Two Types of Sites Required for Meiotic Chromosome Pairing in *Caenorhabditis elegans*

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ABSTRACT

Previous studies have shown that isolated portions of *Caenorhabditis elegans* chromosomes are not equally capable of meiotic exchange. These results led to the proposal that a homolog recognition region (HRR), defined as the region containing those sequences enabling homologous chromosomes to pair and recombine, is localized near one end of each chromosome. Using translocations and duplications we have localized the chromosome *I* HRR to the right end. Whereas the other half of chromosome *I* did not confer any ability for homologs to pair and recombine, deficiencies in this region dominantly suppressed recombination to the middle of the chromosome. These deletions may have disrupted pairing mechanisms that are secondary to and require an HRR. Thus, the processes of pairing and recombination appear to utilize at least two chromosomal elements, the HRR and other pairing sites. For example, terminal sequences from other chromosomes increase the ability of free duplications to recombine with their normal homologs, suggesting that telomere-associated sequences, homologous or nonhomologous, play a role in facilitating meiotic exchange. Recombination can also initiate at internal sites separated from the HRR by chromosome rearrangement, such as deletions of the *unc-54* region of chromosome *I*. When crossing over was suppressed in a region of chromosome *I*, compensatory increases were observed in other regions. Thus, the presence of the HRR enabled recombination to occur but did not determine the distribution of the crossover events. It seems most likely that there are multiple initiation sites for recombination once homolog recognition has been achieved.

MEIOTIC pairing of homologous chromosomes involves the recognition of homologs, resulting in synapsis, recombination, and segregation of chromosomes at meiosis I. The mechanisms that mediate the pairing and synapsis of homologous chromosomes are not fully understood. In some models gene conversion events have been proposed to facilitate homologous pairing of chromosomes early in prophase by detecting DNA sequence identity (SMITHIES and POWERS 1986; POWERS and SMITHIES 1986; CARPENTER 1987; ALANI, PADMORE and KLECKNER 1990; ENGEBRECHT, HIRSCH and ROEDER 1990). Other models propose that DNA sequence identity is not the only basis of homolog pairing and that specific sites promote pairing and recombination, perhaps with the aid of filamentous or fibrillar DNA binding proteins (FABERGE 1942; SYBENGA 1966; COMINGS and RIGGS 1971; BURNHAM *et al.* 1972; HOLLIDAY 1977; HAWLEY 1980; MAGUIRE 1984, 1985; CHANDLEY 1986; GIROUX 1988).

It is becoming clear in the nematode *Caenorhabditis elegans* that there are discrete sites involved in meiotic pairing and recombination (ROSENBLUTH and BAILLIE 1981; ROSE, BAILLIE and CURRAN 1984; MCKIM, HOWELL and ROSE 1988; HERMAN and KARI 1989; ROSENBLUTH, JOHNSEN and BAILLIE 1990). In this organism, translocation heterozygosity causes severe reductions in the frequency of recombination on only one side of the translocation breakpoint [*eT1(III;V)* (ROSENBLUTH and BAILLIE 1981); *mnT2(II;X)* (HERMAN, KARI and HARTMAN 1982); *szT1(I;X)* and *hT1(I;V)* (MCKIM, HOWELL and ROSE 1988)]. Unlike the crossover-suppressed region, the other portion of each translocation recombines with and segregates from the normal homolog, indicating that it contains chromosomal features necessary for meiotic homolog pairing.

Studies with *C. elegans* have also shown that crossing over between homologs is regulated both in the frequency and position of events along the chromosome. For example, there is a "gene cluster" near the center of each autosome, a region where the genes are packed tightly together on the meiotic recombination map (BRENNER 1974). Comparison of the recombination map with the physical map (COULSON *et al.* 1986) demonstrates that the apparent clustering is in part a consequence of decreased recombination frequency per base pair compared to the genome average (GREENWALD *et al.* 1987; PRASAD and BAILLIE 1989; STARR *et al.* 1989). Showing that there are genetic

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controls on the regulation of recombination frequency, the genetic map can be expanded or altered by radiation treatment (KIM and ROSE 1987), a mutation which generally increases the recombination frequency (ROSE and BAILLIE 1979a; RATTRAY and ROSE 1988) and phenotypic sex (ZETKA and ROSE 1990). Recombination frequency is regulated in most organisms where it has been looked at (JONES 1984, 1987; SZAUTER 1984; CARPENTER 1988; GIROUX 1988). For example, the frequency with which crossing over occurs at a given site depends on its chromosomal location (BEADLE 1932; BAKER and CARPENTER 1972; HAWLEY 1980; JONES 1984; LICHTEN, BORTS and HABER 1987; LAMBIE and ROEDER 1988). Regulation of recombination frequency and distribution at least in part reflects its involvement in ensuring disjunction of homologs (DARLINGTON 1937) [reviewed in BAKER *et al.* (1976) and HAWLEY (1988)]. For example, every bivalent has at least one chiasma and the distribution of exchanges on each chromosome and among all the chromosomes is narrower than predicted by the Poisson distribution.

We addressed the regulation of pairing and recombination in *C. elegans* by observing the effect that chromosome rearrangements have on homologous pairing and the distribution of recombination events. ROSE, BAILLIE and CURRAN (1984) initiated meiotic studies on chromosome *I* of *C. elegans* with an analysis of two free duplications, *sDp1(I;f)* and *sDp2(I;f)*. Although the duplications were of similar size, they covered opposite halves of chromosome *I* and their meiotic properties were dramatically different. Only *sDp1(I;f)* paired and recombined with the normal homologs. These authors proposed there were sites on chromosome *I* within the region covered by *sDp1* that enabled the homologs to pair for recombination. From the analysis of two chromosome *I* translocations, MCKIM, HOWELL and ROSE (1988) proposed that a single region at the end of each of the chromosomes was required for pairing and recombination. To further the understanding of the localized chromosome features essential for meiotic pairing and recombination in *C. elegans*, we studied the effects of different types of chromosome rearrangements on meiotic recombination and segregation.

MATERIALS AND METHODS

General: Wild-type and mutant strains of *C. elegans* were maintained on Petri plates containing nematode growth medium (NGM) streaked with *Escherichia coli* OP50 (BRENNER 1974). Unless otherwise noted, experiments were conducted at 20° (ROSE and BAILLIE 1979b). The nomenclature for genes and alleles follows the uniform system adopted for *C. elegans* (HORVITZ *et al.* 1979). Mutations on translocation chromosomes (*T*) are shown in square brackets.

The wild-type strain N2 and some mutant strains of *C. elegans* var. Bristol were obtained from D. L. BAILLIE, Simon Fraser University, Burnaby, Canada, or from the Caenorhabditis Genetics Center at the University of Missouri, Columbia. Map distances (Figure 1) and bibliographic information on the mutations listed below can be found in EDGLEY and RIDDLE (1990).

Visible mutations: I: *dpy-5(e61)*, *dpy-5(h660)*, *bli-3(e767)*, *bli-4(e937)*, *dpy-14(e188)*, *lev-11(x12)*, *unc-11(e47)*, *unc-13(e450)*, *unc-29(e403)*, *unc-29(h1011)*, *unc-40(e271)*, *unc-54(e190)*, *unc-59(e261)*, *unc-63(e384)*, *unc-75(e950)*, *unc-101(m1)*.

III: *dpy-1(e1)*, *dpy-17(e164)*, *dpy-18(e364)*, *dpy-18(h662)*, *unc-32(e189)*, *unc-36(e251)*, *unc-45(e286ts)*, *unc-64(e246)*.

IV: *dpy-13(e184sd)*.

V: *dpy-11(e224)*, *unc-42(e270)*, *unc-60(m35)*.

X: *dpy-3(e27)*, *dpy-7(e88)*, *dpy-7(sc27)*, *dpy-8(e130)*, *lin-15(n309)*, *lon-2(e678)*, *unc-1(e719)*, *unc-3(e151)*, *unc-7(e5)*, *unc-9(e101)*, *unc-20(e112)*.

Lethal mutations on chromosome *I*: *let-360(h96)*, *let-362(h86)*, *let-363(h60)*, *let-365(h129)*, *lin-6(h92)*, *let-201(e1716)*, *let-202(e1720)*, *let-204(e1719)*, *let-208(e1718)*, *lin-6(e1466)* and *sup-11(n403n682)*.

Existing chromosome rearrangements: *Deficiencies: eDf3*, *eDf4*, *eDf6*, *eDf7* and *eDf24* (ANDERSON and BRENNER 1984); *nDf23*, *nDf24* and *nDf25* (FERGUSON and HORVITZ 1985); *mnDf7*, *mnDf11*, *mnDf20*, *mnDf41* and *mnDf43* (MENEELY and HERMAN 1979, 1981); *tDf3* (R. FEICHTINGER, personal communication).

Duplications: mnDp1(I;V) (HERMAN, ALBERTSON and BRENNER 1976); *mnDp25(X;I)* (HERMAN, MADL and KARI 1979); *sDp1* (ROSE, BAILLIE and CURRAN 1984); *sDp30* (ROSENBLUTH *et al.* 1988); *hDp12(I;f)*, *hDp14(I;X)*, *hDp31(I;X;f)*, *hDp39(I;f)*, *hDp51(I;X;f)*, *hDp56(I;X;f)*, *hDp69(I;X;f)* and *hDp70(I;X;f)* (MCKIM and ROSE 1990). Two half translocations are maintained as duplications (MCKIM, HOWELL and ROSE 1988): *hDp133(I;V;f)* (= $hT1\ I = I^R V^L hT1$) and *szDp1(I;X;f)* (= $szT1\ X = I^L X^L szT1$).

Translocations: szT1(I;X)[*lon-2*] (FODOR and DEAK 1985) and *hT1(I;V)* (MCKIM, HOWELL and ROSE 1988).

New chromosome rearrangements: *Translocation hT2(I;III):* This translocation was isolated in a screen for mutations causing pseudolinkage. *bli-4(e937)* males were irradiated with 1500R gamma radiation and crossed to *unc-13(e450)I;dpy-18(e364)III* hermaphrodites and the wild-type hermaphrodite progeny were placed individually on Petri plates. The progeny of the F_1 worms were screened for the presence of Dpy Uncs in the absence of Dpys and Uncs. One wild type (*hT2*), exhibiting pseudolinkage between chromosomes *I* and *III*, was isolated among 1400 F_1 worms examined. The *dpy-5(h660)*, *dpy-18(h662)* and *unc-29(h1011)* mutations were subsequently induced on *hT2[bli-4]* chromosomes using 12 mM EMS in precomplementation screens (ROSENBLUTH, CUDDEFORD and BAILLIE 1983). *unc-54(e190)* was placed onto *hT2* by recombination. *hT2* is homozygous viable.

Structure of hT2: hT2 is composed of two parts (see Figure 2). The first is *hT2 I*, which is defined as the half-translocation which segregates from chromosome *I*. The second is *hT2 III*, which is defined as the half-translocation which segregates from chromosome *III*. Two experiments showed that the structure of *hT2 I* is the *unc-54* end of chromosome *I* linked to the *dpy-17–unc-64* end of chromosome *III*. First, we isolated one of the *hT2* half-translocation chromosomes as a duplication (*hDp134*). *hDp134(I;III;f)* was isolated among rare Dpy-5 progeny recovered from *dpy-5/hT2(I);unc-36/hT2(III)* hermaphrodites. These Dpy-5 progeny were of the genotype *dpy-5;unc-36;hDp134*, indicating *hDp134* carries *unc-36(+)* but not *dpy-5(+)*. Since the half translocation was now present as a duplication, it must have been isolated as the result of nondisjunction between the

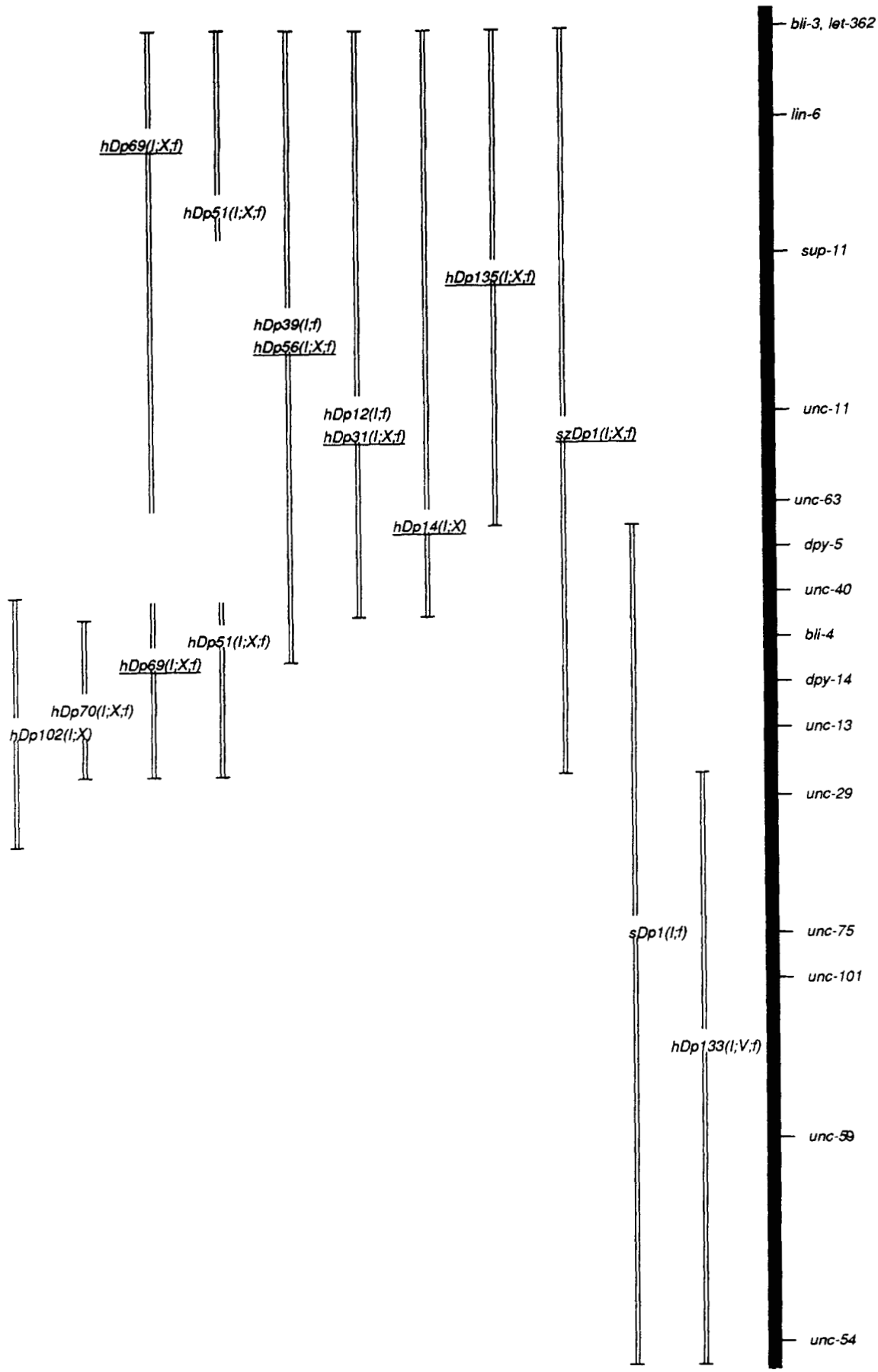

FIGURE 1.—Simplified genetic map of chromosome *I* showing markers and duplications used in this study. For clarity, the "gene cluster" (*unc-11* to *unc-29*) has been expanded approximately twofold relative to the flanking regions. The effect is to make the genetic map more representative of the physical map. The *hDp(I;X;f)* chromosomes also have a component from the *X* chromosome (see Figure 3). Those with a Him phenotype are underlined.

half translocation chromosome and the normal homolog. Further analysis (McKim 1990), showed *hDp134* carries the wild-type alleles of *dpy-17*, *dpy-18* and *unc-64* (see Figure 2).

Second, we determined what part of chromosome *I* is physically linked to the chromosome *III* segment of *hDp134* by using *dpy-18* to mark *hT2* and *unc-54* as the chromosome *I* marker. Linkage between *unc-54* and *dpy-18* was demonstrated by scoring the progeny of homozygous *hT2* hermaphrodites (*hT2[dpy-18 unc-54;bli-4]/hT2[+ +;bli-4]*). The number of Non-Unc Dpy-18s recovered was less than expected for independent segregation, consistent with physical linkage of these markers on one of the translocation chromosomes (19.4 m.u.; Table 1). In contrast, the number of Dpy-18 and Unc-29 progeny recovered from worms homozygous for *hT2* but heterozygous for *dpy-18* and *unc-29* was consistent with independent assortment. There were 538 wild type, 166 Dpy-18, 192 Unc-29 and 76 Dpy Unc progeny, giving close to a 9:3:3:1 ratio. Thus the half-translocation represented by *hDp134(I;III;f)* has the *dpy-17–unc-64* end of chromosome *III* (containing the *dpy-18* locus) attached to the *unc-54* end of chromosome *I* and therefore is the same chromosome as *hT2 I*. The *hT2* breakpoint on chromosome *I* must lie between *unc-29* and *unc-54*. The latter experiment also shows that the *hT2* chromosome containing *unc-29* does not have *dpy-18*. These data show that *dpy-5* and *unc-29* are on *hT2 III*.

Rearrangements isolated in screens for radiation-induced lethal mutations: hT3(I;X), hDp102(I;X), hDf10 and *h904* were isolated in a screen for lethal mutations using *hT2(I;III)* as a balancer (McKim, Howell and Rose 1988; McKim 1990). They were induced on *dpy-5 unc-29* marked chromosomes using 1500 or 3000 R γ-irradiation. *hDp102* was associated with the lethal mutation *h915* but was separable from it. *hDf9*, *h654* and *h655* came from a screen using *szT1(I;X)* as a balancer (McKim, Howell and Rose 1988). All these mutations were mapped by complementation testing with other deficiencies, duplications and genes previously mapped on chromosome *I* (McKim and Rose 1990; McKim 1990).

Structure of hT3: hT3 is composed of two parts (Figure 2). The first is *hT3 I*, which is defined as the half-translocation which segregates from chromosome *I*. The second is *hT3 X*, which is defined as the half-translocation which segregates from the *X* chromosome. The structure of *hT3* was deduced by mapping the breakpoints of the half-translocation *hT3 X*, in the form of the duplication *hDp135(I;X;f)*. *hDp135(I;X;f)* was isolated, as a result of nondisjunction between the half-translocation chromosome and the *X* chromosome, from Dpy-14 progeny recovered from an *unc-11 dpy-14/hT3(I;X)[dpy-5 unc-29]* hermaphrodite. Recombinant Dpy-14 progeny, that is *unc-11 dpy-14/hT3[dpy-5 dpy-14]*, could be identified by observing in their progeny the *hT3* homozygotes, which arrest as visible late larvae. Dpy-14 progeny carrying *hDp135*, that is *unc-11 dpy-14/unc-11 dpy-14;hDp135*, were identified because there were no *hT3* homozygotes in their progeny. Further analysis (McKim 1990) showed *hDp135* carries the wild-type alleles of *bli-3* and *unc-11* on chromosome *I* and *unc-1* and *dpy-7* on the *X* chromosome.

The chromosome *I* breakpoint is between *unc-11* and *dpy-14*. It could not be determined if *hDp135* had the *dpy-5* region because the translocation was induced on a *dpy-5(e61) unc-29(e403)* chromosome. The lethal site associated with *hT3*, (*h916*), was mapped to the left of *dpy-5* and is allelic to *let-363* (Howell *et al.* 1987; McKim 1990). It was, therefore, the putative site of the *hT3* chromosome *I* breakpoint. This was further supported by the fact that *let-363* and the crossover suppression boundary (see RESULTS) each mapped between *unc-63* and *dpy-5*, an interval of only 0.3 m.u. For the *X* chromosome, the *hT3* breakpoint is between *dpy-7* and *unc-3*. It is within the *unc-1 dpy-7* interval that recombination occurs in *hT3* heterozygotes (see RESULTS), thus *hDp135* corresponds to the half translocation *hT3 X*. The *hT3 I* chromosome presumably carries the reciprocal components: the *dpy-14–unc-54* end of chromosome *I* and the *unc-3* end of the *X* chromosome.

Duplications derived from szDp1: γ-Irradiation induced deletions of *szDp1* (the half translocation *szT1 X*) were isolated by selecting for derivatives that did not rescue either *dpy-5* or *unc-13* (McKim and Rose 1990). To determine if the derivatives carry sequences from the *X* chromosome, the following crosses were done. *dpy-5;hDpx* males, where *hDpx* carries a deletion of *szDp1*, were crossed to *dpy-5;unc-y* hermaphrodites, where *unc-y* was an *X*-linked mutation. If wild-type males were observed among the progeny from this cross, then the duplication carried *unc-y(+)*. If non-Dpy Unc males were observed, the duplication did not carry *unc-y(+)*. The presence of *X* chromosome sequences on the *szDp1[dpy-5(−) unc-13(+)]* duplication derivatives had to be detected using a different method because crosses to *szDp1[dpy-5(−) unc-13(+)]* strains produced males carrying these duplications at very low frequency. The rare males were usually sterile. To test for coverage of *unc-1, dpy-14 unc-13;hDpx* hermaphrodites were crossed to *+ dpy-14 +/ dpy-5 + unc-13;hDp31;unc-1* wild-type males. Wild-type hermaphrodites from this cross of the genotype *dpy-14 +/dpy-14 unc-13;hDpx; unc-1/+* or *dpy-5 + unc-13/+ dpy-14 unc-13;hDpx;unc-1/+* were progeny tested. If these segregated Non-Dpy-14 Unc-1 progeny, then the duplication did not carry *unc-1(+)*. If the hermaphrodites did not segregate Non-Dpy-14 Unc-1 progeny, then the duplication carried *unc-1(+)*. The results were confirmed by setting more wild-type progeny on plates to isolate *hDpx;unc-1/unc-1* hermaphrodites.

X chromosome nondisjunction in hermaphrodites carrying *szDp1* and its derivatives was assayed by scoring the frequency of male progeny.

Scoring chromosome *I* nondisjunction: The frequency of chromosome *I* nondisjunction was determined by crossing *hT2/+* males to *dpy-5;unc-x* hermaphrodites. The *unc-x* mutation was present to distinguish self-fertilization progeny. Normally only two of the four segregation products (normal I; normal III or *hT2 I;hT2 III*) from *hT2/+* males could fertilize an egg from a normal hermaphrodite and produce a viable zygote. The phenotype of the progeny from this cross were expected to be wild type. One quarter of the gametes from *+/hT2* males would be the correct genotype (*hT2 I*; normal III) to produce a viable worm upon fertilizing a disomic I oocyte. Any Dpy-5 progeny from this cross resulted from fertilization of a disomy I oocyte from the hermaphrodite by a *hT2 I*; normal III sperm. The frequency of nondisjunction was calculated as $8(N)/W$, where N was the number of exceptional progeny and W was the number of wild-type progeny. We have verified that this procedure recovers diplo-II oocytes by crossing *+/hT2* males to *dpy-5;unc-64;him-3* or *dpy-5;unc-36;him-6* hermaphrodites. The frequency of diplo-I oocytes from Him-3 hermaphrodites was 0.076. In the same experiment, the diplo-III oocyte frequency was 0.039. The frequency of diplo-I oocytes from Him-6 (high incidence of males) hermaphrodites was 0.013, and the diplo-III frequency was 0.007. The nondisjunction rate of chromosome *I* in *him-6* mutants was determined by Haack and Hodgkin (1991) and was similar to our results.

Recombination in the absence of rearrangements: Recombination frequencies between pairs of markers were determined by scoring the self progeny of *cis*-heterozygous

hermaphrodites. In experiments using normal chromosomes, the recombination frequency, p, was calculated using the formula $p = 1 - (1 - 2R)^{1/2}$, where R is the fraction of marked (non-wild type) recombinant individuals over total progeny (BRENNER 1974). Map distances are reported as map units (m.u. = $100p$). Confidence limits of 95% were calculated using the Poisson statistics according to CROW and GARDNER (1959). The total number of progeny (the denominator) was calculated as 4/3 × (the number of wild type plus one recombinant class). When the viability of one recombinant class was reduced, the number of recombinant individuals (the numerator) was calculated as twice the number of the more viable recombinant class (ROSE and BAILLIE 1979b).

Recombination in the presence of rearrangements: *Translocations:* Due to their unique segregation patterns, new formulas were derived for calculating recombination frequencies in translocation heterozygotes. Based on the assumption that the four types of gametes from the translocation heterozygote *a b/hT(I;?)* are produced at equal frequency and p was small, examination of a Punnett square (MCKIM, HOWELL and ROSE 1988) shows that recovery of the *b* recombinant was expected at twice the frequency of the *a* recombinant. As p increased, the ratio of the two recombinants was expected to approach one. Recombination frequencies between genes *a* and *b* in *a b/hT(I;?)* heterozygotes were calculated as follows. If the interval straddled the breakpoint and "*a*" was on the crossover suppressed side, recombination was calculated as either

$$p = (1 - (1 - [4B/W+B])^{1/2})/2; \quad (1)$$

where B is the number of recombinant B progeny and W is the number of wild types, or

$$p = [(4A + 2W) - (4W^2 - 48A^2)^{1/2}]/2(4A + W); \quad (2)$$

where A is the number of recombinant A progeny.

When recombination could occur between the interval being examined and the translocation breakpoint, for example in the *unc-101 unc-54/hT3(I;X)* experiment, formula (2) had to be modified to compensate for the loss of Wt progeny caused by recombination in this interval. In a heterozygote *a b/hT*, where "*a*" was closest to the breakpoint, the recombination frequency was calculated as:

$$p = [(4A - 4Ai + 2W+2Wi) - ((4A - 4Ai + 2W + 2Wi)^2 - 4(4A - 2Ai + 3Ai^2)(4A +W))^{1/2}]/2(4A + W); \quad (3)$$

where A is the number of A recombinants. The "i" value is the recombination frequency between the breakpoint and the interval being scored. One arrives at formula (2) if i = 0 is inserted into formula (3).

Duplications: Recombination between a duplication and the normal chromosome was measured by scoring the progeny of *a b/a b;Dp* hermaphrodites. A formula to calculate "p," the frequency of recombinant gametes, could not be derived because it was not known how often the duplication pairs. In order to estimate the number of recombination events involving a duplication, we used the ratio of recombinant *a* progeny (r), where the ratio = $A/(W + A)$. This ratio underestimates the number of recombinant events as recombination frequency (in the two germlines) increases. In order to estimate the frequency at which the duplication paired with a normal homolog we calculated a value, q. This formula was derived assuming that one crossover occurs each time the duplication pairs with a normal homolog, that the interval being examined surveyed the entire region of the duplication which could recombine, the other normal chromosome segregated at random, and there was no duplication loss.

$$q = (20D + 8W) - 4(4W^2 + 6WD - 15D^2)^{1/2}/(20D + 7W) \quad (4)$$

where the hermaphrodite is *a b/a b;Dp[+ +]* and A was the number recombinant *a* progeny.

Deletions: In most cases recombination in deletion heterozygote strains was calculated using the standard formula. Total progeny was calculated as 2(wild types + one recombinant class). A new formula was required if recombination occurred between the interval being scored and the deletion breakpoints. In the *h655 + +/+ unc-101 unc-54* heterozygote, we deduced from the *dpy-14 unc-101/h655 + +* experiments that there was 18.6 m.u. between *unc-101* and *h655*. To compensate for this recombination, the following formula was derived:

$$p = [(1.9A + 2W) - (4W^2 - 12.42A^2 - 0.41AW)^{1/2}]/2(2A + W); \quad (5)$$

where A is the number of Unc-101 recombinants.

Hermaphrodites heterozygous for *X*-linked deletions and markers were constructed by crossing *mnDp1/Df* males to *dpy unc* homozygous hermaphrodites. All hermaphrodite progeny from this cross were *Df/dpy unc*. The presence of *mnDp1* was ignored when the interval being scored was outside the duplication. When the interval was covered by *mnDp1*, such as with *unc-7 lin-15*, only the progeny of non-duplication worms were scored. These were easily distinguished from duplication worms because approximately 25% of their progeny were Unc Lin. In contrast, less than 10% of the progeny from duplication worms were Unc Lin.

RESULTS

To study the mechanism of homolog pairing, we studied the meiotic properties of a variety of chromosome rearrangements. The approach was to determine the breakpoint(s) and the meiotic recombination and segregation properties of each rearrangement. The isolation and characterization of each rearrangement is described in MATERIALS AND METHODS.

Translocations

hT2(I;III): *hT2* is a translocation involving chromosomes *I* and *III* (Figure 2 and MATERIALS AND METHODS). The *hT2 III* chromosome contains the *bli-3–unc-101* portion of chromosome *I* attached to the *unc-45* end of chromosome *III* and recombines with chromosome *III*. The other half-translocation chromosome, *hT2 I*, contains the *unc-54* end of chromosome *I* attached to the *dpy-17–unc-64* portion of chromosome *III* and recombines with chromosome *I*.

Recombination in hT2 heterozygotes: Using pairs of *cis*-linked markers, the extent of crossover suppression in *hT2* heterozygotes was measured (Table 1 and Figure 2). On chromosome *I* crossover suppression extended from *bli-3* to *unc-101*. The suppression ended between *unc-101* and *unc-59*. While no recombinants have

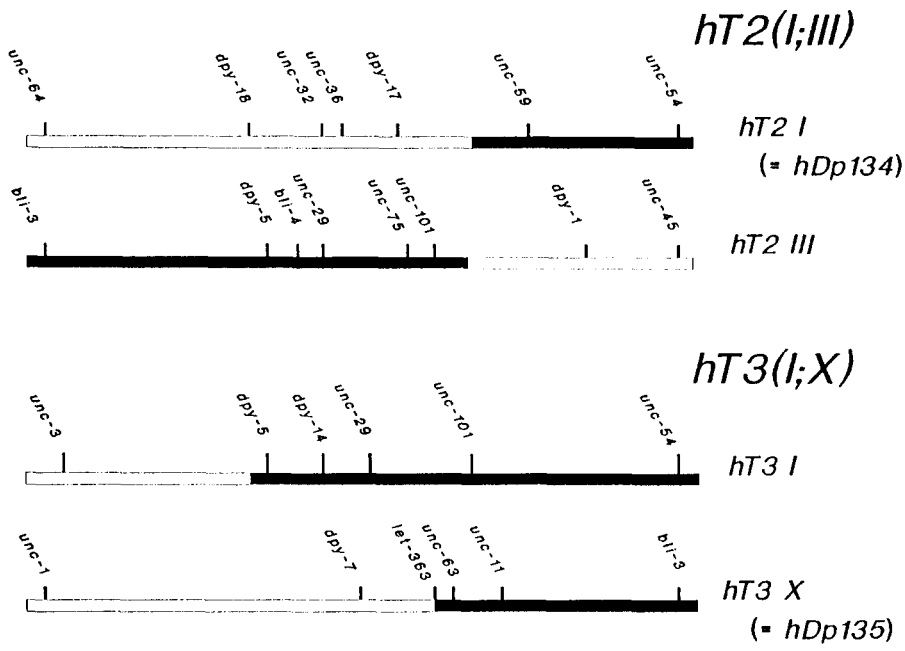

FIGURE 2.—Diagram of the chromosomes comprising *hT2(I;III)* and *hT3(I;X)*. The portions of chromosome *I* are shown with filled lines. The orientations of the translocation arms are not known; they are drawn in a manner requiring the least number of breaks. For *hT3*, the close proximity of the breakpoint and crossover suppression boundary suggests the chromosome *I* breakpoint and the lethal site [*let-363(h916)*, which is 0.3 m.u. to the left of *dpy-5*] (MCKIM 1990) are probably in the same place (MATERIALS AND METHODS).

been observed in the crossover suppressed region with *cis*-linked markers, rare recombinants have been observed using markers pseudolinked by the translocation (see footnote "*e*" of Table 1). On chromosome *III*, recombination was suppressed between *dpy-17* and *unc-64*. In combination with an experiment measuring recombination between *dpy-1* and *unc-32* in *hT2* heterozygotes, the recombination suppression boundary in *hT2* heterozygotes was shown to be between *dpy-1* and *dpy-17* on chromosome *III*. In short, the effect of *hT2* heterozygosity was to almost entirely suppress recombination on one half of chromosomes *I* and *III*. On the other half, recombination occurred at high frequency. These data demonstrate the existence of a site (HRR) required for exchange and presumably pairing mapping near *unc-54* on chromosome *I* and near *unc-45* on chromosome *III*.

That secondary controls on exchange frequency and distribution are then superimposed on the decision to pair or not to pair, is suggested by the changes in the distribution of exchanges in those regions where exchange occurs. For example, recombination frequency was increased relative to controls in the regions where crossing over occurred in *hT2* heterozygotes. Since crossing over on chromosome *I* was suppressed from *bli-3* to a region between *unc-101* and *unc-59*, measuring recombination between *dpy-5* and *unc-54* in *hT2* heterozygotes was actually a measure of recombination between *unc-101* and *unc-54*. This gave an apparent distance of approximately 43 m.u. (Table 1). Since in the absence of *hT2* the normal distance between *unc-101* and *unc-54* is only about 14 m.u. (see Table 2), the recombination frequency was increased approximately threefold in this region compared to controls. The frequency observed would be expected if chromosome *I* and *hT2 I* were pairing and recombining at nearly every meiosis.

Increases in recombination frequency compared to controls were also observed in the case of chromosome *III*. The recombination frequency in the *unc-45* to *dpy-17* interval, which represents the portion of chromosome *III* which recombines in *hT2* heterozygotes, was higher than normal. Unlike the enhancements on chromosome *I*, however, the increase failed to fully compensate for the recombination suppression on chromosome *III*. That is, the whole chromosome *III* recombination frequency in *hT2* heterozygotes was 0.32 while in the control it was 0.46.

Segregation in hT2 heterozygotes: In this section we demonstrate that, presumably as a consequence of exchange events, the *hT2 I* chromosome segregates from chromosome *I* at meiosis I, while *hT2 III* and chromosome *I* segregate at random.

This conclusion is based on two separate types of experiments. First, we demonstrated that *hT2 III* segregates at random from chromosome *I*. To test this, *unc-13;dpy-18/hT2[bli-4;dpy-18]* hermaphrodites, in which *hT2* was marked with *dpy-18(h662)*, were mated to *+/hT2[bli-4]* males. Knowing that *dpy-18(h662)* was on *hT2 I*, Dpy-18 progeny produced from this cross would result from the fertilization of an oocyte of genotype *hT2I;III* by a sperm of genotype *I;hT2III*. Both chromosomes in the oocyte would carry *dpy-18* mutations while neither chromosome in the sperm would carry the *dpy-18* locus. In a total of 51 progeny scored from this cross, 8 were Dpy-18, indicating that *hT2 I* did carry *dpy-18(h662)* and was segregating independently of the normal chromosome *III*. Fur-

TABLE 1

Recombination in *hT2(I;III)* hermaphrodites

Genotype[a]	Wt	Wt/D[b]	Recombinants	m.u. (C.I.)
Chromosome *I*				
hT2[bli-4; dpy-18 unc-54]/hT2[bli-4; + +]	907		120 Dpy-18	19.4 (15.5–23.5)
dpy-5; unc-36/hT2[bli-4 unc-29; dpy-18]	1274	4.3[c]	22 Dpy-5[e]	
			4 Unc-36[e]	
bli-3 unc-11; +/hT2[+; dpy-5 bli-4]	1035	4.1[d]		0
bli-3 unc-11/+ +	723		86 Unc-11	17.5 (13.5–21.9)
dpy-5 unc-29; +/hT2[bli-4]	1082	3.7[c]		0
dpy-5 unc-29/+ +	1767		38 Unc-29	3.1 (2.1–4.1)
dpy-5 unc-75; +/hT2[bli-4]	716			0
dpy-5 unc-75/+ +	1767		108 Unc-75	8.9 (7.6–11.2)
dpy-5 unc-101; +/hT2[bli-4]	1575	4.5[c]		0
dpy-5 unc-101/+ +	889		66 Unc-101	12.0 (10.1–14.0)
			79 Dpy-5	
dpy-5 unc-59; +/hT2[dpy-18; + bli-4]	479	3.5[c]	10 Unc-59	2.1 (1.0–3.8)
dpy-5 unc-54; +/hT2[dpy-18; + bli-4]	444	4.5[d]	100 Dpy-5	43.4 (33.7–57.1)
dpy-5 unc-54/+ +[f]	1620		349 Dpy-5	31.6 (30.3–32.9)
Chromosome *III*				
+; unc-45 dpy-17/hT2[bli-4]	375		96 Unc-45	28.3 (21.8–38.3)
			65 Dpy-17	32.1 (24.8–41.8)
unc-45 dpy-17/+ +	727		117 Dpy-17	23.7 (20.2–27.5)
			119 Unc-45	
+; dpy-1 unc-32/hT2[bli-4]	127		25 Dpy-1	20.8 (13.4–32.9)
			14 Unc-32	
+; dpy-17 unc-36/hT2[bli-4]	854			0
dpy-17 unc-36/+ +	2211		25 Dpy-17	1.7 (1.3–2.0)
+; dpy-17 unc-64/hT2[+; dpy-5 bli-4]	679	4.4		0
dpy-17 unc-64/+ +	859		125 Dpy-17	22.3 (19.2–25.4)
			136 Unc-64	

[a] All *hT2* chromosomes carried *bli-4(e937)*.
[b] Ratio of wild type (Wt) to homozygote Dpy or DpyUnc progeny.
[c] Ratio calculated from normal chromosome homozygote.
[d] Ratio calculated from translocation homozygote.
[e] The recovery of Dpy-5 and Unc-36 progeny from this cross indicated a breakdown in pseudolinkage. We have identified two sources for pseudolinkage breakdown in *hT2*. The first, described in the text, is nondisjunction of *hT2 I* and chromosome *I* (20 Dpy-5). The second source of pseudolinkage breakdown was recombination between chromosome *I* and *hT2 III* (4 Dpy-5, all Unc-36; data not shown), a region normally without recombination in *hT2* heterozygotes. This, and other experiments giving similar results (data not shown) indicate that the crossover suppression in *hT2* heterozygotes is not absolute.
[f] Data from M.-C. ZETKA (personal communication).

thermore, a similar experiment showed that a *dpy-5* mutation induced on *hT2 III*, segregated independently of the normal chromosome I. *dpy-5(e61) unc-13/hT2[dpy-5(h660) +]* hermaphrodites were crossed to *+/hT2* males. Approximately 1/6 of the male progeny were Dpy-5, indicating that they had come from *dpy-5 unc-13;hT2(III)[dpy-5 +]* oocytes. These observations demonstrate that *hT2 III* segregates independently of chromosome *I* and that *hT2 I* and *hT2 III* segregate independently of each other.

Second, we have shown that *hT2 I* rarely nondisjoins from chromosome *I*. This was measured by scoring the progeny of *dpy-5/hT2[dpy-18] I;unc-36/hT2 [bli-4 unc-29] III* hermaphrodites (Table 1). Dpy-5 progeny were possibly the result of nondisjunction. Of the ten Dpy-5 worms that were analyzed, eight were products of nondisjunction. They were aneuploid segregants; *dpy-5;unc-36* homozygotes carrying an additional wild-type allele of the *unc-36* locus (*hT2 I = hDp134*). Based on these data, the frequency of *hT2 I/normal I* nondisjunction was approximately 3% (2[0.8 × 22]/1274). In a control experiment involving two normal sequence chromosomes (*dpy-5;unc-36* hermaphrodites), no Dpy-5 progeny were observed in 1882 progeny (MATERIALS AND METHODS).

Finally, if *hT2 I* and *hT2 III* segregate independently, and *hT2 I* and *hT2 III* segregate independently of chromosomes *III* and *I*, respectively, as the data above suggest, then the four types of gametes produced from a translocation heterozygote, in this case *hT2I;hT2III*, *hT2I;III*, *I;hT2III* and *I;III*, are produced at equal frequencies. If this is true, and if only euploids survive, then the ratio of translocation heterozygote to either homozygote (translocation or normal chromosomes) progeny produced from a self-fertilizing heterozygous hermaphrodite should be 4:1. This ratio comes from the fact that there are 16 possible genotypes from a translocation heterozygote, 10 are aneu-

TABLE 2

Recombination in *hT3(I;X)* heterozygotes

Genotype[a]	Wt	Recombinants	m.u. (C.I.)
Chromosome *I*			
bli-3 unc-11; +/hT3[unc-29]	431 (7)	31 Unc-29	0
bli-3 unc-11/+ +	723	86 Unc-11	17.5 (13.5–21.9)
bli-3 unc-63; +/hT3[dpy-5]	707 (19)	3 Dpy-5	0
+; +/hT3[unc-29]	294 (6)	13 Unc-29	
unc-11 dpy-14; +/hT3[unc-29]	449 (4)	5 Unc-11	See text
		14 Dpy-14	
		24 Unc-29	
dpy-14 unc-101; +/hT3[unc-29]	408	103 Unc-101[b]	25.6 (20.5–33.0)
		29 Unc-29	
dpy-14 unc-101/+ +	529	47 Unc-101	13.1 (9.3–17.1)
unc-101 unc-54; +/hT3	336 (10)	42 Unc-101[c]	17.5 (12.6–23.4)
		1 Dpy-5	
unc-101 unc-54/+ +[d]	874	84 Unc-101	14.2 (11.3–17.3)
X chromosome			
+; dpy-7 unc-3/hT3	536	5 Dpy-7[b]	0.9 (0.4–2.1)
		7 Unc-3[c]	3.0 (0.7–5.1)
dpy-7 unc-3/+ +	1186	149 Dpy-7	19.1 (16.8–21.5)
		160 Unc-3	
+ unc-1 dpy-7/hT3[unc-29]	271 (1)	63 Dpy-7[c]	43.9 (33.0–>50)
		75 Unc-1[b]	30.8 (23.3–50.0)
		6 Unc-29	
unc-1 dpy-7/+ +[d]	1996	275 Dpy-7	19.7 (18.1–21.4)
		262 Unc-1	

The number of male progeny is indicated in parentheses. See the text for the map distance between the *hT3* breakpoint and *dpy-5* or *unc-29*.

[a] All *hT3* chromosomes carried the *dpy-5(e61)* mutation.

[b] Recombinant a translocation heterozygote (see text). The *hT3* heterozygotes have relatively reduced viability. That is, there was a reduction in both the percent of viable progeny (25% compared to the expected 31%) as well as the ratio of translocation heterozygote to normal chromosome homozygotes (3.45:1 compared to the expected 4:1). Furthermore, there was an excess of recombinants that were normal chromosome homozygotes relative to the wild-type (Wt) translocation heterozygotes.

[c] Recombinant a normal chromosome homozygote (see text).

[d] Data from McKim, Howell and Rose (1988).

ploids and die young, four are heterozygotes, one is homozygous for the normal chromosomes and the other is homozygous for the translocation. In the recombination experiments of Table 1, ratios close to 4:1 were observed.

hT3(I;X): *hT3* is a translocation between chromosomes *I* and *X* (Figure 2), and is tightly linked to a recessive lethal mutation *let-363(h916)* (MATERIALS AND METHODS). The *hT3 X* chromosome carries the *bli-3–unc-11* end of chromosome *I* attached to the *unc-1–dpy-7* end of the *X* chromosome, while the *hT3 I* chromosome carries the *dpy-14–unc-54* end of chromosome *I* attached to the *unc-3* end of the *X* chromosome. We observed a low level of *X* chromosome nondisjunction in *hT3* heterozygotes, 56 spontaneous males among 4604 wild types, or 1.2%.

Recombination in hT3 heterozygotes: Recombination on chromosome *I* in *hT3* heterozygotes was suppressed between *bli-3* and *unc-63* (Table 2), the region carried on *hT3 X* (Figure 2). The crossover suppression boundary was to the left of *dpy-5* and close to the putative breakpoint site at *let-363* (Figure 2). That is, in *hT3* heterozygotes recombination was suppressed between *bli-3* and *unc-63* (Table 2) but could occur to the left of *dpy-5* [between *let-363(h916)* and *dpy-5*, both on *hT3*], as demonstrated by the recovery of Dpy-5 recombinants (Table 2). Combining the data from all experiments with *hT3* heterozygotes (Table 2 and data not shown), eight Dpy-5 and 2049 wild-type progeny were recovered, for a distance between *h916* and *dpy-5* of 0.4 m.u. This is consistent with the distance between *dpy-5* and *let-363* (0.3 m.u.; Howell *et al.* 1987), the proposed site of the *hT3* breakpoint. This indicates that the crossover suppression boundary and the breakpoint are very close. Furthermore, these data are consistent with the results from *hT2*. Recombination occurred only on the half of the translocation carrying the *unc-54* region, the location of the chromosome *I* HRR.

The mapping of the chromosome *I* breakpoint indicated that in *hT3* heterozygotes (as in *hT2* heterozygotes) recombination on chromosome *I* occurred only to the right of the breakpoint. Some of the recombination frequencies shown in Table 2 may be

underestimates because of the reduced viability of *hT3* heterozygotes. In spite of this problem, it is evident that there are compensatory increases in recombination to the right of the chromosome *I* breakpoint when compared to controls. For example, combining all experiments in which an *unc-29* marked *hT3* was used (103 Unc-29s and 1853 wild types), we calculated the distance between *let-363(h916)* and *unc-29* to be 5.6 m.u. This is an enhancement compared to the normal distance of 3.4 m.u. [0.3 m.u. for *let-363* to *dpy-5* (HOWELL *et al.* 1987) plus 3.1 m.u for *dpy-5* to *unc-29* (Table 1)]. Recombination frequency was also enhanced in other intervals on *hT3 I* (Table 2 and Figure 2). The total map distance of chromosome *I* in *hT3* heterozygotes was approximately 45 m.u., which is higher than the 32 m.u. normally observed between the site of the breakpoint and *unc-54*, but was equivalent to that normally observed on the whole chromosome.

On the *X* chromosome, recombination was reduced in the *dpy-7 unc-3* interval but enhanced in the *unc-1 dpy-7* interval (Table 2). The *dpy-7 unc-3* experiment measures recombination between *dpy-7* and the breakpoint because the breakpoint and crossover suppression boundary are in this interval. Assuming that no double crossovers occurred, 31% of the *X* chromosomes from *hT3* heterozygotes were recombinant, 14% short of the control.

Summary of translocation data: In agreement with our previous results with chromosome *I* translocations (MCKIM, HOWELL and ROSE 1988), recombination is suppressed on only one side of the breakpoints but on the other side is increased relative to controls. These results show there is a discrete boundary and recombination occurs on one side, but is suppressed on the other. The data with *hT2* localizes to the *unc-59 unc-54* region a segment of the chromosome essential for recombination, which we designate the "homolog recognition region" (HRR). These results also agree with previous studies in *C. elegans* showing that chromosomes that recombined segregated from each other while chromosomes that did not recombine segregated independently (ROSENBLUTH and BAILLIE 1981; MCKIM, HOWELL and ROSE 1988; ZETKA and ROSE (1992).

Duplications

Chromosome *I*: Both *sDp1* (ROSE, BAILLIE and CURRAN 1984) and *hDp133(I;V;f)* cover the right portion of chromosome *I*, proposed to contain the homolog recognition region. Recombination between the normal homologs and the duplication was measured by scoring the progeny of *a b/a b;Dp* hermaphrodites (Table 3). With these data we estimated the frequency at which the duplication pairs with a normal homolog, and compared the distribution of recombination events using the ratio of recombinant progeny (see MATERIALS AND METHODS).

Recombination over most of the length of *sDp1* could be measured since *dpy-5* and *unc-54* are at opposite ends of the duplication (Figure 1). The fraction of meiocytes where the duplication paired and recombined was 14%. Assuming high interference (HODGKIN, HORVITZ and BRENNER 1979), this was much less than the 66% expected for random pairing of three homologs and showed that *sDp1* inefficiently competed with the normal homologs for pairing. Furthermore, *sDp1* had no effect on recombination between the normal homologs in an interval not covered by the duplication (*let-362 dpy-5 unc-13/+ + +/sDp1*). *hDp133* was more effective than *sDp1* at competing for pairing with the normal chromosomes. Because the *unc-29 unc-54* interval covers most of the duplicated region, we were able to calculate that *hDp133* paired with the a normal homolog in 40% of the meiocytes. Thus the HRR is not always sufficient in a competitive situation to guarantee normal pairing. It is possible that such differences may reflect not the absence of a pairing site, but its position in the genome. A similar set of observations have also been made in Drosophila by Grell (1964).

As was true for the translocations, the duplications also demonstrate the existence of secondary and compensatory controls of recombination. The number of recombination events involving *sDp1* was higher at the right end of the chromosome than in the middle. In the *unc-101 unc-54* interval the observed number of recombination events was not reduced as much as in the *dpy-5 unc-101* interval (Table 3). Furthermore, ROSE, BAILLIE and CURRAN (1984) showed that recombination in the *dpy-5 unc-13* region of *sDp1* was exceedingly rare; crossovers were recovered at a frequency of less than 10^{-4}. In summary, while *sDp1* contains sequences enabling it to recombine, the normal homologs preferentially pair and recombine with each other. In addition, the distribution of recombination events involving *sDp1* does not follow the wild-type pattern. In the case of *hDp133*, the distribution of recombination events was similar to the normal chromosome. On the normal chromosome, 14% of the crossovers in the *unc-29 unc-54* interval occur between *unc-29* and *unc-75*. On the duplication, 10% of the crossovers in the *unc-29 unc-54* interval occur between *unc-29* and *unc-75*.

hDp101, a recombination defective derivative of *hDp133*, was isolated spontaneously from an *unc-29 unc-54;hDp133* strain. From scoring recombination in the *unc-29 unc-54* interval we calculated that *hDp101* paired with a normal homolog in only 4% of the meiocytes (Table 3). The structure of *hDp101* was determined by genetic complementation analysis. *hDp101*, like its parent *hDp133*, covers *unc-60* and

TABLE 3

Recombination involving chromosome *I* duplications

Genotype	Wt	Recombinants	$p^a q^b r^c$
dpy-5 unc-54/dpy-5 unc-54/sDp1	774	63 Dpy-5	$r = 0.16$
			$q = 0.14$
dpy-5 unc-54/+ +[d]	1620	349 Dpy-5	$p = 0.31$
dpy-5 unc-75/dpy-5 unc-75/sDp1	823	13 Dpy-5	$r = 0.031$
		13 Unc-75	
dpy-5 unc-75/+ +	1767	108 Unc-75	$p = 0.09$
dpy-5 unc-101/dpy-5 unc-101/sDp1	580	8 Dpy-5	$r = 0.027$
		8 Unc-101	
dpy-5 unc-101/+ +[d]	889	66 Unc-101	$p = 0.12$
		79 Dpy-5	
dpy-5 unc-29/dpy-5 unc-29/sDp1	836	1 Dpy-5	$r = 0.004$
		2 Unc-29	
dpy-5 unc-29/+ +	1767	38 Unc-29	$p = 0.03$
let-362 dpy-5 + unc-13/+ + +/sDp1	731	27 Dpy-5 Unc-13	$p = 0.19$
let-362 dpy-5 unc-13/+ + +[e]	1406	149 Dpy-5 Unc-13	$p = 0.15$
unc-29 unc-75/unc-29 unc-75/hDp133	660	23 Unc-29	$r = 0.04$
		3 Unc-75	
unc-29 unc-75/+ +	877	21 Unc-29	$p = 0.03$
		18 Unc-75	
unc-29 unc-54/unc-29 unc-54/Dp133	359	86 Unc-29	$r = 0.39$
			$q = 0.40$
unc-29 unc-54/unc-29 unc-54; hDp101	728	15 Unc-29	$r = 0.04$
			$q = 0.04$
unc-29 unc-54/+ +	551	92 Unc-29	$p = 0.24$

[a] p = frequency of recombinant gametes.
[b] q = frequency Dp-normal chromosome *I* pairing resulting in recombination.
[c] r = recombinants/(recombinants + wild-types (Wt)).
[d] Data from ZETKA and ROSE (1992).
[e] Data from HOWELL *et al.* (1987).

dpy-11 but not *unc-42* on chromosome *V* and the *unc-29–unc-54* region of chromosome *I*. Thus, the recombination-defective phenotype did not result from a large deletion of material from *hDp133*. Furthermore, the recombination-defective phenotype was not observed when the chromosome *I* material of *hDp101* was crossed onto a normal chromosome and tested for recombination in a euploid situation. Our hypothesis is that *hDp101* carries a mutation in the homolog recognition region, but it has a significant effect on recombination only when competing among three homologs for pairing.

X chromosome duplications: In hermaphrodites, *szDp1(I;X;f)* causes *X* chromosome nondisjunction because it carries the segment (the HRR) of the *X* chromosome near *unc-1* required for pairing and recombination (MCKIM, HOWELL and ROSE 1988). We analyzed derivatives of *szDp1* which had part or all of the chromosome *I* material deleted (MATERIALS AND METHODS) to determine if the *X* chromosome HRR was sufficient to cause *X* chromosome nondisjunction. Duplications that retained material from the *bli-3* end of chromosome *I* (*i.e.*, *hDp31*, *hDp56* and *hDp69*; Figures 1 and 3), retained the Him phenotype (5% males); whereas duplications which had the *bli-3–unc-11* end of chromosome *I* deleted (*hDp70*, see also

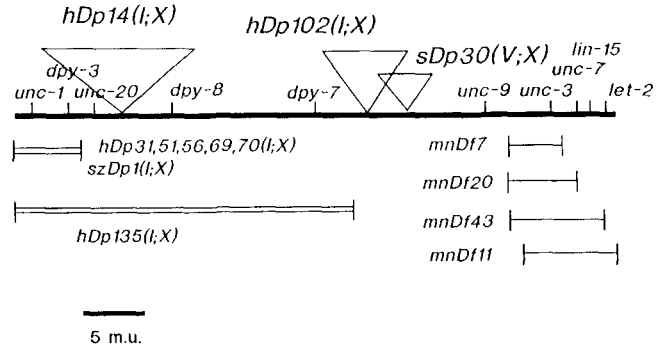

FIGURE 3.—Diagram of *X* chromosome rearrangements. The *hDp(I;X)* and *szDp1* chromosomes also have a component from chromosome *I* (Figure 1).

MCKIM and ROSE 1990), lacked the Him phenotype. All of these duplications have the *X* chromosome material around *unc-1* intact. These data demonstrate that material near the *bli-3* end of chromosome *I* contribute to the meiotic pairing activity of *szDp1*.

To differentiate this pairing activity from the phenomenon of nonhomologous segregation observed in *C. elegans* males (HERMAN, MADL and KARI 1979; MCKIM and ROSE 1990), we investigated the role of recombination in *X* chromosome nondisjunction for *hDp56* and *hDp31*. In hermaphrodites, recombination between the duplications and the normal *X* chromo-

TABLE 4

Recombination in males carrying an *X* chromosome duplication

Duplication	Wt	Wt male	Dpy-5	Dpy-5 Unc-1 male	Unc-1	Unc-1 male
hDp31	2	159	79	10	0	87
hDp56	4	63	29	6	0	31

All crosses were *dpy-5; hDp(I; X; f); unc-1* male × *dpy-5; unc-1* hermaphrodite. Wt = wild type.

somes was assayed by scoring the progeny of *dpy-5/dpy-5;unc-1/unc-1;hDp56*. Among 886 wild types and 648 Dpy-5 Unc-1 hermaphrodites, 18 Dpy-5 and 19 Unc-1 hermaphrodites and 29 wild-type males were recovered. The presence of Dpy-5 and Unc-1 progeny indicated recombination was frequent between *hDp56* and the *X* chromosome. The number of wild-type males indicated the Him phenotype of *hDp56* probably resulted from recombination with and disjunction from the *X* chromosome.

The low level of nondisjunction and recombination observed in duplication hermaphrodites shows that the HRR is not sufficient for normal pairing in a competitive situation. That is, the two *X* chromosomes preferentially pair and recombine. This same observation was made with the chromosome *I* duplications. In males there is only a single *X* chromosome, allowing us to assay pairing behavior of the *Dp(I;X;f)*'s without competition from a second *X* chromosome. Now *hDp56 and hDp31* segregated from the single *X* chromosome at a high frequency. Recombination between the duplication and the *X* chromosome was scored by crossing *dpy-5;hDpx(I;X)[unc-1(+)];unc-1/O* males to *dpy-5;unc-1* hermaphrodites (Table 4). The data for the two duplications were similar. Greater than 90% of the time *hDp31* or *hDp56* segregated from the *X* chromosome. This was indicated by the relatively infrequent recovery of wild-type hermaphrodites and Dpy-5 Unc-1 males, which resulted from *Dp-X* nondisjunction. All nondisjunctional chromosomes in this experiment were nonrecombinant, since no Unc-1 hermaphrodite progeny were recovered. Thus there was a high correlation between recombination and disjunction. Furthermore, recombination was very high in the homologous region; 30% of the duplications were recombinant in the interval between *unc-1* and the right end of the duplication, producing Dpy-5 hermaphrodites and Unc-1 males, and all these recombination events ensured segregation. This amount of recombination in the *unc-1* region was 10-fold higher than between normal chromosomes (HERMAN and KARI 1989; EDGLEY and RIDDLE 1990).

Homozygous *hDp31* strains were stable, producing very few nullo-*Dp* gametes, indicating the two duplication chromosomes segregated from each other at high frequency. Duplication homozygotes had a distinctive phenotype; they were sick, thin, clear and showed reduced fertility. No Dpy-5 progeny were observed in 226 wild-type progeny segregating from *dpy-5/dpy-5;hDp31/hDp31* hermaphrodites. To determine the fraction of nullo-*Dp* gametes produced by a duplication homozygote, *dpy-5/+* males were crossed to *dpy-5;hDp31/hDp31* hermaphrodites. One Dpy-5 was observed in 400 progeny. *hDp31* chromosomes segregated from each other because of the *X* chromosome HRR that they contained. This was shown with duplications which contain the same segment of chromosome I as *hDp31*, but no *X* chromosome HRR (Figure 1). For example, 30 Dpy-5 hermaphrodites were recovered among 132 wild types from a *dpy-5;hDp39/hDp39* strain. Similarly, 129 Dpy-5 progeny were recovered among 458 wild types from a *dpy-5;hDp12/hDp12* strain. The large number of Dpy-5 progeny indicated the two duplications did not segregate from each other during hermaphrodite meiosis. Since the duplication homozygote had two identical chromosomes, they did not segregate from each other because they lacked localized pairing information.

Although *hDp51* (Figure 1) did not have a Him phenotype, meiotic pairing was detected in *unc-13;hDp51/hDp51* strains. No Unc-13 progeny were observed among 425 wild types. Homozygotes from other *hDp(I;X;f)* duplications, except *hDp31* and *hDp56*, did not have this property, showing that the chromosome I segment of *hDp51* enhanced its pairing activity in homozygotes. *hDp51* strains do not have a Him phenotype, perhaps because *hDp51* has less chromosome *I* material than *hDp31* or *hDp56*.

Summary of duplication data: In summary, the data from both the chromosome *I* and *X* duplications show that the homolog recognition region is not sufficient for normal levels of meiotic recombination. We have shown that nonhomologous sequences can stimulate the efficiency at which a duplication engages in meiotic recombination. In addition, we have isolated a new duplication, *hDp101*, which may carry a subtle loss-of-function mutation in the HRR.

We wondered if the sequences that enhance duplication pairing and recombination were also the ones affected by deficiencies (ROSENBLUTH, JOHNSEN and BAILLIE (1990) and insertions (MCKIM and ROSE 1990) that act as crossover suppressors. Next, we report on a variety of deletions and insertions in an effort to integrate their effects with those of the homolog recognition region.

Effect of insertions on recombination

***hDp14(I;X)*:** *hDp14(I;X)* is a duplication of chromosome *I* inserted between *unc-20* and *dpy-8* on the *X* chromosome (Figures 1 and 3). Heterozygous and homozygous *hDp14* hermaphrodites produce males at a frequency of 10%. MCKIM and ROSE (1990) showed that *X* chromosome recombination in *hDp14/+* her-

TABLE 5

Recombination involving *X* chromosomes carrying chromosome *I* insertions

Genotype	Wt	Recombinants	m.u. (C.I.)
dpy-5; unc-3/hDp14	1189	25 Unc-3	2.7 (2.0–3.1)[a]
		18 Dpy-5	
dpy-5; unc-1/hDp14	207	49 Dpy-5	34.7 (24.0–48.8)[a]
		38 Unc-1[b]	
unc-1 dpy-7/+ +	1996	275 Dpy-7	19.7 (18.1–21.4)
		262 Unc-1	
dpy-5/+; hDp14/unc-7 lin-15	932	1 Unc-7	0.1 (<0.5)
		9 Dpy-5[c]	3.9 (1.7–7.3)[a]
unc-7 lin-15/+ +	858	14 Unc-7	1.6 (0.9–2.6)
unc-13; hDp102/dpy-7 unc-3	852	5 Dpy-7	0.9 (0.3–1.9)[d]
		26 Unc-3	5.2 (3.5–7.4)[e,f]
		4 Unc-13	4.5 (2.9–6.7)[e]
dpy-7 unc-3/+ +	1186	149 Dpy-7	19.1 (16.8–21.5)
		160 Unc-3	
unc-13; hDp102/unc-1 dpy-7	802	83 Unc-1	15.0 (12.1–19.1)[g]
		1 Dpy-7	
		5 Unc-13	
unc-13/+; hDp102/unc-7 lin-15	2114	31 Unc-7	2.1 (1.5–3.0)[h]
		26 Unc-13	7.5 (4.8–11.1)[i]
dpy-11; dpy-7 unc-3/sDp30	1710	54 Dpy-7	16.2 (13.8–18.9)
		135 Unc-3	
unc-1 dpy-7/sDp30	879	128 Unc-1	21.3 (17.3–25.6)

Wt = wild type.

[a] Distance between marker and *hDp14*.

[b] Some of the Unc-1 progeny were not true recombinants, but instead carried two normal *unc-1 X* chromosomes and a new duplication resulting from breakage at the *hDp14* insertion site [*i.e.*, *Dp(I; X; f) [unc-1(−) dpy-5(+)]*; K. McKim (unpublished results)]. In this experiment, the recombination frequency was calculated from the number of Dpy-5 progeny.

[c] The Dpy-5 recombinants were multiplied by 8 in order to calculate the insertion to *unc-7* distance.

[d] Insertion–*dpy-7* distance. $R = 2 \times$ Dpy-7/total progeny = 10/1176.

[e] *dpy-7–unc-3* distance. $R = 2$(Unc-3 + Unc13)/total progeny = 60/1176.

[f] Insertion–*unc-3* distance. $R = 2$(Unc-3)/total progeny = 52/1176.

[g] *unc-1–dpy-7* distance. $R = 2$(Unc-1)/total progeny = 166/1180.

[h] *unc-7–lin-15* distance. $R = 2$(Unc-7)/total progeny = 62/2895.

[i] Insertion–*unc-7* distance. $R = 8$(Unc-13)/total progeny = 208/2895.

maphrodites was reduced in the *dpy-7 unc-3* interval. To determine the recombination frequency between the insertion site and a marker, we scored the progeny of hermaphrodites homozygous for *dpy-5* but heterozygous for *hDp14* and an *X* linked marker. For example, in *dpy-5/dpy-5;hDp14 +/+ unc-3* hermaphrodites, the frequency of Dpy-5 and Unc-3 recombinants was determined by the position of the insertion site relative to *unc-3* (Table 5). This experiment showed that the recombination frequency was enhanced in the *unc-1–hDp14* interval (0.347) compared to the control (*i.e.*, *unc-1* to *dpy-7* = 0.197). Crossing over was suppressed in *hDp14* heterozygotes over the entire portion of the *X* chromosome to the right of the insertion. Even in the *unc-7 lin-15* interval, which is located at the far right end of the chromosome (Figure 3), recombination was reduced 10-fold in *hDp14* heterozygotes (Table 5). The total recombination frequency on the *X* chromosome in *hDp14* heterozygotes was approximately 0.39. Thus, there was some compensation for the recombination suppression.

hDp102:(I;X): *hDp102(I;X)* is also an insertion of chromosome *I* material into the *X* chromosome (Figures 1 and 3). In contrast to *hDp14*, this insertion did not cause high levels of *X* chromosome nondisjunction (5/2916 = 0.2%). The insertion site was mapped to the *dpy-7–unc-3* interval because both Dpy-7 and Unc-3 recombinants were recovered among the progeny of *unc-13/unc-13; + hDp102(I;X) + /dpy-7 + unc-3* hermaphrodites (Table 5). These data also show that recombination was reduced fourfold in this interval. In contrast to *hDp14*, recombination suppression did not extend to the right end of the chromosome; recombination in the *unc-7 lin-15* interval of *hDp102* heterozygotes was not significantly different from the control (Table 5). The total frequency of recombination on the *X* chromosome in the *hDp102* heterozygote was 0.24, a value substantially lower than wild-type recombination frequencies on the *X* chromosome. It was thus surprising that the amount of *X* chromosome nondisjunction was so low in *hDp102* strains.

sDp30(V;X): Rosenbluth *et al.* (1988) showed *sDp30* (Figure 3) is a fragment of chromosome *V* attached to the *X* chromosome. We have mapped the insertion site by three-factor analysis to the *dpy-7 unc-*

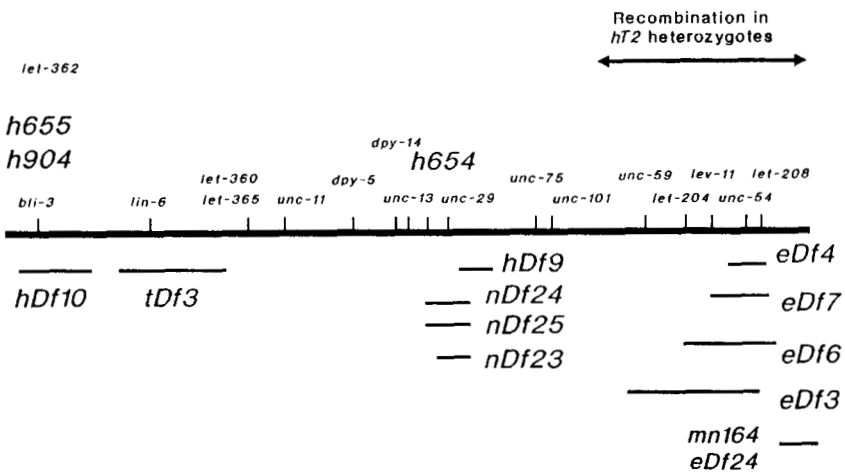

FIGURE 4.—Genetic map of chromosome *I* deficiencies. *let-362* (Figure 1) complements *hDf10* and *tDf3*. As with Figure 1, the "gene cluster" has been expanded relative to the flanking regions.

3 interval. The progeny of *dpy-11/dpy-11;sDp30/dpy-7 unc-3* hermaphrodites were scored (Table 5). Because the Dpy-11 Dpy-7 progeny looked Dpy-11, recombinant Dpy-7 or Unc-3 progeny were recovered only if the recombinant chromosome picked up the insertion. As both Dpy-7 and Unc-3 progeny were recovered, *sDp30* must be inserted between these two markers. Almost 3/4 of the recombinants had an Unc-3 phenotype, suggesting the insertion site was closer to *dpy-7*. The insertion also caused a low but significant level of *X* chromosome nondisjunction. Unlike *hDp14* and *hDp102*, however, *sDp30* did not have a significant effect on *X* chromosome recombination. The recombination frequencies in the *dpy-7 unc-3* and *unc-1 dpy-7* intervals of *sDp30* heterozygotes (Table 5) were similar to the controls. The total frequency of recombination on the *X* chromosome in *sDp30* heterozygotes was 0.37.

Summary of insertion data: The fact that the insertions on the *X* chromosome suppress recombination in a polar direction suggest the HRR is strictly cis-acting. While it is possible these data reflect a zipper-like synapsis mechanism, the fact that the smaller insertions have a smaller effect on recombination suggests that recombination suppression is caused by the distance that the *X* chromosome material is separated from the HRR. Since the deficiency data reveal a difference in pairing between the autosomes and the *X* chromosome (see below), different results might be expected with insertions into an autosome.

Deficiencies

Chromosome *I* deficiencies: Five lethal mutations mapping near the left end of chromosome *I* (Figure 4) suppressed recombination in adjacent regions (Table 6). Two of these mutations, *hDf10* and *tDf3*, have been shown to be deficiencies. The frequency of recombination between *hDf10* and *dpy-5* (0.023) is lower than expected for this interval, which should be at least 10.5 m.u., the *lin-6–dpy-5* distance (HOWELL *et al.* 1987). The distance between the right breakpoint of *tDf3* and *dpy-5* (0.4 m.u.) was 10-fold lower than expected for this interval, which was estimated from the distance from *dpy-5* to *let-360* or *let-365* (4.5 m.u.; HOWELL *et al.* 1987). Two other mutations, *h655* and *h904*, failed to complement each other and *hDf10*, but no other loci. The suppression of recombination is not due to the deletion of a single site as *tDf3* does not overlap with *hDf10* (Figure 4).

Recombination was measured in other regions of chromosome *I* in *h655* heterozygotes (Table 6). Recombination suppression continued from the left end to the *unc-29* region. In contrast, the recombination frequency in the *unc-101 unc-54* interval was elevated compared to controls. This enhancement may be mechanistically similar to recombination enhancements which accompany recombination suppression in translocation heterozygotes.

To test the generality of crossover suppression in deficiency heterozygotes, we determined if deficiencies in other regions of chromosome *I* reduced crossing over in adjacent regions. Deficiencies in the *unc-29* region of chromosome *I* (Figure 4) reduced recombination in adjacent regions. Two γ-irradiation-induced lethal mutations in the *unc-29* region, *hDf9* and *h654*, reduced the recombination frequency in the *unc-11 unc-13* region (Table 7). To the left of *unc-11*, as measured with *bli-3 unc-11*, recombination was not reduced, but was possibly enhanced. To the right of *hDf9*, measured using *dpy-14 unc-101*, recombination was not affected. In addition to *hDf9*, *nDf24* and *nDf25* reduced the recombination frequency for a short distance to their left but not to their right. In contrast, a smaller deficiency of the *unc-29* region, *nDf23*, did not reduce recombination in the *dpy-5 unc-13* region. *nDf23* was the only mutation, however, to reduce recombination in the left end of chromosome *I* (*bli-3–unc-11*).

In contrast to deficiencies at the left end of chromosome *I*, deficiencies at the right end did not affect recombination in adjacent regions (Figure 4 and

TABLE 6

Recombination in deficiency heterozygotes: the left end of chromosome *I*

Genotype	Wt	Recombinants	m.u. (C.I.)
h655 + +/+ bli-3 unc-11	568	0 Unc-11	0.0 (0.0–0.5)
bli-3 unc-11/+ +	723	86 Unc-11	17.5 (13.5–21.9)
h655 + +/+ dpy-14 unc-101	602	122 Unc-101	18.6 (14.9–22.4)
dpy-14 unc-101/+ +	529	47 Unc-101	13.1 (9.3–17.1)
h655 + +/+ unc-101 unc-54	635	155 Unc-101	23.1 (19.6–26.7)
unc-101 unc-54/+ +	874	84 Unc-101	14.2 (11.3–17.3)
h904 + +/+ bli-3 unc-11	651	13 Unc-11	2.0 (1.1–3.2)
hDf10 dpy-5 unc-29/+ + +	250	4 Dpy-5 Unc-29	2.3 (0.3–6.0)
		2 Unc-29	1.2 (0–4.2)
dpy-5 unc-29/+ +	1767	38 Unc-29	3.1 (2.1–4.1)
tDf3 dpy-5/+ +	1613	4 Dpy-5	0.4 (0.1–0.9)

Wt = wild type.

TABLE 7

Recombination in deficiency heterozygotes: the *unc-29* region of chromosome *I*

Genotype	Wt	Recombinants	m.u. (C.I.)
+ + nDf23/dpy-5 unc-13 +	1225	18 Dpy-5	1.5 (1.0–2.0)
		18 Unc-13	
+ + + nDf23/let-362 dpy-5 unc-13 +	376	22 Dpy-5 Unc-13	5.7 (3.6–8.4)
+ + nDf24/dpy-5 unc-13 +	2210	12 Dpy-5	0.6 (0.4–0.9)
		14 Unc-13	
+ + nDf25/dpy-5 unc-13 +	1687	13 Dpy-5	0.6 (0.3–0.9)
		6 Unc-13	
+ nDf25 +/dpy-14 + unc-101	485	39 Unc-101	8.0 (6.2–9.8)
		40 Dpy-14	
+ + + nDf25/let-362 dpy-5 unc-13 +	257	36 Dpy-5 Unc-13	13.2 (8.9–18.4)
dpy-5 unc-13 hDf9/+ + +	791	0	0.0 (0–0.6)
+ dpy-5 + unc-13 hDf9/unc-11 + dpy-14 + +	1281	4 Unc-11	0.3 (0.1–0.8)
+ + dpy-5 unc-13 hDf9/bli-3 unc-11 + + +	712	159 Unc-11	20.3 (16.8–24)
dpy-5 + unc-13 hDf9 +/+ dpy-14 + + unc-101	676	79 Unc-101	11.8 (8.8–13.9)
dpy-5 unc-13 h654/+ + +	710	0	0.0 (0–0.6)

Wt = wild type.

Table 8). We found no effects on recombination frequency with any of the deficiencies tested including *eDf24*, which deletes part of the ribosomal gene cluster, the most distal genetic marker on chromosome *I*. Recombination was observed between two large heterologies. In *hT2/eDf3*, *hT2/eDf4*, *hT2/eDf6* and *hT2/eDf7* hermaphrodites, there was a high frequency of recombination between the translocation breakpoint and the deficiency breakpoint (Table 8).

***X* chromosome deficiencies:** We tested deficiencies located near the right end of the *X* chromosome [MENEELY and HERMAN (1979, 1981); Figure 3] for recombination suppression (Table 9). Only a small effect was seen with *mnDf11*, a putative terminal deficiency. The rest of the *X* chromosome deficiencies did not suppress recombination. The known internal deficiencies, *mnDf20* and *mnDf7*, had no effect on recombination. This was tested for an interval to the left (*dpy-7 unc-9*) and an interval to the right (*unc-7 lin-15*) of the deficiencies.

Summary of insertion and deficiency data: The results with the deficiencies show that the autosomes, but not the *X* chromosome, have secondary pairing regions near the end of the chromosome opposite the HRR.

DISCUSSION

Localization of sequences enabling homolog pairing and recombination: Previous studies have shown that isolated portions of *C. elegans* chromosomes are not equally capable of meiotic exchange (ROSENBLUTH and BAILLIE 1981; ROSE, BAILLIE and CURRAN 1984; MCKIM, HOWELL and ROSE 1988; HERMAN and KARI 1989). These authors proposed that sequences required for pairing and recombination were localized to discrete sites on each *C. elegans* chromosome. MCKIM, HOWELL and ROSE (1988) went on to propose that these sites were localized to one end of each *C. elegans* chromosome. The data presented in this paper support these proposals.

We have now mapped the breakpoints and determined the distribution of recombination events in heterozygotes of four chromosome *I* translocations, *szT1(I;X)* and *hT1(I;V)* (MCKIM, HOWELL and ROSE

TABLE 8

Recombination in deficiency heterozygotes: the right end of chromosome *I*

Genotype	Wt	Recombinants	m.u. (C.I.)
unc-101 unc-54 +/+ + eDf24	344	52 Unc-101	14.1 (10.1–18.7)
unc-101 unc-54/+ +	874	84 Unc-101	14.2 (11.3–17.3)
let-202 unc-54/+ +	2384	50 Unc-54	3.1 (2.3–4.1)
let-202 unc-54 +/+ + eDf24	996	20 Unc-54	2.0 (1.3–3.0)
let-201 unc-54/+ +	2741	56 Unc-54	3.0 (2.3–3.9)
let-201 unc-54 +/+ + eDf24	220	5 Unc-54	2.2 (0.9–4.9)
+ + eDf3/dpy-5 unc-101 +	404	39 Unc-101	12.1 (8.5–16.5)
+ + eDf6/dpy-5 unc-101 +	408	71 Unc-101	16.1 (12.2–20.7)
+ + eDf7/dpy-5 unc-101 +	187	31 Unc-101	15.4 (10.1–22.2)
dpy-5 unc-101/+ +[a]	889	66 Unc-101 79 Dpy-5	12.0 (10.1–14.0)
unc-101 lev-11 +/+ + eDf4	218	20 Unc-101 17 Lev-11	8.1 (5.6–11.2)
unc-101 lev-11/+ +	680	32 Lev-11 25 Unc-101	6.2 (4.6–7.6)
dpy-5 eDf3; +/hT2	122	9 Dpy-5	13.9 (6.4–25.9)[b]
dpy-5 eDf4; +/hT2	244	76 Dpy-5	>50.0 (47.6–)[b]
dpy-5 eDf6; +/hT2	144	26 Dpy-5	33.7 (22.0–54.6)[b]
dpy-5 eDf7; +/hT2	44	10 Dpy-5	43.9 (21.2–>50.0)[b]

Wt = wild type.
[a] Data from ZETKA and ROSE (1992).
[b] See Table 1 for the expected distance between *dpy-5* and *unc-54* in *hT2* heterozygotes.

TABLE 9

Recombination in *X* chromosome deficiency heterozygotes

Genotype	Wt	Recombinants	m.u. (C.I.)
dpy-7 unc-9 + +/+ + unc-3 let-2	979	100 Unc-9	9.7 (7.7–11.8)
dpy-7 unc-9 +/+ + mnDf20	930	108 Unc-9	11.0 (9.0–13.3)
dpy-7 unc-9 +/+ + mnDf11	962	44 Unc-9	4.5 (3.2–6.0)
dpy-7 unc-9 +/+ + mnDf41	790	70 Unc-9	8.5 (6.6–10.7)
dpy-7 unc-9 +/+ + mnDf7	635	76 Unc-9	11.3 (8.7–14.2)
dpy-7 unc-9 +/+ + mnDf43	1227	129 Unc-9	10.0 (8.2–11.9)
+ unc-7 lin-15 +/unc-3 + + let-2	858	14 Unc-7	1.6 (0.9–2.6)
+ unc-7 lin-15/mnDf7 + +	1078	19 Unc-7	1.7 (1.0–2.6)
+ unc-7 lin-15/mnDf20 + +	1631	32 Unc-7	1.9 (1.3–2.6)

Wt = wild type.

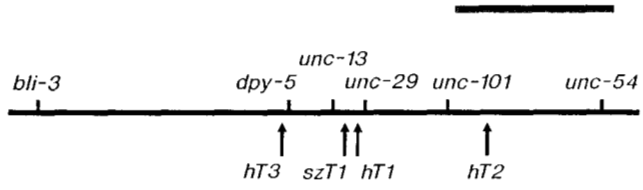

FIGURE 5.—Summary of translocation breakpoint on a genetic map of chromosome *I*. The breakpoints are indicated with an arrow below the map. Recombination is suppressed to the left of each breakpoint, but is increased (or compensated) to the right. The location of the strongest compensatory increases are indicated by the bar above the map.

1988) and the two reported here, *hT2(I;III)* and *hT3(I;X)*. Although the four breakpoints are in different locations spread over half the chromosome, the pattern of recombination suppression is the same (Figure 5). Recombination is suppressed on the *bli-3* (left) side of each breakpoint but occurs at high frequency on the *unc-54* (right) side (Table 10). These data define a region, the homolog recognition region (HRR), which is localized to the *unc-54* region of chromosome *I*. We have used the term homolog recognition to draw attention to the fact that the missing function is required for subsequent meiotic exchanges to occur between homologs, and that the reason for recombination suppression in translocation heterozygotes is the failure to pair. Data from the other chromosomes of *C. elegans* [reviewed in MCKIM, HOWELL and ROSE (1988) and ROSE and MCKIM (1992)] is consistent with our proposal that each chromosome has a localized region required for the initiation of meiotic exchange events.

Similar results are found with duplications of chromosome *I*. Only those fragments that carry material from the *unc-54* end, such as *sDp1* and *hDp133* (ROSE, BAILLIE and CURRAN 1984; this paper), pair and recombine with a normal homolog (Table 10). Duplications derived from the other end (*bli-3*) of chro-

TABLE 10

Summary of recombination in rearranged chromosomes

Genotype	m.u. in the following intervals	
	bli-3 unc-11	(*dpy-5 or unc-101*) – *unc-54*
+/+	17.5	26.2
hT2/+	0	43.4
hT3/+	0	45
h655/+	0	41.7
sDp2/+/+	0[a]	ND[b]
sDp1/+/+	19.0	7[c]
hDp133/+/+	ND	20[c]

[a] Data from ROSE, BAILLIE and CURRAN (1984).
[b] ND = not determined.
[c] Estimated from Table 3.

mosome *I* do not recombine with the normal homologs, nor do they influence recombination between the normal homologs (*sDp2*; Table 10; ROSE, BAILLIE and CURRAN 1984; MCKIM and ROSE 1990). Along these lines, we have shown here that two copies of a duplication [*i.e.*, *hDp12(I;f);hDp39(I;f)*] ignore each other during meiosis, despite their identical sequence, unless they carry an HRR [*i.e.*, *hDp31(I;X;f)*].

Localization of the HRR can be derived from experiments with *hT2* heterozygotes, where recombination is suppressed over most of chromosome *I*, from *bli-3* to *unc-101*. This localizes the HRR to the *unc-59–unc-54* region. We were unsuccessful in attempts to further localize the homolog recognition region with deletions. The deletions which uncovered a large part of (but not all) the region between *unc-101* and the end of chromosome *I* had no effect on recombination in adjacent regions.

The HRR does not ensure the proper frequency and distribution of crossover events: Deletions located near the left (non-HRR) end of chromosome *I* suppressed recombination for a considerable distance in adjacent regions (Table 10). ROSENBLUTH, JOHNSEN and BAILLIE (1990), studying deletions near the non-HRR end of chromosome *V*, observed that recombination was suppressed only on the side proximal to the deletion and was normal on the distal side. These authors proposed that the recombination suppression was caused by a unidirectional disruption of synapsis which was initiated distally. The proposed pairing mechanism was secondary to and required an HRR. As well, it is possible that the deficiencies located near the middle of chromosome *I*, which suppress recombination to their left, could be deleting sites needed for recombination across the gene cluster. The processes of pairing and recombination appear to utilize at least two chromosomal elements, the HRR, and other pairing sites.

Our results show that recombination suppression caused by deficiency heterozygosity may be a generality for *C. elegans* autosomes, but not for the *X* chromosome. Deficiencies of the right (non-HRR) end of the *X* chromosome, had no effect on recombination frequencies in adjacent regions. This is the third example of the unique meiotic properties of the *X* chromosome. HODGKIN, HORVITZ and BRENNER (1979) identified *X* chromosome-specific meiotic mutations and BRENNER (1974) observed that the *X* is the only chromosome in *C. elegans* that does not have a central clustering of genes on the genetic map. Since the *X* chromosome appears to have a single HRR, the unique meiotic properties of the *X* chromosome may be a consequence of events occurring subsequent to homolog recognition.

Nonhomologous sequences can modify the meiotic behavior of chromosomes. We compared two duplications containing the HRR end of chromosome *I*, *sDp1(I;f)* and *hDp133(I;V;f)* (Table 10). *hDp133*, which carries half of chromosome *V* attached to the chromosome *I* material, recombined with chromosome *I* more frequently than *sDp1*. In the case of *sDp1*, the reduction in recombination frequency was not equal along the chromosome with the result that the distribution of events was altered. On the other hand, *hDp133* recombined with chromosome *I* at nearly normal frequency and distribution. This may have been the result of the larger (nonhomologous) size or the provision of a natural chromosome end from chromosome *V*. Similarly, we found that chromosome *I* sequences enhanced the ability of duplications containing the *X* chromosome HRR to engage in pairing and recombination. It is tempting to speculate that telomere associated sequences, either homologous, as suggested by the studies with deficiencies, or nonhomologous, as suggested by the studies with duplications, play a role in facilitating meiotic pairing and exchange. GOLDSTEIN (1982) observed that either end of chromosome *I* can be found attached to the nuclear envelope at pachytene stage. Chromosome pairing in other organisms, including other nematodes, has been observed to occur while the chromosomes are attached via their telomeres to the inner nuclear membrane (VON WETTSTEIN, RASMUSSEN and HOLM 1984). It is clear, however, that in *C. elegans* the ends of chromosomes are not equivalent with regard to initiating meiotic exchange and that telomeric attachment *per se* is not performing the role of the HRR.

There is a mechanism to ensure one crossover per chromosome bivalent at meiosis: Translocation (MCKIM, HOWELL and ROSE 1988; this paper), deficiency (*i.e.*, h655/+) and inversion (ZETKA and ROSE 1992) heterozygotes cause recombination suppression in one region of chromosome *I* but compensatory enhancements of recombination in other regions. The enhancements are restricted to the crossover suppressed chromosomes, suggesting the enhancements represent chromosomal compensation for crossover

suppression (McKim, Howell and Rose 1988; Zetka and Rose 1992), that is a system regulating the number of crossovers per chromosome. The compensatory mechanism is also efficient. Indeed, these enhancements can compensate fully for severe recombination suppression, even when the amount of chromosome *I* available for recombination is reduced to 10% of its normal genetic size, as in the *eDf7/hT2* heterozygotes. The largest deficiency heterozygote, *eDf3/hT2*, did not fully compensate, demonstrating the limits on the regulatory mechanism.

We suggest that this represents a general meiotic process in *C. elegans* and that exceptional cases where full compensation is not observed can be explained by reduced interference. Recombination was compensated in the homologous paired regions to only 80% of the control values in two translocations of chromosome *III*, *eT1(III;V)* (K. McKim, unpublished results) and *hT2(I;III)* (this study), and in two *X* chromosome translocations, *szT1(I;X)* (McKim, Howell and Rose 1988) and *hT3(I;X)* (this study). With *hT3*, for example, 31% of the *X* chromosomes from *hT3* heterozygotes were recombinant, 14% short of the control. If an absence of crossing over resulted in nondisjunction, we would expect 7% of the progeny from a *hT3* heterozygote to be males, but we observed only 1.2%. Thus, either nonrecombinant chromosomes segregated from each other, or the observable amount of recombination was reduced by frequent double crossover events. Similarly, since only 60% of the *Dp-X* segregation events were associated with a detectable recombination event, the remaining 40% could be double crossover events or segregation without recombination [see also Herman and Kari (1989)]. Since high interference is normally observed on *C. elegans* chromosomes (Hodgkin, Horvitz and Brenner 1979), these translocations could be recombining with the normal homolog in every meiosis if interference is reduced. We suggest that translocations and duplications can disrupt the regulatory mechanism preventing double crossover events. By analogy in Drosophila, we note that disruptions of the normal meiotic process, such as with meiotic mutants (Baker *et al.* 1976), and the interchromosomal effect (reviewed in Lucchesi 1976), cause changes in the distribution of crossovers.

The HRR is not sufficient for disjunction: In the previous discussion we have argued that pairing and the control of recombination frequency are separable genetic functions. Segregation functions can also be genetically separated from the HRR. While under most conditions it appears that chromosome segregation patterns are determined by crossovers, we have observed nondisjunction in situations where the lack of recombination is probably not the causative factor. For example, there is elevated chromosome *I* nondisjunction in *hT2* heterozygotes even though recombination occurs at wild-type frequencies. Furthermore, *szT1(I;X)* and *hDp14(I;X)* heterozygotes cause elevated *X* chromosome nondisjunction but *hT3(I;X)* and *hDp102(I;X)* do not, while all four have the same amount of *X* chromosome recombination. Even rearrangement homozygotes, such as *hDp14(I;X)* (McKim and Rose 1990; this paper) and *mnT10(V;X)* (Herman, Kari and Hartman 1982), which probably do not effect recombination frequencies, can induce *X* chromosome nondisjunction. These results suggest that chromosomal features in addition to the HRR and pairing sites are required for proper disjunction.

What is the relationship between the HRR, which is required for pairing and recombination, and the centromere, which holds chromatids together until their separation at meiosis II? Translocation studies (Rosenbluth and Baillie 1981; McKim, Howell and Rose 1988) showed that during metaphase I there could be only a single functional centromere, that is, the region where the sister chromatids are held together until meiosis II. Centromere activity could not be present in both the components of the translocation or the chromosomes would be torn apart at anaphase. The results indicated that the meiotic chromosomes are not holocentric as are the mitotic chromosomes (Albertson and Thomson 1982). Cytological observations with Parascaris nematodes (Goday and Pimpinelli 1989), *Myrmus miriformis* (Nokkala 1985) and *C. elegans* (D. Albertson, personal communication) have shown that the mitotic chromosomes are holokinetic but that the meiotic spindles attach to a localized region of each chromosome. Although centromeres are necessary for proper segregation during meiosis, they need not have any influence on the determination of segregation patterns (Hawley 1988; Surosky and Tye 1988). In the case of chromosome *I*, based on the meiotic behavior of an inversion, Zetka and Rose (1992) proposed that the centromere is located to the left of *unc-75*. If proven correct, this would place the centromere outside the region proposed to contain the HRR.

A model for HRR function: We have proposed that the HRR is required early in the process of homolog pairing (McKim, Howell and Rose 1988). Following homolog recognition, synapsis apparently proceeds on the basis of DNA identity because the boundary of crossover suppression and the translocation breakpoints are probably the same site. For example, both are close to the *unc-36* gene in *eT1(III:V)* (Rosenbluth and Baillie 1981), and in *szT1(I;X)*, *hT1(I;V)* (McKim, Howell and Rose 1988) and *hT3(I;X)* the breakpoints and crossover suppression boundaries are less than 0.5 m.u. apart.

The behavior of *hDp31(I;X;f)* illustrates this proposal. If the homolog recognition region is required

for homolog pairing, how is it that the two *X* chromosomes preferentially pair at the exclusion of the duplication? In our proposal, the homolog recognition region facilitates pairing between *hDp31* and the *X* chromosome, and then other sequences recognize the greater amount of homology between the two *X* chromosomes than between *hDp31* and the *X* chromosomes. The result is that when there are four chromosomes with the same homolog recognition region, such as in *hDp31* homozygotes, greater than 99% of the time the two *X* chromosomes pair and the two duplications pair. ROSENBLUTH, JOHNSEN and BAILLIE (1990) also proposed that the sequences disrupted by chromosome *V* deficiencies that suppress recombination acted secondarily to the homolog recognition region.

In other organisms it has been proposed that the early stages of homolog pairing are mediated by sequence homology searches (SMITHIES and POWERS 1986; ALBINI and JONES 1987; CARPENTER 1987; ALANI, PADMORE and KLECKNER 1990; KLECKNER, PADMORE and BISHOP 1991; HAWLEY and ARBEL 1993). These models are compatible with the nonequivalence observed for the translocation chromosomes in *C. elegans*, if one postulates that the HRR pairs homologs from a distance, followed by DNA homology searches to promote synapsis and synaptonemal complex formation based on DNA sequence. Alternatively, the HRR could be required following a DNA homology search, perhaps as the region where synapsis initiates (*e.g.*, ZICKLER *et al.* 1992). If the HRR were a loading site for synaptonemal complex or recombination proteins, translocations and insertions might be expected to suppress recombination by blocking the progression of the complex. On the contrary, recombination can initiate at internal sites (in the *unc-75 unc-101* region) separated from the HRR by chromosome rearrangement, such as deletions of the *unc-54* region of chromosome *I*, and between *szT1* and the inversion, *hIn1* (ZETKA and ROSE 1992). Given this data and the size of *C. elegans* chromosomes, it seems much more likely that, following homolog recognition, there are multiple entry sites along the chromosome for synapsis and recombination.

A feature of the HRR is that it promotes recombination along the entire chromosome. Long range attractions, which have been observed cytologically between chromosomes (reviewed in VON WETTSTEIN, RASMUSSEN and HOLM (1984), FUSSELL (1987) and GIROUX (1988)], could be mediated by the HRR. Compatible with this suggestion is the behavior of insertions into the *X* chromosome. In these cases, recombination suppression was correlated with the size of the insertion. *sDp30* is small and does not reduce recombination. *hDp102* mildly suppresses recombination, and its size appears to be intermediate. In the case of the large insertion of chromosome *I* material into the *X* chromosome, *hDp14*, the HRR may be functionally unlinked from the distal *X* chromosome segment. Nonhomologous insertions, which separate a portion of the chromosome from the HRR, reduce recombination in the separated portion. Thus, whenever portions of the chromosome become separated from the HRR, due to translocation, free duplication or interruption by nonhomologous insertion, subsequent meiotic processes are disrupted.

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