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Tandem Duplications in *Drosophila melanogaster* II. Meiotic Pairing and Exchange in Heterozygous Tandem Duplications

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Summary. In heterozygous females of tandem duplication Dp(1;1)Gr,y^2(w^-spl sn^3)(w^c sn^3) the frequency and distribution of exchange events were measured by the phenotypically different F_1 recombinants. In comparison with wild type chromosomes the crossover values were strongly reduced within the heterozygous chromosome sections (between white and singed from 19.5 per cent to 2.1 per cent). Additionally, there was 0.24 per cent intrachromosomal exchange in the same chromosome section after the formation of a double loop (Fig.2). Crossing over was also reduced in both chromosome regions adjacent to the heterozygous duplication. A comparison of the conceivable pairing configurations with those configurations which are indicated by the recombinants gives an initial insight into the pairing behaviour of heterozygous tandem duplications during meiosis. The hypothesis of "polarized pairing" in *Drosophila melanogaster* is disproved by this kind of experiment.

Crossover values within and adjacent to the duplication were also measured in heterozygous tandem duplications differing in the genetic length of their duplicated section. Here, meiotic pairing behaviour was found to depend on the genetic length and other parameters of the duplicated section. Conceivable sources for the different kinds of behaviour are discussed.

Introduction

It is not possible to analyse cytologically the meiotic pairing behaviour of structurally heterozygous chromosomes in *Drosophila melanogaster* because the chromosomes are too small for light microscopic studies. On the other hand, because the number and position of the exchanges are relatively easy to determine by the recombinants of multiple marked chromosomes, there have been repeated attempts to interpret the meiotic pairing behaviour of heterozygous chromosome mutations by crossing over analyses. Numerous detailed studies of this type are already available concerning inversions and translocations (lit. until 1966 in Rieger and Michaelis 1967, as well as Roberts 1965a). Comparable analyses for duplications, particularly tandem duplications, were only partially possible because not all recombination types could be simultaneously analysed, due to the lack of proper marker genes within the duplicated section (Altenburg 1964; Bender 1967; Green 1962, 1968; Judd 1964, 1965; Laughnan and Gabay 1970; Peterson and Laughnan 1963a; Roberts 1965b). The present paper attempts to determine meiotic pairing behaviour in the sections of a heterozygous X chromosome tandem duplication marked by several gene mutations.

Material and Methods

1. In General

Table 1 shows the chromosome markers used in the experiments (acccording to Lindsley and Grell 1967). The stocks were kept on *Drosophila* standard medium at a temperature of 25 ± 1 °C and transferred twice, each time after five days, to fresh medium. Each *Drosophila* stock used in the experiments was cytologically tested before the beginning of the experiments. A detailed description of the tandem duplication Dp(1;1)Gr has been given in Kalisch 1973. The flies, hemizygous for Dp(1;1)Gr, are not viable. The tandem duplication itself shows no phenotypical characteristics distinguishable from the wild type, but the presence of Dp(1;1)Gr in the heterozygous females used was clearly detectable through the combination of the different white and split alleles in both sections of the tandem duplication and in the second female X chromosome. The flies used in the experiments originated from a stock in which the second X was a 'balancer chromosome':

Dp(1;1)Gr,y^2(w^-spl sn^3)(w^c sn^3)/y Hw dl-49 w m^2 g^4 × Hw dl-49 w m^2 g^4/Y.

Positions of the individual marker genes in relation to the limits of the tandem duplication are shown by Fig. 3a.

Dp(1;1)B, Dp(1;1)Bx^{r49k}, Dp(1;1)lz-1: Intrachromosomal recombinants (Fig.2) were phenotypically identified in the stocks through breeding with C(1)DX, y f females. The same breeding procedure was used for the double mutant, Dp(1;1)B + Dp(1;1)Bx^{r49k} described in the text (Table 4D). Details of the composition and the special characteristics of the tandem duplications used, as well as data from duplications repeatedly mentioned in the text for comparison with our results, are to be found in Table 2 and in the literature mentioned there.

Table 1. Synopsis of gene symbols used in text

Symbol	Location Constitution	Phenotype Properties
y (yellow)	X-0.0	body colour yellow, hairs and bristles brown with yellow tips
y^2 (yellow-2)	y-allele	body colour yellow, hairs and bristles black
sc (scute)	X-0.0	0-3 scutellar bristles
Hw = Dp(1;1)Hw (Hairy wing)	X: 1A8-B1; 1B2-3	extra hairs and bristles along wing veins, on head and on thorax
w (white)	X-1.5	white eyes
w^- (white-def.)	w-allele	white eyes; def. of the white locus; viable in males
w^{11E4} (white-11E4)	w-allele	white eyes
w^{bf} (white-buff)	w-allele	eyes light buff
w^c (white-crimson)	w-allele	red eye colour; distinguishable from wild type (Green 1969)
spl (split)	X-3.0	split bristles; rough eyes
ec (echinus)	X-5.5	eye surface rough; facets large
cv (crossveinless)	X-13.7	crossveins absent or only traces present
sn^3 (singed-3)	X-21.0	bristles twisted and shortened
v (vermilion)	X-33.0	eye colour bright scarlet; ocelli colourless
m^2 (miniature-2)	X-36.1	wings less transparent than normal; wing size reduced
g^4 (garnet-4)	X-44.4	eye colour translucent yellowish ruby
f^{36a} (forked-36a)	X-56.7	hairs and bristles extremely crooked
car (carnation)	X-62.5	eye colour dark ruby
dl-49 = ln(1)dl-49 (delta-49)	X: 4D7-E1; 11F2-4	balancer of the X-chromosome; wild phenotype

Table 2. Details of tandem duplications used in experiments and text

Symbol	Constitution	Dupl. bands*	Phenotype
Dp(1;1)Gr [Dupl. of Green]	3A2-3; 8B4-C1	ca. 280	for details see text and Kalisch 1973
Dp(2;2)619	26A; 28E	ca. 123	wild phenotype; Roberts 1966
Dp(1;1)lz-1 [lozenge-1]	8D; 8F	ca. 34	rough eye surface; Bender 1967
$Dp(1;1)Bx^{r49k}$ [Beadex]	17A; 17C	ca. 25	slight scalloping of posterior wing margin: Green 1953 and 1962
Dp(1;1)z-w	3A3-4; 3C1-2	12	wild phenotype; Green 1961
Dp(1;1)B [Bar]	15F9-16A1; 16A7-B1	7	bar-like eyes, rough eye surface; Bridges 1936

* Number of those salivary gland chromosome bands in wild type larvae, which are found twice within the tandem duplications

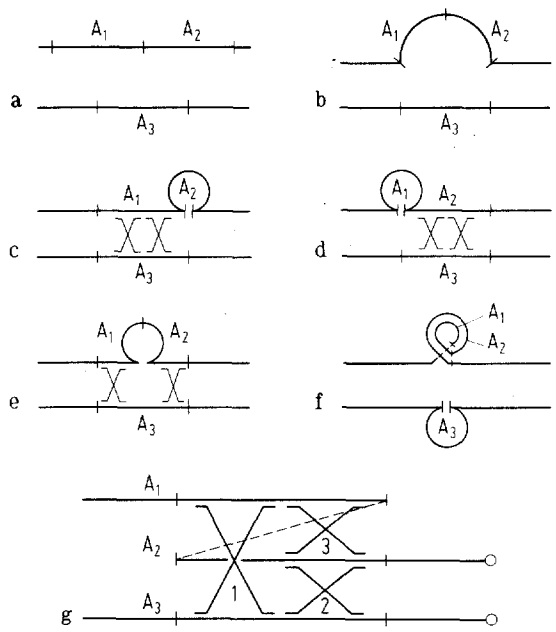

Fig. 1a-g. Possibilities of meiotic pairing and exchange of heterozygous tandem duplications. For details see text

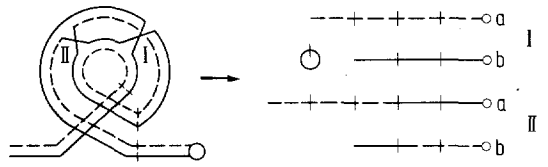

Fig. 2. Possibilities of intrachromosomal exchange within the double loop of a tandem duplication (changed after Peterson and Laughnan 1963). Type I: isochromatid exchange, Type II: unequal sister strand exchange

2. Meiotic Pairing and Exchange Possibilities in Heterozygous Tandem Duplications

From studies in triploid organisms it is known that meiotic pairing can only occur at one point between two of the three chromosomes. One would expect similar behaviour during meiosis in the three homologous chromosome sections A_1, A_2 and A_3 of a heterozygous tandem duplication (Fig. 1a). - Assuming that the pairing of two homologous chromosome sections during meiosis is the necessary condition for a chromatid exchange, then the appearance of the corresponding recombinants, and their frequencies, can serve to indicate a particular pairing figure during meiosis.

It is assumed that, due to the differing lengths of the chromosomes in a heterozygous tandem duplication, meiotic pairing is often omitted. The unpaired region could include only the structurally heterozygous section (schematically illustrated in Fig. 1b) or extend also to neighbouring regions (Fig. 1a). It is conceivable that the difference in length of the chromosomes encourages mis-pairings, i.e. those of nonhomologous sections. Exchange processes with such configurations should lead to recombinants, which carry either a deficiency or a chromosome mutation, deviating from the original tandem duplication. In X chromosome tandem duplications these exceptional flies should, in as far as the males are viable, be phenotypically distinguishable from the rest of the progeny through appropriate marker genes of the three sections A_1 - A_3. - Appropriate marker genes exist when the three sections A_1, A_2 and A_3 carry phenotypically distinguishable alleles of a gene at both ends and when additional markers of different positions occur in the middle portion of the three sections.

The conceptual figures, in which only two of the three homologous sections pair, are represented in Fig. 1. - In Fig. 1f sections A_1 and A_2 are paired in a double loop and A_3 is unpaired.[1] The exchange processes within such a double loop have already been described in several publications (see Peterson and Laughnan 1963a). In Fig. 2 the important aspects of such exchange processes are summarized.[2] In long tandem duplications, such as the present case with Dp(1;1)Gr, it is unlikely that recombinants with a triplication originate through an exchange between sister chromatids of the double loop. This is because the Dp(1;1)Gr chromosome is found more seldom in the egg nucleus than the wild type X chromosome in Dp(1;1)Gr/+ females (Kalisch 1973). A "reduction" of the duplication to a wild type chromosome (Fig. 2, exchange type Ib and IIb) is nonetheless possible in Dp(1;1)Gr.

Further pairing figures, particularly those in which only short portions of A_1, A_2 or A_3 alternately pair with each other, must be considered. - In Fig. 1g A_1, A_2 and A_3 are arranged beneath one another. This is only possible if one imagines that the sectional limit between A_1 and A_2 is stretched to a great extent (dotted line). Although this manner of pairing is not expected during meiosis, it can illustrate the theoretically possible exchange types: exchange type 1 corresponds to the single exchange in Fig. 1c; exchange type 2 fits the single exchange in Fig. 1d; types 1 and 2 demonstrate the possibilities of single and double exchanges in Fig. 1e; type 3 represents the most important exchange type within the double loop (type I in Fig. 2).

Dp(1;1)Gr: Fig. 3a shows the gene markers used in the heterozygous Dp(1;1)Gr females (see also Tables 1 and 2) as well as their positions relative to one another and to the limits of the tandem duplication. Since Dp(1;1)Gr males are not viable, only three recombination types (C_1 - C_3 in Fig. 3b) can arise from the six types in Fig. 1g among the F_1 male progeny.[3] By drawing the three exchange types C_1 - C_3 individually between the gene markers of Fig. 3a, it can be seen to what extent a phenotypic analysis of the individual recombinants is possible for the male progeny.

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[1] Since the exchange processes within a double loop occur between one and the same chromosome, it is necessary to refer to them as intrachromosomal events. In the exchange processes, which occur between A_1, A_2 and A_3 in Fig. 1c-1e interchromosomal events (crossing-overs) are concerned.

[2] Accordingly, if the exchange occurs within a double loop between the distal and the proximal section of the same chromatid (exchange type I: isochromatid exchange) or between a proximal and a distal section of the sister chromatids (exchange type II: unequal sister chromatid exchange), then, in the case of appropriate marker genes, the recombinants in the next generation are in part phenotypically and in part cytologically distinguishable from one another.

[3] Male recombinants of type Ib; Fig. 2 (the acentric ring is lost) and of type IIb; Fig. 2 can be recognized in respect to the exchange type C_3 among the F_1 males. Type Ia is a non-exchange chromatid and type IIa is not viable as an F_1 male.

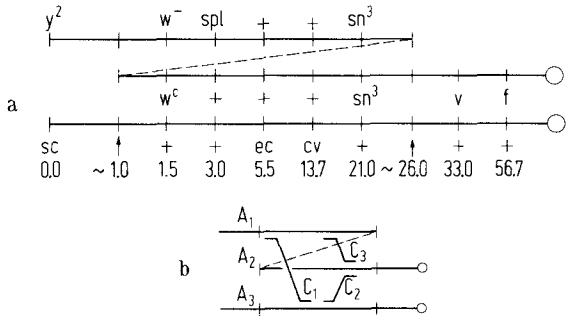

Fig.3. a) Schematic view of the position of marker genes used in the X-chromosomes of heterozygous Dp(1;1)Gr females. Morgan-units under the gene symbols are related to the wild type chromosomes; b) Recombination types among A_1, A_2 and A_3 in heterozygous Dp(1;1)Gr females, which occur within the viable male progeny

Results

1. Exchanges within the Heterozygous Tandem Duplication Dp(1;1)Gr

In each of 365 separate breedings, one virgin female, which carried the tandem duplication Dp(1;1)Gr with the marker genes $y^2(w^-spl\,sn^3)(w^c\,sn^3)$ in the one X chromosome and the marker genes listed in Table 3 in the other X, was crossed with males, which were genotypically $sc\,w^{11E4}spl\,sn^3$. The F_1 progeny was scored and the recombinants of type C_1, C_2 and C_3 (inter- and intrachromosomal exchanges between white and singed: see Fig.3a and b) classified and tabulated. - Table 3 shows the results: (1) Recombinants of type C_3, which originate from intrachromosomal exchanges, occurred significantly less often than those of both interchromosomal types C_1 and C_2, which were found with approximately the same frequency. (2) Because of the marker genes used in the individual experiments of Table 3, intra- and interchromosomal double exchanges should have been phenotypically recognizable with only few exceptions (see Fig.1a-g and Fig.3a and b).[4] However, double exchange recombinants within the heterozygous duplication could not be found among the progeny of the experiments listed in Table 3. (3) The exchange frequency within the heterozygous region of the tandem duplication was markedly less than in a comparable region of wild type chromosomes: Although approximately 19.5 Morgan units exist in wild type chromosomes between white and singed, 2.1 per cent interchromosomal exchange (C_1 and C_2) occurs in this region of the heterozygous tandem duplication. (4) Among the 15269 males of the F_1 progeny in Table 3, 11 (1 : 1388) 'patrocline' males ($sc\,w^{11E4}spl\,sn^3/Y$) were found. These exceptional males were crossed individually with wild type females, and all proved to be sterile. It can be assumed that in these 11 cases the males were XO [frequency of XO males from crosses with wild type females: 1 : 1200 (Bridges 1916)].

Single cultures in the experiments of Table 3 were necessary in order to determine if the flies of recombination type C_3 occur in clusters. The impetus for these studies was provided by the data of Peterson and Laughnan (1963b), Gabay and Laughnan (1970), as well as Kalisch and Becker (1970), which show that the intrachromosomal recombinants in the double loop of a tandem duplication can occur individually, as well as in clusters. Among the 365 crosses tested, one exceptional fly was found in each of 31 crosses and two such flies in each of three further crosses. Their origin can only be explained by an intrachromosomal exchange (recombination type Ib or IIb in Fig.2), on the basis of the marker genes used and the cytological analyses of their salivary gland chromosomes. One can assume that, as far as the origin of the six exceptional flies in the three individual crosses is concerned, independent coincidental events are involved, since the empirical and theoretical sums of squares of relative deviation from the Poisson distribution tally with each other (χ^2emp. = 1.16; p = 20 per cent, χ^2theor. = 4.64). - Scoring of the recomination types C_1 - C_3 and their complementary exchange types (types 1-3 in Fig.1g) is also possible for the F_1 females, but since these recombinants, which arise through multiple exchanges or unequal crossing over, are only partially recognizable among the F_1 females, an analysis of these flies has been omitted in general. In those cases where such analysis was carried out for other reasons, deviations from the results listed in Table 3 could not be found.

All the 37 C_3 recombinants of Table 3 arose from an intrachromosomal exchange within the split-singed region. In comparable experiments (Kalisch, in preparation) the C_3 recombination type occurred significantly less often in the white-split region than would be expected on the basis of the C_3 recombinants found in the split-singed region and the distances between these marker genes in wild type chromosomes. Therefore, it

[4] This refers to double exchanges which originate either through two (interchromosomal) crossing overs or through an inter- and intrachromosomal exchange event. Intrachromosomal double exchange is not visible because the Dp(1;1)Gr chromosome is lethal in males.

Table 3. Exchange frequencies within the heterozygous tandem duplication Dp(1;1)Gr. Females of the P-generation were crossed to sc w^{11E4} spl sn^3 males in 365 single cultures. (Total number of F_1-females: 26523)

Nr.	Genotype of P-♀♀*	Total F_1-♂♂**	F_1-Exceptional males*** C_1 %	C_2 %	C_3 %
1	Dp(1;1)Gr/+	2349	47 (2.0)	34 (1.4)	13 (0.55)
2	Dp(1;1)Gr/w^{bf} cv	4544	33 (0.7)	43 (0.9)	3 (0.07)
3	Dp(1;1)Gr/spl cv f	4610	39 (0.8)	37 (0.8)	6 (0.13)
4	Dp(1;1)Gr/sc ec cv	3766	36 (0.9)	56 (1.5)	15 (0.40)
	Total	15269	155 (1.0)	170 (1.1)	37 (0.24)

* The Dp(1;1)Gr chromosome was always marked by: $y^2(w^-$ spl $sn^3)(w^c sn^3)$

** Among 15269 F_1-♂♂ 11 patrocline males (sc w^{11E4} spl sn^3/Y) were found

*** For the C_1, C_2 and C_3 crossing over types see Figure 3b

must be assumed that meiotic pairing is more strongly disturbed near the limits than in other parts of the double loop. The following finding supports this assumption. The intrachromosomal exchange frequency between the distal end of the tandem duplication and the white locus is measurable in heterozygous Dp(1;1)Gr females. F_1 males, which originate through an exchange of type C_3 between the distal end of the duplication and w^c (Fig. 3a and b), must be viable and should be easily distinguishable from the other recombinants by their white-crimson eye colour. Since this recombination type could not be observed among more than 60000 F_1 males [5], it must be assumed that the distribution of the intrachromosomal exchange processes in the double loop differs from the distribution of the interchromosomal exchange processes in the comparable region of the wild type chromosomes. In contrast, the distribution of the interchromosomal exchange processes within the duplication is similar to that of the wild type X chromosomes. The number of cases observed (Table 3) is, however, too small to allow a definitive statement to be made.

It must be mentioned that the C_3 recombinants, which arise through exchange between singed and the proximal end of the A_2 section, can not always be phenotypically distinguished from the C_1 recombinants within the same chromosome region (experiments No. 1, 2 and 4 in Table 3). In experiment No. 2 in Table 3 the marker gene forked is too far from the proximal end of the A_2 section to exclude the possibility that an additional exchange occurred in this part of the chromosome. For this reason the values for the intrachromosomal exchanges in the experiments of Table 3 may be too high. This does not alter the frequencies of the C_1 and C_2 recombinants tabulated in these experiments, since in this case all exchange types were scored between white and singed.

2. Crossover Frequencies in the Chromosome Regions adjacent to the Heterozygous Tandem Duplication Dp(1;1)Gr

Because of the lack of marker genes in the heterozygous Dp(1;1)Gr flies, the crossover frequency of the adjacent non-duplicated chromosome regions could only be ascertained indirectly. From the following considerations, based partly on the exchange results within heterozygous tandem duplications, the crossover value for the chromosome section between the distal end of the X chromosome (yellow locus) and the distal end of the A_1 section of Dp(1;1)Gr can be 'calculated'. This results in a crossover suppression from 1.0 per cent, or rather 1.39 per cent (see below), in wild type X chromosomes to 0.27 per cent in heterozygous Dp(1;1)Gr flies:

Among 18125 F_1 males of

Dp(1;1)Gr, $y^2(w^-$ spl $sn^3)(w^c sn^3)/+$ x $y^2 w^-/Y$,

49 flies (0.27 per cent) were found which must have arisen through a crossover between y^2 and w^+. In contrast, 24 recombinants (1.39 per cent) occurred in the

[5] On the basis of the intrachromosomal exchange frequency of 37/15269 (Table 3) in the spl - sn region (18.0 Morgan units in the wild type chromosome), one would expect, from the different genetic lengths, an exchange frequency of approximately 4/60000 in the region between the distal end of Dp(1;1)Gr and the white locus (0.5 Morgan units in the wild type chromosome).

control ($y^2w^-/+$ x y^2w^-/Y) among a progeny of 1728 F_1 flies. These 24 recombinants must have originated through a crossing over between yellow and white. From cytological investigations it is known that the distal end of Dp(1;1)Gr is very close to the double band 3A2-3 (Kalisch 1973). The zeste locus (1.0 Morgan unit from the yellow locus in the wild type X chromosome) has the same position cytologically (3A3). Since the genetic distance between white and singed in the wild type chromosome is 36 times as large as the distance between zeste and white, it must be concluded on the basis of the results in Table 3 that the interchromosomal recombinants between zeste and white in heterozygous Dp(1;1)Gr females (equivalent to the recombinants between the distal end of Dp(1;1)Gr and white) are so rare that they can be neglected in this context. For these reasons, the crossover value of 0.27 per cent between yellow and white in the heterozygous Dp(1;1)Gr females corresponds closely to the value between yellow and the distal end of Dp(1; 1)Gr.

The same 'calculation' of the crossover value was made for the chromosome region between the proximal end of Dp(1;1)Gr and the vermilion locus. Since the proximal end of the A_2 section of the duplication can not be correlated with a marker gene as clearly as can the distal end of the A_1 section, an elaboration of these 'calculations' will not be presented. Even though the 'calculations' for this chromosome region also indicate crossing over suppression, it can be excluded that crossing over between the proximal end of Dp(1;1)Gr and vermilion is suppressed with the same strength as in the yellow-zeste region.

Roberts (1966) produced similar results for the tandem duplication Dp(2;2)619. In heterozygous females the crossover frequency between aristaless and dumpy was 0.88 per cent (control in wild type chromosomes: 12.2 per cent) and between black and purple 2.5 per cent (control: 6.0 per cent). Both regions, aristaless-dumpy (distal) and black-purple (proximal), lie outside the duplication limits. Although the length of the Dp(2;2)619 tandem duplication and the distance of the tandem duplication from the centromere differ from the comparable values in Dp(1;1)Gr (see Table 2), and in spite of the fact that the duplications occur in different chromosomes, both show similar behaviour in that the stronger crossover suppression occurs in the distal part of the chromosome.

3. Exchange Events in Heterozygous Tandem Duplications with different Lengths of the Duplicated Section

Analyses of Dp(1;1)Gr and Dp(2;2)619 (Roberts 1966; Table 4C) show that in long[6] heterozygous tandem duplications, exchange events are suppressed within the duplication as well as towards both sides beyond the limits of the duplication[7]. In these two tandem duplications, not only do the number of the duplicated bands and the genetic length of the duplicated sections differ, but also the distances of the marker genes from their appropriate duplication limits and the position of these chromosome mutations in the genome. Therefore, the extent of exchange suppression can not be related to the number of chromosome bands duplicated or to the genetic lengths of the duplicated sections. The results for long heterozygous tandem duplications (Table 4C) seem then to contradict those in short heterozygous tandem duplications, where a comparable suppression of the exchange events is to be found neither within nor outside the sections of the duplications (Table 4A).

Sturtevant (1925) has already shown in a comprehensive study that the crossover frequency between forked and fused in heterozygous Dp(1;1)B females is not decreased compared with the control values for wild type chromosomes. Green (1962) reproduced these results for the fused-Bar region in homozygous and heterozygous Dp(1;1)B flies and also found comparable behaviour in the tandem duplications Dp(1;1)z-w (Table 4A) and Dp(1;1)Bx^{r49k}. He found 0.15 per cent crossover between forked and Dp(1;1)B among 3366 F_1 flies from Dp(1;1)B,f/+ females of the P-generation. However, in the same chromosome region of homozygous Dp(1;1)B females [Dp(1;1)B,f/Dp(1;1)B], he found 0.34 per cent recombinants among 4122 F_1 flies. This analysis proves that the increase in exchange values for short homozygous tandem duplications also arises through additional crossovers outside the duplicated section. Although comparable studies for short heterozygous tandem duplications exist, the corresponding control values are lacking because the duplication itself has always been used as one of the two marker genes in these analyses. For this reason a comparison with the wild type chromosomes is not possible.

It is notable that the crossover values in the short heterozygous tandem duplications of Table 4A are somewhat increased compared with the control in wild type chromosomes. Since the results of the three X chromosomal tandem duplications used confirm this (as shown in Table 4A) and since the number of flies scored is very large, it must be assumed that this increase in crossover values in heterozygous, just as in homozygous tandem duplications (Green 1962) is not coincidental. On the basis of this contrasting behaviour in long and short duplications the crossover frequency in a heterozygous tandem duplication of middle length has been analysed using the tandem duplication Dp(1;1)lz-1 (34 duplicated chromosome bands; Table 2). The results in Table 4B indicate a slight suppression of the crossover values between singed and vermilion. It must be assumed that in heterozygous tandem duplications - depending upon the length of the duplicated section and certainly upon other factors too - the crossover values are altered compared with the control values of wild type chromosomes. The crossover increase is reversed

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[6] The arbitrary classification into long, middle, and short tandem duplications results from the large differences in the number of duplicated bands (Table 2).

[7] Recently Nix (1973) has shown in a study of the 5S RNA genes in *D. melanogaster* that, in heterozygous Dp(2;2)M2 females (56C-D; 59C-D), crossover between the two marker genes nw^D (2-83.0) and Pu^2(2-97.0) is suppressed by about 75 per cent compared with the corresponding values in wild type chromosomes.

Table 4. Exchange frequencies of heterozygous tandem duplications which are different in the length of their duplicated region

Genotype of P-♀♀	Interval	% exchange/interval		Literature
		P-♀♀	Control	
A				
$Dp(1;1)Bx^{r49k}/fcar$	f - car	5.52(N = 4273)	5.1(N = 1834)	-
Dp(1;1)B/fcar	f - car	5.25(N = 1391)	5.1(N = 1834)	-
Dp(1;1)B,ffu/+	f - fu	2.74(N = 7396)	2.65(N = 107376)	Sturtevant 1925
$Dp(1;1)z\text{-}w,y^2w^a/z$	y^2 - w^a	0.92(N = 2166)	0.87(N = 3329)	Green 1962
B				
$Dp(1;1)lz\text{-}1,v/y\,sn^3$	sn^3 - v	10.0(N = 2536)	12.88(N = 2686)	-
C				
$Dp(1;1)Gr,y^2(w^-spl\,sn^3)(w^csn^3)/v$	y^2 - v	7.9(N = 1520)	33.0	Control: Lindsley and Grell 1967
Dp(2;2)619/al dp b pr	dp - b	3.9(N = 3085)	35.2	Roberts 1966; Control: Lindsley and Grell 1967
D				
$Dp(1;1)B + Dp(1;1)Bx^{r49k}/fcar$	f - car	3.09(N = 2586)	5.1(N = 1834)	-

by increasing the duplication length, leading to crossover suppression in long tandem duplications. To what extent this behaviour can be explained on the basis of our current knowledge of meiotic pairing will be discussed in the following.

Discussion

1. Frequency of the Recombination Types and their Relation to the Meiotic Pairing

From analyses of translocations and free duplications Dobzhansky (1931 and 1934) came to the conclusion that the altered crossover values of the chromosome mutations reflect a different meiotic pairing situation within and adjacent to the altered regions of the chromosomes. Dobzhansky put forward the hypothesis that the frequency of the exchange process in the region of a chromosome mutation is conditioned by 'competitive pairing' between the participating chromosomes, which leads to: decreased pairing frequency according to the spatial order of the participating chromosome regions; and consequently, a reduced exchange frequency compared with the wild type chromosomes. This kind of exchange suppression is not limited to translocations and free duplications, since it has also been observed in heterozygous inversions (Beadle and Sturtevant 1935), as well as in heterozygous deficiencies (Lefevre and Moore 1968). The following findings lend additional support to Dobzhansky's hypothesis. In *Drosophila* there is a direct relation between crossover frequency in structurally heterozygous chromosomes and the somatic pairing frequency of the corresponding chromosome regions, the latter being visible in the salivary gland chromosomes. Hoover (1938) was able to prove cytologically that a relationship exists between crossover suppression in heterozygous inversions and the extent of non-pairing between the two homologous, but inverted, chromosome sections in the polytene chromosomes. Such a relationship, between exchange frequency and somatic pairing, could only exist in Dp(1;1)Gr/+ for the 3AB subdivisions[8], and not for the other subdivisions of the duplication (3C-8B) or for the neighbouring regions outside the duplication limits. In more than 300 Dp(1;1)Gr/+ chromosomes, the 3C-8B region was found only twice in an unpaired condition, and only one case of mis-pairing within the region was observed. Accordingly, the tandem duplication seems to be a chromosome mutation type which does not follow the relation between exchange frequency and somatic pairing

[8] The 3AB subdivisions of the proximal duplication section (A_2; Fig. 1) are always unpaired in the squash preparations of the Dp(1;1)Gr/+ larvae, in contrast to both the other 3AB subdivisions which are always found to be paired. An explanation for this behaviour has been given in Kalisch (1973) and in Kalisch and Hägele (1973).

frequency.[9] It seems reasonable to assume that the differences in exchange values between the heterozygous tandem duplication and the wild type chromosomes result from different meiotic pairing situations.

The decreased exchange frequency of Dp(1;1)Gr/+, in comparison with the wild type chromosomes could be caused by frequent omission of pairing of the three homologous chromosome sections or frequent mis-pairing between these sections (non-homologous pairing between two of the three homologous sections of the heterozygous tandem duplication). The three duplicated sections were sufficiently marked and the corresponding recombinants should have been viable in several cases at least. In the experiments of Table 3 recombinants of these types were not found, so that it can be assumed that frequent non-pairing is either the major or the only reason for the reduced exchange frequencies. The crossover values outside the duplicated sections in heterozygous tandem duplications can be explained similarly to those outside heterozygous inversions and translocations.

It is possible - with the multiplicity of marker genes used - that gene combinations may arise which severely limit the viability of their carriers, but preliminary studies have shown that the number and combination of the different gene markers in Table 3 do not cause strong differences in the viability of their carriers. It might be, however, that the relatively large deviations in the exchange frequencies of the individual experiments of Table 3 are partly due to this cause.

After analyses of intralocal duplications in the white locus, Judd (1964) concluded that the pairing of meiotic chromosomes in *Drosophila* must be polarized. Altenburg (1964), however, was able to show that Judd's results could be interpreted as indicating that the stocks used did not carry a tandem duplication but two closely neighbouring duplications, which simulated a polarized pairing.

There are three principal kinds of meiotic pairing. (1) Non-polarized pairing: In this situation the chromosome sections A_1, A_2 and A_3 (Fig. 1) enter into competition, since only two of the three homologous sections can pair during meiosis. The formation of all configurations listed in Fig. 1a-f is possible. (2) Polarized pairing: Meiotic pairing starts from one or both ends of the chromosome simultaneously and continues in a 'zipper-like' fashion the length of the chromosome. In relation to the pairing configurations of Fig. 1, this means that Fig. 1f (double loop formation) could not arise. (3) Non-polarized 'recognition' of individual chromosome sections or bands, followed by polarized pairing between all other chromosome regions: In long tandem duplications this kind of pairing could hardly be distinguished from the type of non-polarized pairing described under (1). In very short tandem duplications this type could hardly be distinguished from the sort of polarized pairing described in (2), since the formation of a double loop is not possible in this type.

The results of the long tandem duplication Dp(1;1)Gr shown in Table 3 demonstrate that: (1) all three exchange types, C_1, C_2 and C_3, were found in the four individual experiments listed there; (2) exchange types C_1 and C_2 were found with approximately equal frequency. Since intrachromosomal recombinants (Peterson and Laughnan, 1963a) were also found in very short tandem duplications, the non-polarized pairing described under (1) can be considered the best explanation for the meiotic pairing in *D. melanogaster*. - In short homozygous X chromosomal duplications and triplications the frequency and distribution of the (interchromosomal) unequal crossing overs within the duplication are determined in addition to the frequency of the C_3 recombinants (Peterson and Laughnan 1963a; Green 1968). The appearance in about equal frequencies of the different complementary recombination types allows the assumption that a preferred pairing direction does not exist in *Drosophila* during meiosis.

2. Frequency of the Exchange Events Depending upon the Length of the Tandem Duplication

An explanation of the differing exchange frequencies in long and short tandem duplications by different hypotheses (Green 1962; Roberts 1966) appears unsatisfactory, especially since we know that there are no additional structural differences among the tandem duplications described. An attempt will, therefore, be made to develop a concept which explains the behaviour of the long and short tandem duplications on a common basis. The considerations based on Dp(1;1)Gr, involving the meiotic pairing possibilities as well as the genetic results of all presently known tandem duplications, will serve as a point of departure. The results in Table 5, and those of comparable experiments (Green 1962), indicate that the meiotic pairing behaviour depends upon the length of the duplicated section not only in heterozygous but also in homozygous tandem duplications. In short tandem duplications the interchromosomal exchange values in the heterozygous and homozygous condition of the duplication (within and outside the limits

[9] A generalization of this somatic pairing behaviour appears to be applicable, in the light of the investigations by Roberts (1966) and Nix (1973), to all heterozygous tandem duplications, in which the duplicated chromosome sections are very long. Comparable studies on short heterozygous tandem duplications, as for example Dp(1;1)B/+, have shown no clear results so far, because of the well known difficulties in such cytological analyses.

of the duplication) are higher than the control values in the wild type chromosomes, the increase being more noticeable in the homozygous than in the heterozygous condition (Green 1962). In tandem duplications of middle length, the exchange values for the named regions are only slightly suppressed compared with the control values for wild type chromosomes. In long tandem duplications they are clearly suppressed. The exchange frequency in long tandem duplications is also higher in the homozygous than in the heterozygous condition (Roberts 1966). There appears to be a direct relation between the meiotic pairing behaviour and the size (cytologically measurable length) of the duplicated sections. On the other hand, the degree of increase or suppression of exchange events in the tandem duplications certainly depends on the genetic length (in the wild type chromosome) of the duplicated section. Finally, the position of the duplication in relation to the chromosome ends and to the centromere must determine the degree of change caused by the chromosome mutation in the appropriate region. The influence of this parameter was clearly proven in heterozygous inversions (Sturtevant and Beadle 1936) and one must assume that the meiotic pairing behaviour of a tandem duplication could similarly be affected. Additionally, those chromosome bands or band groups, which are characterized by high breakage frequency, ectopic pairing and late incorporation of tritiated thymidine and which are distributed all over the chromosomes (Slizynski 1945; Arcos-Terán and Beermann 1968), should have an influence on the exchange values. The influence of these chromosome sections (so-called 'intercalar' heterochromatin) on the exchange frequencies has been shown by the meiotic behaviour of the structurally heterozygous chromosomes in an X chromosomal inversion (Kalisch 1970).

2. a) Increase of Crossing over in Short Tandem Duplications

A satisfactory explanation for the exchange increase in short tandem duplications is only partly possible on our present knowledge of the meiotic exchange processes in general, and the regionally specific unequal distribution of these processes between wild type chromosomes and chromosome mutations in particular. Green (1962) attempted to explain the increased exchange values in short homozygous tandem duplications by Prichard's (1960) 'effective pairing' hypothesis. But there are already difficulties in explaining the meiotic behaviour of short heterozygous tandem duplications by this hypothesis. Roberts (1966) has already demonstrated that the 'effective pairing' hypothesis is not consistent with the meiotic behaviour of long tandem duplications.

The fact that the exchange values are increased in comparison with the wild type chromosomes does not conflict with the explanation since comparable behaviour is also caused by the 'intrachromosomal effect' of different chromosome mutations (Kalisch 1973). In the following it will be assumed that the increased exchange values in short homozygous and heterozygous tandem duplications occur by the 'competitive pairing' already described (Dobzhansky 1931, 1934).

The pairing situation in which the short homozygous and heterozygous tandem duplications are found during meiosis can be compared with the meiotic pairing behaviour of triploids and tetraploids in the following aspects. On the basis of the observed exchange frequencies, it can be assumed that in short tandem duplications the sections of the chromosome mutation are 'recognized' by their homologous partners without difficulty. The three (or four) homologous sections of the heterozygous (or homozygous) tandem duplications should have the same chance of pairing with one of the other sections 'similarly' as in triploid or tetraploid flies. This existing pairing competition could, therefore, be the reason for the comparable change in the crossover frequencies of polyploid stocks and tandem duplications. Analyses of XXX and $\widehat{XX}$ X triploids in *Drosophila* have shown (Bridges and Anderson 1925; Rhoades 1933; Beadle 1934, 1935) that the crossover frequency among the X chromosomes of triploids is higher than that of diploids, if local deviations in the individual chromosome sections are neglected. These results seem to indicate that the crossover frequency in short heterozygous tandem duplications can already be increased on the basis of 'competitive pairing'. - A competitive pairing must also be postulated for short homozygous tandem duplications, and the high values of unequal crossing over in short homozygous tandem duplications (Green 1962) suggest such behaviour. The possibility that the 'synaptonemal complex' of the meiotic chromosomes is visibly altered through this kind of pairing, should be recognized from Moens' (1970) studies on an allotriploid form of *Lilium tigrinum*.

It will be shown that the behaviour of this competitive pairing must be differentiated in short and long tandem duplications. In short tandem duplications the pairing of homologous sections is always possible on the basis of their spatial order, possibly increasing the exchange values.

In long tandem duplications however, the competitive pairing is seldom on the basis of their spatial order and this results in a reduced pairing frequency leading to decreased exchange values between the chromosomes.

2. b) Suppression of Crossing over in long Tandem Duplications

On the 'recognition' of homologous chromosome sections there are three different views, all of which have been discussed in the first chapter of this discussion. The preferred view is that which assumes a simultaneous and non-polarized pairing of the chromosomes. From the results in translocations and free duplications previously mentioned, it is assumed that the spatial distance in which homologous 'subunits' of the chromosomes 'recognize' each other during meiosis must be limited so that pairing difficulties occur with increasing size of the duplicated section in a tandem duplication.

In order to interpret these processes - initially in heterozygous tandem duplications - it seems appropriate to return briefly to the conceptual model in Fig. 1. Through Fig. 1a it is clear that the lateral distance between the homologous duplication sections of the homologous chromosomes (A_3 in contrast to both sections A_1 and A_2) increases with increasing length of the duplication. The same is true for the neighbouring regions to the right and left of the structurally heterozygous chromosome region. Since the tandem duplications mentioned here are relatively short in comparison with the total length of the appropriate chromosome [Dp(1;1)Gr also includes only one quarter of the euchromatic part of the X chromosome], the pairing in the additional regions of the chromosome is either very minimally or not at all influenced by the tandem duplication. Within the tandem duplication as well as outside the duplication in the adjacent chromosome regions, the pairing will be more frequently omitted the greater the spatial distance between the homologous sections. This pairing behaviour naturally does not exclude that either A_1 or A_2 can completely pair with A_3, although admittedly the frequency of such an event is low in long tandem duplications. Although both sections A_1 and A_2 probably compete with one another in order to pair with A_3, it is assumed that this action is inhibited in most cases by the distance from the homologous partner in the homologous chromosome.

In the same way, pairing in the neighbouring regions of the tandem duplication is probably inhibited or suppressed. With increasing distance from the structurally heterozygous region in the chromosomes, these differences should be neutralized. The results in Dp(2;2)619 and Dp(1;1)Gr seem to indicate such pairing behaviour.

A further indication of the correctness of these explanations of exchange suppression in long heterozygous tandem duplications is provided by the results of Dp(1;1)B and Dp(1;1)Bx^{r49k} (Table 4A), as well as by those of the double mutant of both these chromosome mutations (Table 4D). The tandem duplications Dp(1;1)B and Dp(1;1)Bx^{r49k} are too short to cause a measurable exchange suppression in the heterozygous condition, but the double mutant shows such an effect. This probably originates from the meiotic pairing behaviour of the chromosome sections lying between the two tandem duplications. If the meiotic pairing is omitted due to structural heterozygosity in the Bar and Beadex regions, then this middle chromosome section frequently occurs unpaired. Such a pairing configuration should also lead to a suppression of crossover values.

At this point it must be mentioned that several data concerning crossover frequencies in homozygous and heterozygous duplications have been published which appear to contradict the results and explanations discussed above. These cases, however, exclusively concerned analyses of homozygous and heterozygous tandem triplications and tandem quadruplications. These can not be simply compared with tandem duplications because the different meiotic pairing configurations possible in triplications and quadruplications are much greater and therefore more difficult to survey. Nevertheless it can be shown (Kalisch, unpublished data) that the above interpretation of pairing behaviour and exchange events in tandem duplications can also be used in principle to explain the behaviour of triplications and quadruplications.

If one studies the pairing behaviour of long homozygous tandem duplications, further assumptions are necessary to interpret the exchange values. To begin with, there is no structural heterozygosity to explain the pairing difficulties of the heterozygous tandem duplications. In the homozygous condition the pairing difficulties in the adjacent regions of the tandem duplication do not exist and the length of the tandem duplication should hinder asymmetrical pairing of the four duplication sections in long homozygous tandem duplications. The data of Roberts (1966) show that the crossover frequency within long homozygous tandem duplications as well as in their adjacent chromosome regions is reduced in comparison with the wild type chromosomes, although not to the same extent as in the heterozygous condition.

The following pairing configurations could be responsible for the measurable crossover suppression in the long homozygous tandem duplications. If both duplication sec-

Table 5. Frequency of C_3-recombinants in homo- and heterozygous tandem duplications in dependency on the lengths of the duplicated region

Genotype of P-♀♀	Dupl. bands (see also Table 2)	Total number of C_3-recombinants	C_3-recombinants/no. of Dp(1;1)Gr-chromosomes scored	Literature
Dp(1;1)Gr/+	ca. 280	37	1/ 413	Table 3
$Dp(1;1)Bx^{r49k}/Dp(1;1)Bx^{r49k}$	ca. 25	1	1/39553	Green 1968
Dp(1;1)B/Dp(1;1)B	7	2	1/19776	
Dp(1;1)B/Dp(1;1)B	7	6	1/ 9440	Peterson and Laughnan 1963a
Dp(1;1)B/Df263-20	7	3	1/11663	
Dp(1;1)B/ClB	7	2	1/15762	

tions of one of the X chromosomes form a double loop with each other, there will be much stronger interference during meiosis than in the heterozygous condition. In such a configuration the sections of the homologous chromosome are unable to find a partner for the meiotic pairing, so that crossover could be strongly suppressed in the adjacent chromosome regions. If the duplicated section of the homologous chromosome also forms a double loop, then the pairing difficulties outside the tandem duplication do not occur, but for that very reason interchromosomal exchange events within the tandem duplication can not take place. The consequences of possible coincidental asymmetrical pairing (A_1 of one chromosome with A_2 of the homologous chromosome or vice versa) have already been discussed under the short tandem duplications. The smaller crossover suppression in the homozygous condition shows at any rate that the meiotic pairing difficulties of the tandem duplications appear to be markedly decreased in the homozygous condition.

2. c) The Frequency of the Intrachromosomal Exchange Events

Very few data are available for the intrachromosomal exchange frequency in short tandem duplications because it is very difficult or impossible to determine them owing to the lack of multiple marked sections of most of the currently known short tandem duplications. Occasionally in such tandem duplications, in which the presence of the duplication itself causes a phenotypically visible change, as for example Dp(1;1)B and $Dp(1;1)Bx^{r49k}$, the frequency of C_3 recombinants in the homozygous and heterozygous condition could be determined exactly (Table 5). - A comparable analysis in Dp(1;1)Gr is only possible in the heterozygous condition since Dp(1;1)Gr hemizygotes are lethal. In Dp(2;2)619 the necessary marker genes are missing within the duplicated section.

The data on Dp(1;1)Gr demonstrate, in opposition to the results of Green (1968) [10] in Dp(1;1)B and $Dp(1;1)Bx^{r49k}$, that the frequency of the C_3 recombinants must depend, among other factors, on the genetic length of the duplicated section (Table 5). It must be assumed that not only the position of these two duplications in the chromosome, but probably also the existence and distribution of the so-called "ectopic pairing points", whose influence has already been discussed, are responsible for the frequencies of the C_3 recombinants in Dp(1;1)B and $Dp(1;1)Bx^{r49k}$, observed by Green. In the present two cases, both these factors would then cause the intrachromosomal exchange processes to occur without the corresponding frequency in both duplications, in spite of the different genetic lengths of the duplicated sections and their differing numbers of duplicated chromosome bands.

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