

# Organization of the *sex-ratio* Meiotic Drive Region in *Drosophila simulans*

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## ABSTRACT

*Sex-ratio* meiotic drive is the preferential transmission of the X chromosome by XY males, which occurs in several *Drosophila* species and results in female-biased progeny. Although the trait has long been known to exist, its molecular basis remains completely unknown. Here we report a fine-mapping experiment designed to characterize the major drive locus on a *sex-ratio* X chromosome of *Drosophila simulans* originating from the Seychelles ( $X^{SR6}$ ). This primary locus was found to contain two interacting elements at least, both of which are required for drive expression. One of them was genetically tracked to a tandem duplication containing six annotated genes (*Trf2*, *CG32712*, *CG12125*, *CG1440*, *CG12123*, *org-1*), and the other to a candidate region located ~110 kb away and spanning seven annotated genes. RT-PCR showed that all but two of these genes were expressed in the testis of both *sex-ratio* and standard males. *In situ* hybridization to polytene chromosomes revealed a complete association of the duplication with the *sex-ratio* trait in random samples of X chromosomes from Madagascar and Reunion.

ACCORDING to Mendel's first law, each member of a pair of alleles or homologous chromosomes has an equal probability of being transmitted to the offspring. The physical basis of this principle is the balanced segregation of chromosomes during meiosis. However, a number of cases have been reported in which a particular allele or chromosome furthers its own transmission by altering some aspects of meiotic chromosome behavior or gamete formation in heterozygous individuals. Such infringements of the law, known as meiotic drive, have been observed in a wide range of organisms including fungi, plants, insects, and mammals (LYTTLE 1991; DAWE and HIATT 2004). These infringements could have a considerable impact on the natural history of organisms and on genome evolution (ORR and PRESGRAVES 2000; HURST and WERREN 2001; JAENIKE 2001; PARDO-MANUEL DE VILLENA and SAPIENZA 2001). However, there are very few cases in which any of the molecular players responsible for the drive have been identified and these all correspond to autosomal drive (KUSANO *et al.* 2003; LYON 2003). The work reported here provides the first identification of candidate genes for a case of meiotic drive involving the sex chromosomes.

The *sex-ratio* trait was originally reported in *Drosophila obscura* >75 years ago (GERSHENSON 1928). Since then it

has been reported in a dozen *Drosophila* species and two other Diptera families (JAENIKE 2001); however, its molecular basis remains completely unknown. *Sex-ratio* segregation distorters are typically linked to the X chromosome and prevent the production of Y-bearing sperm in heterogametic XY males, leading to the production of strongly female-biased progeny. In *D. simulans*, the object of this study, the loss of Y-bearing sperm is related to disjunction defects of the Y chromosome sister chromatids during the second meiotic division (CAZEMAJOR *et al.* 2000) and results from the combined action of several loci, one of which has a major impact (MONTCHAMP-MOREAU and CAZEMAJOR 2002). The genetic analysis of the trait in this species is facilitated by two facts: (i) it is not associated with complex chromosomal inversions, as is usually the case, and (ii) gene order is very well conserved between *D. simulans* and its close relative *D. melanogaster*, so that the *D. melanogaster* genome data can be used to perform fine genetic mapping in *D. simulans*. By this means, the major drive locus was recently shown to lie close to the *Nrg* gene, located in the cytological band 7E-F of the X chromosome (DEROME *et al.* 2004).

Using the same *sex-ratio* ( $X^{SR6}$ ) and standard X chromosomes as in DEROME *et al.* (2004) and additional polymorphic molecular markers, we have now more precisely mapped the candidate region for the major drive locus. We found that it contained a duplication, which was also studied by *in situ* hybridization to polytene chromosomes. Its association with the *sex-ratio* trait was then checked by examining X chromosomes sampled in two natural populations. Finally, we used RT-PCR to find out

Sequence data from this article have been deposited with the EMBL/GenBank/DDBJ Data Libraries under accession nos. AM040844-AM040888 and AM040157-AM040171.

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whether the candidate genes revealed by the mapping were expressed in the testis.

## MATERIALS AND METHODS

**Fly stocks used for genetic mapping and *in situ* hybridization:** To map the distorter elements on the X chromosome, we examined a collection of recombinants between the *sex-ratio* chromosome X<sup>SR6</sup> (which produces 95% female progeny in a suppressor-free background) and the *standard* (non-driving) chromosome X<sup>sm,z</sup> carrying mutations at the *singed* (*sn*) and *lozenge* (*lz*) loci flanking the region of interest. The stocks carrying the X<sup>SR6</sup> and X<sup>sm,z</sup> chromosomes, and the crossing scheme used to produce the recombinants, are described in DEROME *et al.* (2004).

*In situ* hybridization was performed on the X<sup>SR6</sup> and the X<sup>sm,z</sup> chromosomes. We also examined X chromosomes randomly sampled in the wild. A first sample of 10 *sex-ratio* and five *standard* X chromosomes was from Antananarivo (Madagascar), collected in 2000 and described in DEROME *et al.* (2004). The second sample was collected in 1999, in La Saline (Reunion). The mean percentages of females produced in a suppressor-free background by the X chromosomes from La Saline were measured as in DEROME *et al.* (2004). Seven were found to be *standard* [X<sup>SA138</sup> (49% of females), X<sup>SA37</sup> (50%), X<sup>SA8</sup> (51%), X<sup>SA131</sup> (51%), X<sup>SA10</sup> (52%), X<sup>SA125</sup> (52%), X<sup>SA40</sup> (52%)] and six *sex-ratio* [X<sup>SA123</sup> (72%), X<sup>SA130</sup> (78%), X<sup>SA141</sup> (82%), X<sup>SA13</sup> (84%), X<sup>SA3</sup> (92%), X<sup>SA22</sup> (93%)].

**DNA and RNA extraction and amplification, cloning, and sequencing:** Extraction of single male genomic DNA and PCR amplification were carried out using conventional protocols (see DEROME *et al.* 2004). Total RNA extraction was performed with the SV total RNA isolation system (Promega, Madison, WI), according to the manufacturer's instructions. We used samples of 10 whole males (5 days old) and of the testes of 50 males dissected in PBS and then kept in RNAlater (Ambion, Austin, TX). RT-PCR was performed using the M-MLV kit (Promega). To prevent any confusion with amplifications of any residual DNA that could have been present in the RNA extracts, the markers were chosen so that they spanned at least one intron (with the exception of *CG12081*, which had no introns).

The PCR and RT-PCR amplification primers are shown in Table S1 (supplemental data at <http://www.genetics.org/supplemental/>). There were designed using the *D. melanogaster* genomic sequences from GenBank (accession nos. AE003443 and AE003444). They span a region ~240 kb long surrounding the *Nrg* gene on the X chromosome of *D. melanogaster* (according to genome annotation Release 4.0). When necessary, they were corrected after BLAST on *D. simulans* sequences available at <ftp://genome.wustl.edu/>. The amplification products were cloned in the pGEM-T Easy Vector (Promega) according to the manufacturer's instructions. Sequencing was carried out using an ABI-3100 sequencer.

***In situ* hybridization:** Polytene chromosome spreads were prepared from salivary glands of male larvae, which had been fixed for 1 min in 45% acetic acid and then for 3 min in lactic acid/H<sub>2</sub>O/acetic acid (1:2:3, v:v:v). The clones used as probes were labeled with biotin, using the nick translation system (Invitrogen, San Diego), or with digoxigenin (DIG)-11-dUTP, using the DIG nick translation mix (Roche). The probe solution (~0.01 μg DNA/μl for each probe) was prepared in 50% formamide/4× SSC/10% dextran sulfate, deposited on the slides (10 μl/slide), and then covered with a coverslip. Chromosome and probe DNA were simultaneously denatured for 5 min at 72° and incubated overnight at 37°. The slides

were then washed for 15 min at 38° in 1× SSC/50% formamide, for 8 min at 38° in 2× SSC, and for 5 min at room temperature in 4× SSC/0.5% Tween. Detection was performed using fluorescein-labeled avidin and rhodamin-labeled anti-digoxigenin (chromosome *in situ* system, Oncor-Appligene), following the manufacturer's instructions. After three washes in 4× SSC/0.5% Tween at room temperature, the preparations were counterstained and mounted in DAPI/Antifade (Oncor-Appligene).

Slides were observed under a Zeiss Axioplan 2 epifluorescence microscope. Chromosome images were generated using a highly sensitive CCD camera (Princeton Instruments, Evry, France) and the Metaview 4.1.7 image analysis system (Universal Imaging, West Chester, PA).

## RESULTS

**Characterization of the *sex-ratio* duplication:** While fluorescent *in situ* hybridization to polytene chromosomes indicated that gene arrangement in the region was conserved between *D. melanogaster* and the *standard* chromosome of *D. simulans*, we did detect a duplication on X<sup>SR6</sup>, extending from gene *Trf2* to gene *org-1* (Figure 1). The four genes located between *Trf2* and *org-1* in *D. melanogaster* (*CG32712*, *CG12125*, *CG1440*, and *CG12123*) were present in the duplication (data not shown), whereas the genes located just outside the *Trf2/org-1* fragment (*CG32711* and *CG32713*) were not detected. The duplication appeared to have been inserted in a direct orientation (supplemental Figure S1 at <http://www.genetics.org/supplemental/>), distally from the original fragment, and within the intergenic region between the *CG32711* and *Trf2* genes. The duplication seemed to contain a complete copy of *Trf2* since, on its distal (telomeric) side, a hybridization signal was obtained with a probe homologous to the noncoding region adjacent to the 5'-end of the gene. It seemed to end close to the 5'-end of *org-1* on its proximal side. Indeed, there was no hybridization signal with a probe spanning the noncoding region adjacent to the 5'-end and the start of exon 1, whereas there was a hybridization signal with a probe straddling exon 1 and intron 1. According to genome data for *D. melanogaster*, the duplicate fragment is expected to be ~40 kb in length. Repeated and independent sequencing of PCR products revealed sequence differences between the original (SRo) and duplicated (SRd) copies of *Trf2*, *CG12125*, and *org-1* markers on the X<sup>SR6</sup> chromosome. The divergence between the SRo and SRd copies was in the same range ( $0.0096 < D < 0.0152$ , depending on the marker) as between either copy and the sequence of the standard chromosome ( $0.0099 < D < 0.0258$ ). In contrast, we obtained only one sequence for the markers within *CG32712*, *CG1440*, and *CG12123*, and this was different from that carried by the standard chromosome ( $0.0116 < D < 0.0150$ , depending on the marker). This implies either that we failed to amplify one copy of these markers or that the SRo and SRd

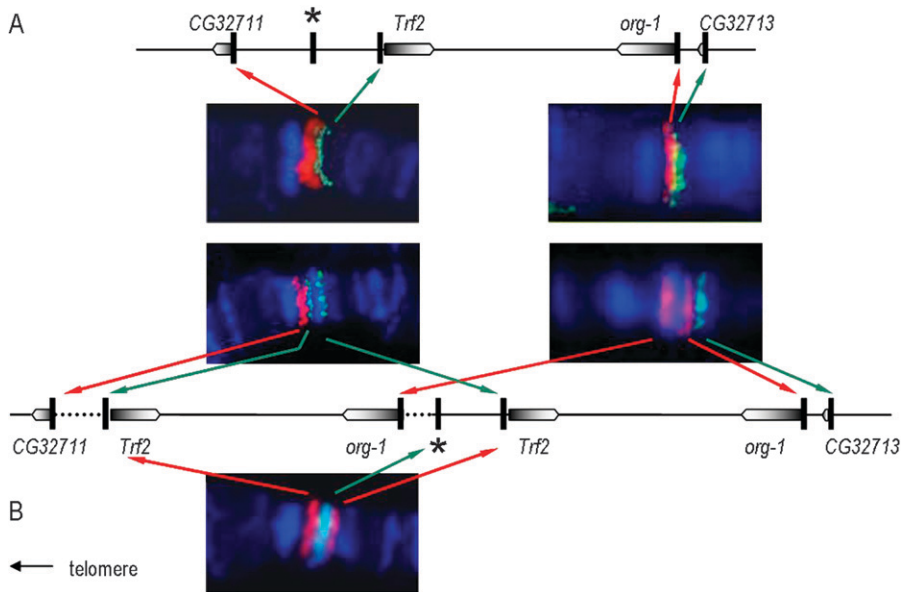


FIGURE 1.—Visualization of the *sex-ratio* duplication by *in situ* hybridization. The gene organization on (A) *D. simulans* standard X and (B) *sex-ratio* X<sup>SR6</sup> chromosomes was deduced from the relative position of hybridization signals obtained with the corresponding markers in a double-labeling experiment with probes marked with fluorescein (green) or rhodamin (red) on polytene chromosomes counterstained with DAPI. Genes are represented by boxes (pointed end is the 3'-end); vertical bars indicate the position of molecular markers. The star corresponds to a marker located in the intergenic region between the *CG32711* and *Trf2* genes.

copies are identical. Comparison with the banding pattern of standard X chromosomes of *D. melanogaster* (Canton-S) and *D. simulans* showed that the duplication is associated with an extra DAPI-positive band located in the 7E subdivision on X<sup>SR6</sup>, which suggested that AT-rich material had also been added (Figure 2).

The *sex-ratio* X<sup>SR6</sup> chromosome was extracted from laboratory stock descended from flies collected in Mahé (Seychelles) in 1981. All 16 *sex-ratio* chromosomes from Madagascar and Reunion that we examined carried both the duplication (*in situ* hybridization with *Trf2* and *org-1* markers) and the extra DAPI-positive band observed on X<sup>SR6</sup>, whereas the 12 *standard* chromosomes from these geographical locations did not have either. We therefore propose that the duplication, or a part of it, is a component of the major *sex-ratio* locus.

**Mapping of the distorter elements:** The segregation ratios of the parental *sex-ratio* X<sup>SR6</sup> and *standard* X<sup>sn,lz</sup> chromosomes as well as those of the recombinant chromosomes are given in Figure 3. All the + + recombinants were *sex-ratio*, although their drive ability was significantly lower on average than that of the parental X<sup>SR6</sup> (91.8 and 95.6% of females in the progeny, respectively; Mann-Whitney rang test  $P < 10^{-4}$ ). The mean percentage of females produced by males carrying the *sn lz* recombinant chromosomes (51%) was slightly but not significantly higher than the values obtained with the parental standard chromosome (49.7%). The segregation ratios of the + *lz* and *sn* + recombinants followed a bimodal distribution, with a group of non-driving chromosomes (<60% of females) and a group of *sex-ratio* chromosomes (>70% of females). In both cases, the recombinant *sex-ratio* chromosomes had very variable segregation ratios and produced a segregation bias that was lower on average than that of the parental X<sup>SR6</sup> (88.7 and 83.4% of females, respectively; Mann-

Whitney rang tests  $P < 10^{-4}$ ). The data thus supported the previous conclusion that an additional locus with little or no intrinsic effect did enhance the sex-ratio bias induced by the major locus (MONTCHAMP-MOREAU and CAZEMAJOR 2002).

The genetic analysis of *sn* + and + *lz* recombinants was performed using the markers listed in supplemental Table S1 at <http://www.genetics.org/supplemental/>. The results were consistent with gene arrangement

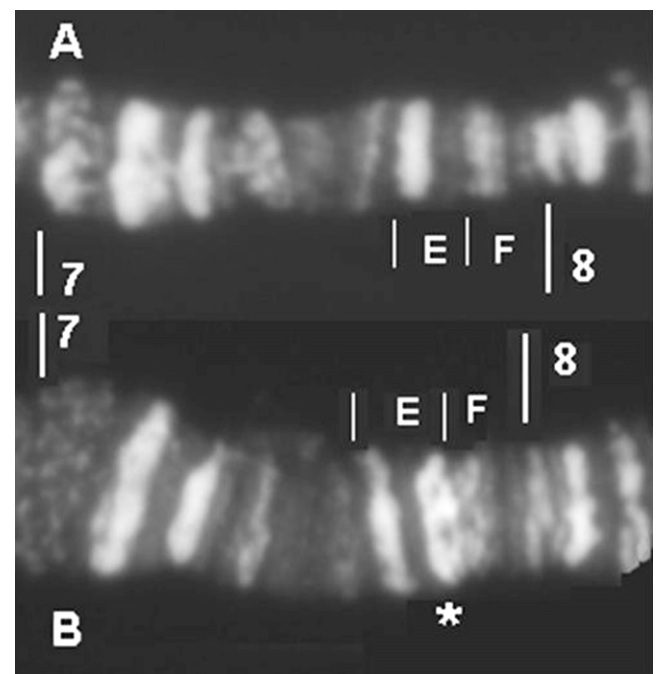


FIGURE 2.—Banding pattern in the 7A-8A division of polytene chromosome X stained with DAPI: (A) *D. simulans* standard. (B) *D. simulans sex-ratio* (X<sup>SR6</sup>). The additional band on X<sup>SR6</sup> is indicated by the star.

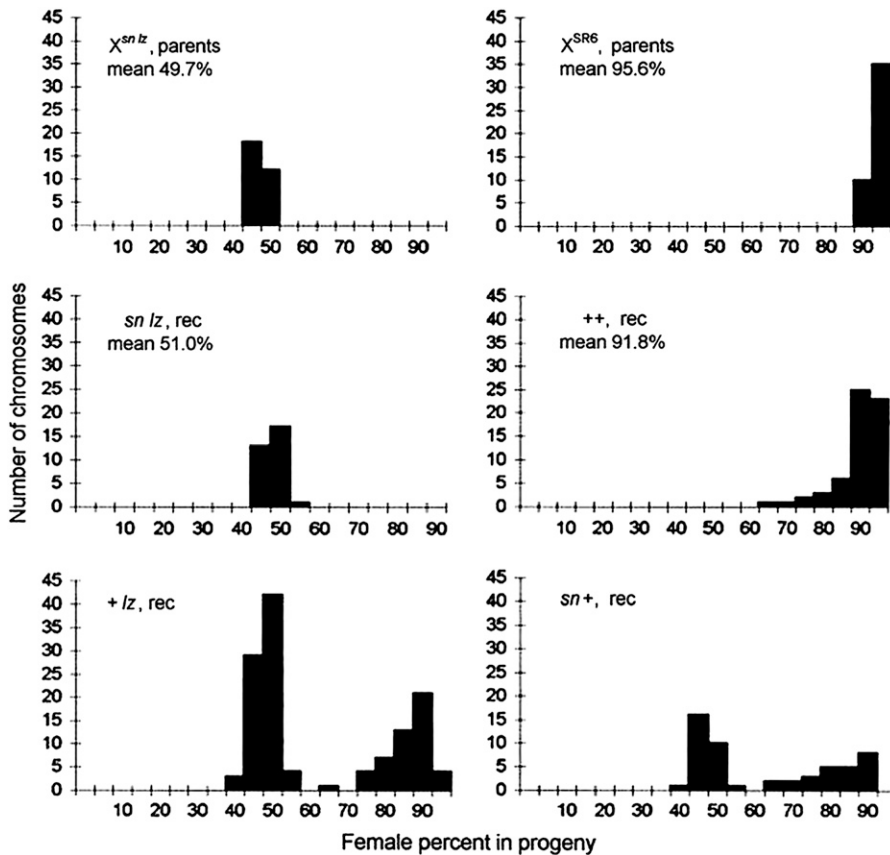


FIGURE 3.—Percentages of females in the progeny of males carrying the parental chromosomes  $X^{sn lz}$  (standard) and  $X^{SR6}$  (*sex-ratio*), and the recombinant chromosomes  $sn lz$ ,  $++$ ,  $sn +$ , and  $+ lz$ . Each value plotted on the histograms corresponds to the mean calculated from the individual progeny ( $\geq 50$  flies each) of five males carrying a given X chromosome in a drive-sensitive reference background (details on the protocol in MONTCHAMP-MOREAU and CAZEMAJOR 2002).

conservation in the surveyed region between *D. melanogaster* and the standard chromosomes of *D. simulans* and the direct orientation of the *sex-ratio* duplication. Several of the markers included in the duplication had polymorphic sites (see above), which made it possible to distinguish breakpoints within the duplicated fragment from those within the original fragment, and thus to find out whether the recombinant chromosomes retained a duplication. The results are shown in Figure 4.

The examination of  $sn +$  recombinants showed that (i) none of the 41 chromosomes that had lost the duplication were able to induce drive, even when they retained part of the original *Trf2/org-1* region from  $X^{SR6}$  (from 44 to 56% of females on average within the progeny), and (ii) the 27 chromosomes that still carried the duplication produced female-biased progeny, even when the breakpoint occurred within the duplicated fragment and replaced part of it with a fragment from the standard chromosome (in one case extending from its distal end to the *org-1* marker inclusive). The mean female ratios observed varied widely (66–94%) among these chromosomes. Using a marker located within the *sniffer* gene ( $\sim 200$  kb distal to *CG10555*), we showed that the source of this variation was located far from the region studied, since it was found in the same range regardless of whether the breakpoint was proximal or distal to *sniffer* (67–94 and 69–94%, respectively; Mann-Whitney test  $P = 0.81$ ).

Among the  $+ lz$  recombinant chromosomes, the phenotypic shift occurred at some distance from the duplication, beyond the *Nrg* marker. Further molecular analysis confirmed that the duplication was not sufficient *per se* for drive to be expressed. Indeed, the six chromosomes with a breakpoint located between the *otu* and *CG11265* markers, which all induced equal-progeny sex ratios (45–55% of females), carried the duplication (control with *Trf2* and *org-1* markers). A slight bias toward females (69%) was obtained with a chromosome that had a breakpoint between the *CG11265* and *CG2056* markers. A chromosome with its breakpoint between *CG2056* and *CG12065* produced an equal sex ratio, whereas all the chromosomes with more distant breakpoints, the closest of which was within the *Crag* gene, produced a marked female bias ( $\geq 77\%$ ). Moderate distorters are known to have very unstable drive expression (MONTCHAMP-MOREAU and CAZEMAJOR 2002), and so we could not be sure that the apparently non-driving chromosome was totally devoid of drive activity. Unfortunately, we had not kept the corresponding iso-X line and so could not check its phenotype. Whatever it is, some other element, located between the *Nrg* and *Crag* markers, is required for drive expression. As had already been found for the  $sn +$  recombinants, a large range of segregation ratios was observed among the 48  $+ lz$  chromosomes with a breakpoint beyond *Crag*. The source of this variation was probably remote from

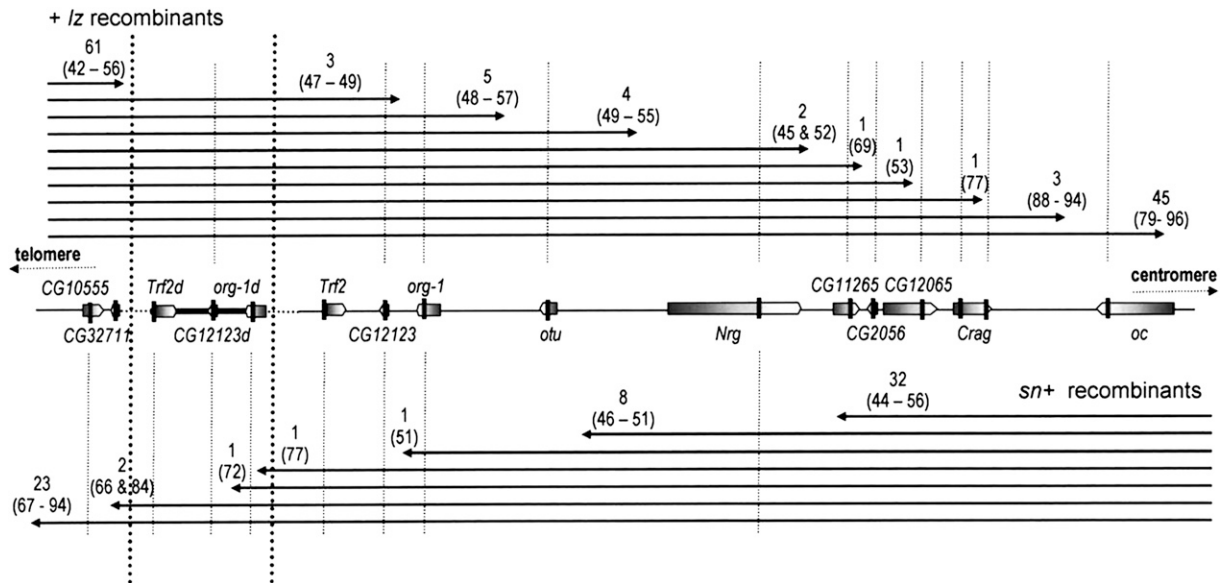


FIGURE 4.—Phenotype and genotype data on recombinant X chromosomes. The chromosomal region, from *CG10555* to *ocelliless* (*oc*), is represented according to its deduced organization on the *sex-ratio*  $X^{SR6}$  chromosome. The boxes represent the genes, the dotted lines aligned with the solid vertical bars show the position of the markers, and the two vertical dotted lines mark off the duplication. The arrows represent the part of the + *lz* (top) and *sn* + (bottom) recombinant chromosomes that comes from  $X^{SR6}$ . The number of chromosomes with a breakpoint falling between two markers is given, together with the corresponding range of the mean percentage of females that they induce (within parentheses).

the region studied since the range of variation was similar regardless of whether the recombination occurred proximal or distal to an additional marker designed within the gene *Lim1*, located ~200 kb from *Crag* (80–96% of females and 77–96%, respectively, Mann-Whitney test  $P = 0.99$ ).

**Testicular expression of genes located within the candidate regions:** The expression in the testis of the six duplicated genes (*Trf2*, *CG32712*, *CG12125*, *CG1440*, *CG12123*, and *org-1*) and the seven genes located in the second candidate region (*CG11265*, *CG12111*, *CG2056*, *CG12065*, *CG12081*, *CG12659*, and *Crag*) was tested by RT-PCR of appropriate markers (supplemental Table S1 at <http://www.genetics.org/supplemental>), followed by cloning and sequencing (sequence accession nos. AM040157–AM040171). All the genes apart from *CG12081* and *CG12659* were found to be expressed in the testes of *sex-ratio*  $X^{SR6}$  and *standard* males. The failure of RT-PCR, with regard to the *CG12081* and *CG12659* markers, probably resulted from the absence or a very low level of transcripts in the testes of both types of males. Indeed, we easily obtained amplification products using RNA extracts from entire flies or genomic DNA (for *CG12659*) or genomic DNA only (for *CG12081*). Regarding the genes included in the duplication, *sex-ratio* males provided two different cDNA sequences for *Trf2*, *CG12125*, and *org-1* markers (four polymorphic positions among 764, one among 929 and six among 926, respectively), which were consistent with those obtained from genomic DNA, indicating that both copies of these genes were expressed. We failed to

detect any trace of a second sequence for *CG32712*, *CG1440*, or *CG12123*, but this was to be expected from the genomic DNA data (no polymorphism was detected between SRo and SRd markers, or polymorphic sites were restricted to introns). Therefore, we cannot draw any conclusion regarding these three genes.

## DISCUSSION

We have shown that the primary *sex-ratio* locus on the chromosome  $X^{SR6}$  of *D. simulans* contains two interacting elements. One of these elements was genetically tracked to a tandem duplication, containing six annotated genes, at least three of which are transcriptionally active in the testis. The observation that drive persists after recombination has changed the alleles within a very large proportion of the duplication suggests that it does not involve specific, functionally divergent alleles from  $X^{SR6}$ , but rather a difference in gene dosage where two copies confer drive. This possibility is worth noting, because it may be a common feature of meiotic drive systems. Indeed, as far as we are aware, the only other driver for which we have sufficient genetic resolution, the autosomal *Segregation distorter* of *D. melanogaster*, also displays a duplication. In that case, it has been demonstrated that gene dosage alone, either of the key distorter locus or of a modifier locus, can confer drive (KUSANO *et al.* 2002).

*Sex-ratio* drive in *D. simulans* is linked to nondisjunction of the Y chromosome sister chromatids during meiosis II (CAZEMAJOR *et al.* 2000). Apart from *Trf2*,

none of the genes included in the duplication are known to be involved in meiosis. *CG32712*, *CG12125*, *CG1440*, and *CG12123* all encode products with an unknown or only putatively assigned function (DRYSDALE and CROSBY 2005), whereas the product of *org-1* is a member of a family of transcription factors that plays a wide range of roles during development (LEE *et al.* 2003). *Trf2* encodes a member of the TATA box-binding protein family (RABENSTEIN *et al.* 1999). The complex utilizing *Trf2* probably has numerous targets (OHLER *et al.* 2002), but interestingly these include genes involved in DNA replication and chromatin remodeling (HOCHHEIMER *et al.* 2002). It has recently been shown that in *D. melanogaster* certain defects in *Trf2* cause chromosome nondisjunction (SIMONOVA *et al.* 2005). In addition, its human and murine homologs are important components of gene expression in the testis (RABENSTEIN *et al.* 1999; JIAO *et al.* 2002). Both copies of *Trf2* are expressed in the testes of *sex-ratio* males, which can be expected to change the transcript level relative to that of standard males. Among the testis-expressed genes located within the second mapped region, *CG12111*, *CG2056*, and *CG12065* encode products with unknown or putative molecular functions, lacking any apparent relationship with meiosis (DRYSDALE and CROSBY 2005). So does the gene *Crag*, which encodes a calmodulin-binding protein that is related to a Rab3 GDP/GTP exchange protein and putatively involved in synaptic transmission (XU *et al.* 1998). In contrast, the product of *CG11265* is a more likely candidate as its yeast homolog is a DNA polymerase required for sister-chromatid cohesion (WANG *et al.* 2000). In planning further studies, however, three points must be borne in mind: (i) the two groups of genes mapped here mark off the chromosomal region required for drive expression, and so other element(s) located between them may also be involved; (ii) it is theoretically possible that the additional AT-rich material accompanying the duplication, rather than the duplication itself, causes drive; and (iii) the function of a segregation distorter is not necessarily directly related to the mechanism of maintaining Mendelian fairness (HAWLEY 2001).

The identification of candidate genes constitutes a major step toward unraveling the molecular mechanism underlying *sex-ratio* drive in *D. simulans*, and beyond it in other *Drosophila* or dipteran species, where a genetic analysis of the trait is difficult or even impossible to perform. This could make it possible to find out whether *sex-ratio* drive is related to a common molecular pathway in all these species. Given their lack of a homologous region, segregation distorters acting against the Y chromosome could theoretically evolve anywhere on the *Drosophila* X chromosome.

*Sex-ratio* drive in *D. simulans* exhibits the genetic complexity shared by all the drive systems that have been investigated in this regard (WU and BECKENBACH 1983; TEMIN *et al.* 1991; HIATT and DAWE 2003; LYON

2003). This supports the view that there is an endless arms race between the X chromosome and the rest of the nuclear genome during which the X chromosome would tend to accumulate distorters, whereas the Y chromosome and the autosomes would accumulate drive suppressors. However, we have no definite evidence so far that cycles of distortion and suppression can happen repeatedly in a given species. The identification of these two interacting elements on the X<sup>SR6</sup> chromosome will give an opportunity to test this hypothesis in *D. simulans*. Indeed, it has been demonstrated that distorter alleles have recently spread in this species, causing a selective sweep at the neighboring locus *Nrg* (DEROME *et al.* 2004). Surveying the pattern of DNA sequence polymorphism and linkage disequilibrium along the two candidate regions mapped here and in the surrounding area should help to identify the distorter elements and also yield information about where and under what conditions each of them became established in the populations. The challenge lying ahead will be to trace the evolutionary history of the *sex-ratio* system.

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