considered as the main architect of this hypothesis. The concept of genetic coadaptation proposed by Dobzhansky, who is popularly known as the 20th century Darwin¹²³, has received support from experimental results concerning interracial hybridization experiments involving chromosomally

polymorphic strains derived from natural populations in different species of *Drosophila* – *D. willistoni*, *D. paulistorum*, *D. pavani* and *D. bipectinata*^{104,124,125}. Interestingly, in all these species the superiority of inversion heterozygotes is lost in interstrain crosses. It has been suggested that coadapted polygenic complexes contained in the chromosomes are disrupted due to crossing-over in interstrain crosses, which leads to the loss of heterosis. In all the four species, the strains polymorphic for inversions derived from natural populations were used. The inversion frequencies were known in their natural populations, which decreased considerably in interracial hybridization experiments after maintaining the hybrid populations in the laboratory for many generations. In general, it was suggested that interracial hybridization leads to breakdown of heterosis as polygenic complexes are disrupted due to crossing-over. Thus superiority of heterozygotes is determined by polygenic complexes which these chromosomes contain, and it is not the necessary consequence of being heterozygous for inversions. Thus, inversions are important to protect the integrity of mutually adjusted polygenic complexes in the chromosomes through the suppression of crossing-over between chromosomes¹²⁴. Natural selection can maintain mutually adjusted polygenic complexes in *D. subobscura*, which is suggested on the basis of extensive genetic differentiation between different gene arrangements of the O chromosome³⁷. Although evidence in favour of genetic coadaptation hypothesis has been presented in some species, there are some exceptions to this concept. Kumar and Gupta¹²⁶ did not find support in favour of coadaptation hypothesis in natural populations of *D. nasuta*, as there was no breakdown of heterosis in interstrain crosses. *D. ananassae* is a genetically unique species⁶². Singh⁷⁰ studied extensively chromosomal polymorphism in a large number of Indian populations of *D. ananassae*, and presented evidence for genetic divergence at the level of chromosomal polymorphism. The concept of genetic coadaptation proposed by Dobzhansky was tested in *D. ananassae* by Singh¹²⁷⁻¹³⁰, who conducted experiments by making different types of crosses using homozygous and chromosomally polymorphic strains. In all the interstrain crosses, there was no breakdown of heterosis. In almost all the crosses, there was persistence of heterosis even though strains from geographically distant localities were used in interstrain crosses. These results clearly demonstrated that the findings in *D. ananassae* did not agree with those of Dobzhansky and other researchers in different species of *Drosophila*. Thus, there is no evidence of coadaptation in natural populations of *D. ananassae*. Thus, there is superiority of heterozygotes in *D. ananassae* without previous selectional coadaptation and luxuriance is important in this species¹³⁰. It has been suggested by Singh¹³⁰ that the role of luxuriance is important in *D. ananassae* and coadaptation of chromosomes does not play any role because heterosis persists in interstrain

crosses. Thus for the organisms to adjust with the environment, luxuriance plays a crucial role^{130,131}. Evidence in support of the coadaptation concept has also been provided using molecular data. According to Schaeffer *et al.*¹³², coadaptation hypothesis has been supported by data with respect to *D. pseudoobscura* third chromosome molecular markers and diversity of nucleotide, and there is the role of epistatic selection. Studies by Hoffmann *et al.*¹³³ provided evidence that patterns of linkage disequilibrium and variations were consistent with coadapted polygenic complexes and inversions were considered as a dynamic system. It has also been emphasized by them that inversions associated with disequilibrium among loci have the potential to lock up mutually adjusted or coadapted alleles. In a number of species of *Drosophila*, studies have been reported on linkage disequilibrium between inversions, and also between inversions and allozyme loci which are important to determine the extent of coadaptation. Thus importance of interaction of genes in evolution is related to coadaptation^{134,135}. By studying inversion polymorphism and genetic load in *D. subobscura*, evidence for genetic coadaptation has been provided¹³⁶. The linkage disequilibrium inside the inversion and pattern of diversity lend support for coadaptation in *D. melanogaster*¹³⁷. It has also been demonstrated that in *D. pseudoobscura*, the chromosomal rearrangement captures a set of genes with different expression levels, which suggests that selection of gene arrangements is important because gene expression is a potential target for it¹³⁸. The coadapted genome for parthenogenesis is known in *D. mercatorum*¹³⁹.

Effects of heterozygous inversions on recombination

Inversions in *D. melanogaster* were discovered for the first time through their suppressive effects on recombination^{9–11}. In *D. melanogaster*, females show recombination but males do not. When a large number of markers became available, genetic maps were constructed for different chromosomes^{140,141}. In different species of *Drosophila*, inversions have been used to test their effects on recombination. Both types of studies were conducted: using genetic markers and inversions as well as using inversions as markers in cytological studies. Inversions are of two types: paracentric (not including the centromere) and pericentric (including the centromere). Duplications and deficiencies are produced when a single crossover occurs in a heterozygote within the pericentric inversion. However, dicentric and acentric fragments are produced when crossing-over occurs in a heterozygote within paracentric inversion. These are eliminated through polar bodies in females and therefore recombinants are not observed. Further, crossing-over may be strongly suppressed in a heterozygote within the inversion. Hete-

rozygous inversions also affect crossing-over outside the inverted area, but different situations have been observed. Inversion heterozygosity prevents recombination not only in the inverted section of the chromosome itself, but also along the rest of the chromosome in *D. pseudoobscura*¹⁴². Sturtevant and Beadle¹⁴³ observed a similar situation for some X-chromosome inversions in *D. melanogaster*. On the other hand, inversion heterozygosity in one arm increases recombination frequency in the opposite arm in *D. melanogaster*^{144,145}. An increase in the frequency of crossing-over in the X-chromosome of *D. melanogaster* bearing heterozygous inversions was observed by Grell¹⁴⁶. Komai and Takaku^{147,148} observed that X-chromosome inversions in heterozygous condition had enhancing effects on recombination in the autosomes and also in the terminal regions of the X-chromosome itself. Thus heterozygous inversions of one chromosome strongly enhance the rate of crossing-over in non-homologous chromosomes^{149–151}. It has also been observed that when inversions are larger in size, there will be further increase in the frequency of crossing-over in other chromosomes¹⁵². Lucchesi¹⁵¹ has reviewed this phenomenon, and different theories have been suggested to explain how inversions of different chromosomes influence recombination in *Drosophila*.

Heterozygous inversions influence recombination in *D. ananassae* and both types of effects, viz. intra- and interchromosomal have been found in this species^{153,154}. The species is also characterized by male recombination⁶² that is affected by heterozygous inversions, which provides evidence that in *D. ananassae* males crossing-over occurs during meiosis¹⁵⁵. Crossing-over between linked inversions of the same chromosome has also been studied cytologically in certain species, and the results vary between the species and also between the chromosomes of the same species^{24,156–160}. In *D. ananassae*, crossing-over is strongly suppressed between linked inversions of the same chromosome, and distance of chromosome and frequency of crossing-over have no correlation, which is considered as an advantage for species having low degree of heterozygosity of inversion in populations¹⁶⁰. However, in *D. willistoni* recombination occurs at high frequency between inversions of the same chromosome, which has relation with highly developed adaptive inversion polymorphism¹⁵⁶.

Non-random associations of linked inversions

Inversions occurring on the same chromosome have been found to show non-random associations. Levitan¹⁶¹ was the first to report that linked inversions in *D. robusta* occur in non-random associations. The phenomenon of non-random associations of inversions is important from the evolutionary point of view, and known to occur in a large number of species in natural and laboratory

populations^{24,25,32}. This phenomenon has been reported in *D. robusta*, *D. ananassae*, *D. bipectinata*, *D. pavani*, *D. subobscura*, *D. guaranunu*, *D. melanogaster*, *D. rubida*, *D. nasuta*, *D. silvestris*, etc.²⁵. Levitan²⁴ pointed out that two main factors, viz. suppression of recombination between inversions and selection operating against recombinant arrangements play an important role for the maintenance of linkage disequilibrium between inversions in different *Drosophila* species. It has also been suggested that the main factor is natural selection because complete suppression of recombination does not occur if there is a free area available between the inversions. This suggestion of Levitan has received support from different studies in various species of *Drosophila*. It is interesting to mention that in *D. subobscura*, the role of both factors has been suggested. Sperlich and Feuerbach-Mravlag¹⁵⁷ found that non-random associations between two autosomal inversions are due to the absence of recombination. However, selection involving epistatic interaction is important in the case of sex-chromosome inversions. According to these researchers, the chromosome is considered as a functional and selectional unit because natural selection is important in the maintenance of favourable linkages between arrangements. Selection of genes interacting to maximize adaptive fitness results from mutual adjustment of favourable linkages between inversions of the same chromosome¹³⁵. When there is evidence for genetic coadaptation, it also extends support for the evolutionary role of genetic interaction¹³⁴. When non-random association is present, it is mainly attributed to differential selection involving multilocus interaction. Hedrick¹⁶² has suggested that besides selection, there are other factors which can generate linkage disequilibrium and these are tight linkage, genetic drift, migration, gene flow and genetic hitchhiking. Singh and Singh¹⁶³ have reported that in *D. ananassae*, non-random association between two inversions of the third chromosome is caused by random genetic drift, and strong suppression of crossing-over between delta and eta inversions increases the probability of random genetic drift (founder effect).

Behavioural basis of inversion polymorphism

Inversion polymorphism in *Drosophila* has been correlated with certain adaptive traits. The different fitness traits are: survival, rate of development, longevity, competitive ability, fecundity, fertility, mating success, etc.⁶. Among these traits, association between mating propensity and inversion karyotypes is important. It was shown for the first time that mating propensity is associated with chromosomal polymorphism in *D. persimilis*¹⁶⁴. Subsequently, a similar phenomenon was demonstrated in *D. pseudoobscura*, *D. persimilis*, *D. pavani*, *D. subobscura* and *D. robusta*¹⁶⁵⁻¹⁶⁸. Ehrman^{169,170} observed mating advantage of rare gene arrangements in certain species.

Interaction between certain chromosome arrangements affects mating speed in *D. robusta*¹⁷¹. There is association between rare male mating advantage and inversion karyotypes in *D. ananassae*¹⁷². Singh and Chatterjee^{173,174} studied mating ability of different inversion karyotypes derived from various populations of *D. ananassae*. Heterosis was observed with respect to male mating ability, but there was no variation for females. Further, it was found that chromosomes occurring in high frequency in natural populations were associated with greater mating success in *D. ananassae*. These results suggested that there is a partial behavioural basis of inversion polymorphism in *D. ananassae* and in comparison to females, males show more variation and thus subject to greater intrasexual selection than females^{173,174}.

Overlapping inversions and phylogeny in certain species

In certain species, there are a number of paracentric inversions which fall under the category of overlapping inversions. These are *D. azteca*, *D. pseudoobscura* and *D. persimilis* which belong to the same species group. In these species, inversion phylogeny has been discussed on the basis of overlapping inversions. In such phylogeny, each sequence differs from the next by a single inversion. Phylogenetic charts of different sequences have been given by Dobzhansky and Sokolov¹⁷⁵ for *D. azteca* and Dobzhansky¹⁰⁵ for *D. pseudoobscura* and *D. persimilis*. Details of these charts may also be found in White¹. In *D. azteca*, seven sequences are known in A-chromosome. *D. pseudoobscura* and *D. persimilis* are closely related sibling species. There are 21 sequences in *D. pseudoobscura* and 11 in *D. persimilis* in the third chromosome¹⁷⁶. The Standard sequence is common in both the sibling species.

Inversion polymorphism in Hawaiian species

About 700 species of the family *Drosophilidae* which are endemic to the Hawaii Islands have been described earlier¹⁷⁷. About 100 species belonging to subgenus *Drosophila* are picture winged species, which have been extensively studied cytologically and from an evolutionary view point. The results of these studies have yielded interesting information pertaining to picture winged species found in the Hawaiian Islands¹⁷⁸⁻¹⁹². Studies have been conducted on inversion polymorphism in these species. The intra- and interspecific inversion polymorphism have been compared and about one-third of species were found to be polymorphic for inversions. Certain unique features of these species are: there are homosequential species having identical banding pattern in polytene chromosomes which occur in clusters: 19 clusters of from 2 to 10 species each. However, these species may be

different from one another morphologically, and physiologically and may be distant with respect to other genetic measures. The feature of pattern of inversion polymorphism in these species is the presence of fixed inversions which are useful in inferring their phylogenetic relationships. It has also been suggested that chromosomal aberrations occur in clusters or bursts, probably due to action of transposable elements as revealed by molecular data. In these species, paracentric inversions are unique and are of monophyletic origin. Another uniqueness of these inversions is that even a short inversion may cover very large number of base pairs in the DNA. Thus inversions permit the monitoring of natural selection, crossing-over and fate in populations of a large genome segment of the species¹⁸³. The chromosome phylogeny based on banding pattern, chromosome breaks and fixed inversions has been discussed in different species subgroups: *D. grimshawi*, *D. hawaiiensis*, *D. glabriapex*, *D. planitibia*, *D. adiostola*, *D. punalua* and *D. primaeva*.

Phylogenetic relationships among different species have also been discussed on the basis of founder events and the pattern of mode of mating preference in which the role of random genetic drift has been suggested^{183,193}. Kaneshiro¹⁷⁷ suggested that the studies on cytogenetics, genetics, ecology, behaviour, morphology, evolution, etc. in these species which are endemic to the Hawaiian Islands resulted in better understanding of these aspects, which was the basis of revising the generic concept of the groups. Later studies concerning phylogeny employing modern tools in the area of molecular biology have proved the monophyletic relationships among species of this group. It has also been suggested that the Hawaiian *Drosophila* is an evolutionary model clade, and it provides a prospectus for future studies in this direction on microbial interactions and genomics¹⁹¹. It has also been suggested that most groups and subgroups within this clade are monophyletic^{192,194}.

Chromosome inversions, allozyme and DNA polymorphisms

Although inversion polymorphism has been studied in detail in different species of *Drosophila*, it is also correlated with molecular data concerning allozyme and DNA polymorphism. Chromosome inversions were detected in *Drosophila* in the beginning of the last century through the suppression of crossing-over^{9,10}. After extensive studies of chromosomal polymorphism due to paracentric inversions in a large number of species, more studies were initiated to reveal genetic polymorphism at the level of proteins and DNA^{195,196}. Lewontin and Hubby¹⁹⁵ made a conceptual breakthrough in the field of molecular population genetics by providing numerical estimates of genic variations in natural populations of *D. pseudoobscura* through the study of allozyme polymorphism. Since then, numerous cases of protein (enzyme) polymorphisms

caused by different alleles of the same locus through the technique of gel electrophoresis have been reported in a large number of *Drosophila* species^{28,197}. Allozyme is the name given to enzymes which differ in electrophoretic mobility caused due to allelic differences of a single gene. Allozyme polymorphism has been extensively studied in *Drosophila*, and results of this analysis in about 50 species have revealed that a large number of loci are polymorphic^{28,197}. Genetic polymorphism at the level of DNA has also been studied in different *Drosophila* species employing various methods. Interesting data have been obtained in nucleotide sequence variations and comparison has been made using these results in different populations of the same species as well as in populations of different species²⁸. Basically, two methods are used to study DNA polymorphism: RFLP (restriction fragment length polymorphism) which detects restriction sites in DNA with the help of restriction enzymes and separating the restriction fragments using electrophoresis (Southern blot using probe DNA molecule), and DNA sequence variation may be studied using Maxam-Gilbert sequencing method or Sanger dideoxy sequencing method. Different studies in *Drosophila* species have demonstrated nucleotide sequence variation in natural populations^{196,198-201}. Interestingly, there are correlations of molecular data with inversion polymorphism in various species of *Drosophila*, and a few cases are cited here. There are reports demonstrating that linkage disequilibrium may be present between the inversions themselves and allozyme loci included within the inversion in certain cases²⁰²⁻²¹¹. Allozyme loci are frequently found non-randomly associated with chromosomal inversions in which they are included, and there is evidence for the occurrence of seasonal cycles of allozymes within inversions reflecting the operation of natural selection in *D. subobscura*²¹². Inversions are also correlated with molecular markers in certain cases. In *D. pseudoobscura*, the concept of genetic coadaptation is supported by molecular data and nucleotide diversity, where epistatic selection maintains genes along a particular gene arrangement¹³². Kennington *et al.*¹³⁷ reported the pattern of genetic variations and linkage disequilibrium in 24 molecular markers located within In (3R) Payne in *D. melanogaster*, which is indicative of genetic coadaptation. With the help of multiple whole-genome sequence data in *D. pseudoobscura*, *D. persimilis* and *D. miranda*, it has been demonstrated that genetic variation is affected by chromosomal inversions, and reduction of recombination in heterokaryotypes partly facilitates the process of speciation²¹³. Studies on gene expression in *D. pseudoobscura* by Fuller *et al.*¹³⁸ demonstrated that chromosomal rearrangements have captured sets of genes which differ in their expression levels extending evidence that for selection of arrangements of genes, the gene expression is a potential target. The effect of two common cosmopolitan inversions on pattern of transcriptional

variations in *D. melanogaster* has been studied by Lavington and Kern²¹⁴, who found that transcript abundance for hundreds of genes across the genome is affected significantly by each inversion and inversion-affected loci appear both on unlinked chromosomes and also within inversion. There are recent molecular mapping studies which show that there may be linkage disequilibrium between areas within inversions well away from breakpoints with each other, and these areas may contain genes which are under natural selection that cause spread and fixation of inversions in populations²¹⁵. Kennington and Hoffmann²¹⁶ presented molecular data pertaining to microsatellite loci and *Adh* locus within inversion in *D. melanogaster* in different populations from Australia, and found significant differentiation between ST and inverted arrangements in them, which suggest that allelic contents within inversions may vary in different populations. Kapun *et al.*²¹⁷ have shown that selection plays an important role in the increase of inversion frequencies over time with the help of diagnostic molecular data in *D. melanogaster*. They also found the existence of frequency clines for certain inversions in both North America and Australia. Further, data on genomic evidence for adaptive inversion clines have been provided in *D. melanogaster*²¹⁸. The geographic origin and age of inversions in *D. melanogaster* were estimated with the help of population genomic data which demonstrated that inversions had newly arisen and most of them originated in Africa, which is consistent with the demography of the species²¹⁹. It has also been found that the inversions are ubiquitous in *Drosophila*, and suppress and redistribute crossing-over and have specific effect on nucleotide variation which is important for DNA variation level²²⁰. Inversion polymorphisms in the third chromosome of *D. pseudoobscura* were used, and nucleotide diversity of different genetic markers near and away from breakpoints were analysed. It was found that markers within the proximal region of the chromosome had low level of nucleotide diversity than those in the distal region of the chromosome. The level of linkage disequilibrium was greater in the central region of the chromosome compared to proximal and distal regions as in this region there is greater suppression of recombination which does not fully support the idea that genetic exchange is the only factor which influences genetic variation on inverted chromosomes²²¹. Gomez and Hasson²²² analysed the distribution of nucleotide variation among three chromosomal arrangements in *D. buzzatii*, and found that derived arrangements were less polymorphic than the ancestral one and that the widely distributed arrangements are genetically differentiated. Further, with the help of nucleotide variability it was also shown that inversions are unlikely to be long-lived, balanced polymorphisms²²³. In the *D. virilis* group, it has been reported that genomic location of mobile genetic elements shows a statistically significant association with the breakpoints of inver-

sions²²⁴. As suggested by Schlotterer *et al.*²²⁵, the evolve and resequence (E and R) is a new approach to study the genomic responses to selection during experimental evolution. *D. simulans* is chromosomally monomorphic (without segregating inversions) and has a greater level of recombination. Because of these characteristics, it is more suitable to study evolve and resequence which is used to test adaptive response of genetic variations²²⁶.

Origin of inversions

Although the spontaneous origin of inversions in nature is not clear, aberrations may be induced in the laboratory by treating the flies with mutagens, particularly ionizing-radiations. There is a chance that the gene pool of a species may include any aberration originating in nature spontaneously, if it is favoured by natural selection. Certainly, inversions are adaptive because they contain adaptive blocks of genes. It is also not clear how much adaptive effects of chromosome inversion can initiate the origin of inversions. However, two hypotheses have been proposed: postadaptation and preadaptation to throw some light on the origin of inversions. The postadaptation hypothesis is related to position effects and preadaptation hypothesis depends on coadaptation which may already be established even in the absence of inversion. If the genes are tightly linked to each other and selection favours certain combinations of genes, then a stable linkage disequilibria may be established²²⁷. Any inversion which by chance includes such a preadapted groups of genes will become selectively favoured because of its suppression of crossing-over in heterokaryotypes²²⁸. Further, it has also been suggested that certain sites in the chromosome may have specificity for its breakage. Evidences in favour of these suggestions have been provided¹⁰. Although different views are suggested for the origin of inversions, it is not clear how inversions originate spontaneously in nature. Future work may provides a clear picture about this phenomenon. Puerma *et al.*²²⁹ have suggested that additional structural changes occurring at different timescales may in general disrupt inversion breakpoint regions in *D. subobscura*.

Conclusion

In *Drosophila*, about 1500 species have been described. There is a possibility that more species may be described in future. Thus, there is a rich species diversity at the global level⁷⁰. Chromosomal polymorphism due to paracentric inversions has been detected in about a 100 species in their natural populations. Numerous species are chromosomally monomorphic as they do not contain inversions in their natural populations. Different species vary in their pattern of inversion polymorphism. It is well demonstrated that inversion polymorphism is adaptive

and has been considered as a device to adjust with environmental diversity. Sometimes very closely related species may vary in their pattern of inversion polymorphism. There are intra- and interspecific variations in the degree of inversion polymorphism. Inversion polymorphism may be rigid or flexible. Inversions may show geographic, latitudinal, altitudinal and seasonal variations in their frequencies. In certain species, central and marginal populations may vary in their degree of polymorphism. For their adjustment with the environment, even the closely related species might have evolved various mechanisms. Inversion polymorphism has also been studied in laboratory populations, and the results have demonstrated that heterosis is associated with inversions, which leads to balanced polymorphism. While using inversions, different phenomena in the area of population genetics, evolution and behaviour genetics have also been studied. Inversion polymorphism has also been discussed in the Hawaiian species as well as their relation with molecular data with respect to allozyme and DNA polymorphism. There is extensive literature on this topic, but the present author has limited the number of references in this article which summarizes research on chromosome inversions in *Drosophila* during the last 100 years. The work done so far provides extensive evidence for the existence of genetic polymorphism in various species of *Drosophila*, although the degree of polymorphism may vary in different species. The role of different evolutionary forces has also been demonstrated in the maintenance of these polymorphisms. It is hoped that the research in this field will continue in future and data will be provided for understanding the mechanisms of evolution. Genetic polymorphisms may be useful to derive inferences about the functioning of evolutionary processes.

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