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Genetics

Repair-defect mutations inhibit rDNA magnification in *Drosophila* and discriminate between meiotic and premeiotic magnification

(unequal sister-chromatid exchange/gene amplification/molecular drive)

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ABSTRACT **We have examined rDNA magnification in *Drosophila melanogaster* males carrying one of 11 recombination- or repair-defective mutations representing seven loci. We show that mutations defined by a defect in postreplication repair (*mus-101*, *mei-41*, and *mus-108*) are also defective in rDNA magnification, whereas mutations that do not affect postreplication repair have little or no effect on magnification. *mei-41* inhibits only premeiotic magnification events, while *mus-108* blocks both premeiotic and meiotic events. This suggests that meiotic and premeiotic events share some but not all functions. A molecular analysis of rDNA magnification reveals that in *mus-108* males, changes in the rDNA restriction pattern can occur within one or a few generations under magnifying conditions. We interpret these data in terms of the role of DNA repair systems in rDNA magnification and in terms of stable maintenance of tandemly repeated genes.**

In *Drosophila* males there are two clusters of tandemly repeated rRNA genes (rDNA), each with ≈250 copies. One of these arrays is located in the proximal heterochromatin of the X chromosome, and the other, on the Y chromosome (1, 2). Each array comprises a number of distinct classes of rRNA genes that differ by the presence or absence of transposon-like insertions and by variations in the spacer length (3, 4). Different wild-type strains of *D. melanogaster* show extraordinary differences in the degree to which various repeat classes are represented in their rDNA (5, 6). Individuals with partial deficiencies at either cluster, known as bobbed (*bb*) mutants, are also found in wild-type populations and in laboratory stock collections (1). However, within individual laboratory stocks, changes in rDNA redundancy or repeat class composition are rare (5). This suggests that there are events or processes that can change the copy number of the rDNA or the representation of various repeat classes.

Alterations in X chromosomal rDNA redundancy occur in males carrying a Ybb^- chromosome or its derivatives (7–9). Ybb^- is a Y chromosome from which >80% of the rDNA is deleted (8). These changes in rDNA redundancy may be observed as either stable reversions (magnification) from *bb* to bb^+ or as mutations (reduction) from bb^+ to *bb* or from *bb* to bb^l (bobbed lethal). Several lines of evidence demonstrate that magnification can occur both meiotically and premeiotically (8, 9). Considerable evidence suggests that meiotic magnification and reduction are reciprocal results of unequal sister-chromatid exchange occurring within the X chromosome rDNA (8–10).

We have examined rDNA magnification in males carrying repair- and/or recombination-defective mutations (11–13) at one of seven X chromosomal loci. Previous experiments showed that two alleles of *mei-41* strongly inhibit magnification (14). We now have extended those observations by further testing one of these alleles and by demonstrating a magnification defect for three other alleles of *mei-41*. Alleles of two other loci required for postreplication repair, *mus-101* and *mus-108*, also strongly suppress magnification. We conclude that at least some components of rDNA magnification are executed by functions that are also involved in postreplication repair systems. We also show that repair-defective mutants that are normal with respect to postreplication repair have little or no effect on magnification.

We show that the germ lines of *mus-108* bb^2/Ybb^- males produce X chromosome *bb* loci that differ from the father's X chromosome *bb* locus. This is a consequence of the amplification of certain repeat classes at the expense of others. Thus $mus\text{-}108^+$ is required for stability of the tandem array under magnifying conditions and for normal frequencies of magnification. We discuss these results in terms of molecular drive (15, 16) within a tandem array.

METHODS

Construction of *bb* Chromosomes Carrying Repair- or Recombination-Defective Mutations. Except where indicated the mutations and chromosomes used in this study have been described (1). The meiotic (mei^-) and/or mutagen-sensitive (mus^-) mutations used in this study are listed in Table 1. $mei\text{-}41^{104D1}$, $mei\text{-}41^{104D2}$, and $mei\text{-}41^{103D1}$ have been shown to be alleles of *mei-41* by J. Mason (personal communication). These mutations were placed on a bb^2-bearing X chromosome by obtaining the appropriate recombinants from females of the genotype *y* (*mei* or *mus*) $y^+/y\ pn\ cv\ m\ f\ bb^2$. The $y\ pn\ cv\ m\ f\ bb^2$ chromosome used here was a single recombinant obtained from a $bb^2/y\ pn\ cv\ m\ f\ bb^+ \cdot y^+$ female. Thus, all of the X chromosomes carry the same bb^2 allele. Moreover, the extensive outcrossing required to construct these crosses randomized the autosomal background of the mutant-bearing bb^2 stocks.

All of these chromosomes were tested for both a *bb* mutation and for mutagen-sensitivity. To test for the presence of bb^2, males carrying each of the recombinant chromosomes were crossed to $sc^4sc^8/dl\text{-}49$ females and the X/sc^4sc^8 females were examined with respect to the bobbed phenotype. (sc^4sc^8 denotes $In(1)\ sc^{4L}sc^{8R}$, y $sc^4sc^8cv\ v\ B$, an X chromosome from which the rDNA has been completely deleted; *dl-49* denotes *In(1) dl-49*, *y Hw m* g^4 and is a bb^+ balancer chromosome.) The bobbed phenotype includes short thin bristles, abdominal etching, and lengthened development time. In this study, flies were scored as bb^+ only when the bristles were of normal length and thickness and when there was no abdominal etching. Tests for sensitivity to 0.08% methyl methanesulfonate are summarized in Table 1.

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Abbreviation: kb, kilobase(s).

Analysis of rDNA. DNA was extracted from single flies (or groups of 10 flies) as described (19) and digested with *Eco*RI, *Hin*dIII, and/or *Bam*HI in buffer supplied by the vendor (International Biotechnologies, New Haven, CT). Digests were electrophoresed in 0.7% agarose gels for 24–36 hr and blotted onto nitrocellulose. The probe was an 11.5-kilobase (kb) *Eco*RI fragment (Fig. 1) corresponding to a contiguous rDNA coding unit inserted into pMB9 (20). Hybridizations were done at 37°C in 53% (vol/vol) formamide. After extensive washing in 10 mM Tris Cl, pH 8.0/0.1% $NaDodSO_4$, the filters were exposed to Kodak XAR film for periods ranging from 8 hr to 1 week.

RESULTS

Postreplication-Repair-Defective Mutants Strongly Inhibit rDNA Magnification. We measured rDNA magnification by crossing bb^2/Ybb^- males to $sc^4sc^8/dl\text{-}49$ females and scoring the X/sc^4sc^8 daughters with respect to the bobbed phenotype. bb^+ revertants were confirmed by test-crossing putative bb^+ X/sc^4sc^8 females to sc^4sc^8/B^SY males. Data for 11 X chromosomes carrying known recombination- or repair-defective mutations are presented in Table 1. Magnification in males carrying either *mus-102*, *mei-9*, or *mus-109* occurs at frequencies similar to that observed in a bb^2 control. Intermediate frequencies of magnification are seen in males carrying $mus105^{A1}$, $mei\text{-}41^{103D1}$, or $mus101^{D2}$. Finally, the frequency of magnification is reduced by a factor of 10 or more in males carrying $mus101^{D1}$, $mus108^{A1}$, $mei\text{-}41^{1}$, $mei\text{-}41^{104D1}$, or $mei\text{-}41^{104D2}$.

The magnification defect in males carrying any one of four alleles of *mei-41* confirms the previous observations of Hawley and Tartof (14). Moreover, the strong suppression of magnification by $mus\text{-}101^{D1}$ and *mus-108* suggests that postreplication-repair mutants may commonly be magnification-defective as well. Even the weak effects of $mus\text{-}101^{D2}$ and $mei\text{-}41^{103D1}$ on magnification are consistent with this conclusion, in that these alleles are only weakly mutagen-sensitive (see Table 1). Moreover, although a defect in postreplication repair has been observed biochemically for strong alleles of *mus-101* and *mei-41* (11, 13), it has not been observed for either of these two weak alleles (13, 18).

Regrettably, $mus\text{-}108^{A1}$ is the only known allele of this locus. Thus, it is not possible to use other alleles to demonstrate that *mus-108*, and not some other closely linked mutation, is responsible for the magnification defect. However, in numerous constructions the magnification defect has always cosegregated with the mutagen-sensitivity.

Table 1. Repair-defective mutations inhibit magnification

Paternal genotype	Repair defect*	Relative survival of $MeSO_2OMe$-treated males†	Frequency of bb^+ revertants‡
bb^2/B^sY	None	1.03	≤0.001 (4049)
bb^2/Ybb^-	None	—	0.173 (283)
$mus\text{-}102^{D1}$ bb^2/Ybb^-	NI	0.02	0.158 (453)
$mus\text{-}109^{D1}$ bb^2/Ybb^-	NI	0.04	0.096 (713)
$mei\text{-}9^{b}$ bb^2/Ybb^-	E	0.00	0.140 (659)
$mus\text{-}105^{A1}$ bb^2/Ybb^-	NI	0.01	0.051 (943)
$mus\text{-}101^{D1}$ bb^2/Ybb^-	PR	0.01	0.006 (316)
$mus\text{-}101^{D2}$ bb^2/Ybb^-	NI	0.17	0.034 (647)
$mus\text{-}108^{A1}$ bb^2/Ybb^-	PR	0.08	0.016 (437)§
$mei\text{-}41^{1}$ bb^2/Ybb^-	PR	0.00	0.019 (529)
$mei\text{-}41^{104D1}$ bb^2/Ybb^-	PR	0.02	0.012 (318)
$mei\text{-}41^{104D2}$ bb^2/Ybb^-	NI	0.06	0.008 (481)
$mei\text{-}41^{103D1}$ bb^2/Ybb^-	NI	0.31	0.016 (437)

*This column denotes only whether or not the indicated allele has been shown to be defective in postreplication repair (PR) or excision repair (E). NI indicates that no biochemical defect has been identified. Although $mei\text{-}41^{1}$ is a strong allele of this locus, it has not been tested for a biochemical defect. It is listed here as a postreplication-defective mutant on the basis of the phenotype of other strong *mei-41* alleles. For details, see refs. 11–13, 17, and 18.

†Survival of mutation-bearing X/B^sY males compared to their $\overline{XX}/B^sY$ sisters after treatment with 0.08% methyl methanesulfonate ($MeSO_2OMe$). (Values have been corrected for the sex-ratio in untreated cultures). $MeSO_2OMe$ treatment was as described (17).

‡Each number in parentheses indicates the number of X/sc^4sc^8 progeny scored.

§Of the seven revertants recovered in this cross, six were recovered in one of the 10 bottles tested.

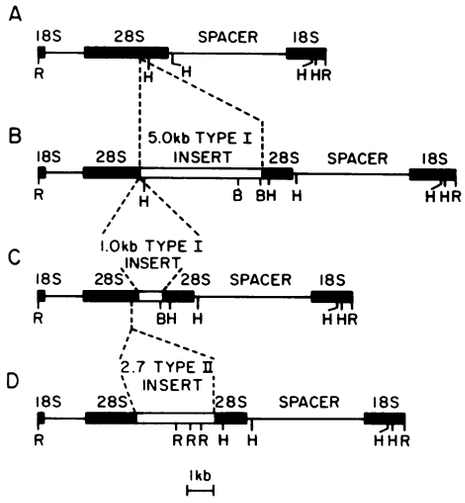

FIG. 1. *Eco*RI (R), *Hin*dIII (H), and *Bam*HI (B) restriction maps for the major rDNA repeat classes. Darkened blocks indicate the 18S and 28S rRNA genes and lines represent spacer sequences. Open blocks depict the major types of insertions. (*A*) The noninserted basic repeat. (*B*) A repeat bearing a 5-kb type I insertion. (*C*) A repeat bearing a variant (1.0-kb) type I insertion. (*D*) A repeat bearing a type II insertion.

Regrettably, $mus\text{-}108^{A1}$ is the only known allele of this locus. Thus, it is not possible to use other alleles to demonstrate that *mus-108*, and not some other closely linked mutation, is responsible for the magnification defect. However, in numerous constructions the magnification defect has always cosegregated with the mutagen-sensitivity.

***mei-41* Inhibits Premeiotic But Not Meiotic Magnification Events.** Tartof (8) has demonstrated that bb^+ reversion may result from both early (premeiotic) magnification events, which are defined as those events that give rise to clusters of bb^+ revertants among the progeny of single males, and from late (meiotic events), which result in small numbers (one or two per male) of bb^+ revertants. Hawley and Tartof (9) have used *bb* and bb^+ derivatives of Ybb^- ($y^+bb\ Ybb^-$) to show that early events require the bobbed phenotype for induction of magnification, whereas later meiotic events are bobbed-independent and appear to be induced as a consequence of a structural anomaly of the Ybb^- chromosome. We have used *mus-108* and *mei-41* to further distinguish between early and late events by examining the progeny of single males in magnification crosses involving these mutants and by using bb^+ derivatives of Ybb^- to induce magnification.

We present two lines of evidence to suggest that *mei-41* blocks only premeiotic magnification. First, magnification of $mei\text{-}41$ bb^2/Ybb^- males did not produce the large clusters of bb^+ revertants that were so common among the progeny of bb^2/Ybb^- males (Table 2). However, in both cases a similar fraction of males (12/49 and 7/22) produced one or two bb^+ revertants. Second, *mei-41* did not inhibit magnification in the presence of $y^+bb\ Ybb^-$. Therefore we conclude that *mei-41* blocked only premeiotic magnification events (i.e., events that are dependent upon the bobbed phenotype and produce large clusters of bb^+ revertants) and did not affect the meiotic or bobbed-independent events that produce small numbers of bb^+ revertants per male.

In contrast, *mus-108* decreased the frequency of both meiotic and premeiotic events in *Ybb*$^-$-bearing males. *mus-108* also greatly diminished the number of *bb*/y$^+$*bb Ybb*$^-$ males that produce *bb*$^+$ progeny. This suggests that the wild-type *mus-108* gene product is involved in both early and late magnification events. However, in two of the three experiments reported here, single clusters of *bb*$^+$ revertant males were produced (see Table 2, experiment B, and Table 1, footnote §). Thus, either the block to premeiotic events is leaky or events other than magnification may produce *bb*$^+$ chromosomes at a low frequency in *mus-108*-bearing germ lines. We conclude that early and late magnification events share some but not all processes.

Molecular Analysis of Magnification in Normal and Mutant Lines. Previous genetic experiments with *mei-41 bb*/*Ybb*$^-$ males revealed high frequencies of X–Y interchange involving the X chromosome *bb* locus. Hawley and Tartof (14) attributed this to chromosome breakage occurring within the rDNA under magnifying conditions. If such events occur in the germ lines of postreplication-repair-defective *bb*/*Ybb*$^-$ males, then one might also detect rearrangements or other changes in the rDNA by molecular means.

To explore such a possibility, control and mutant (*mus-108, mei-9, mei-41*, and *mus-101*^{D1}) *bb*^{2} males were backcrossed to *C(1)RM*/*Ybb*$^-$ females for four generations (G_0 through G_4, with G_0 indicating the first generation of *X*/*Ybb*$^-$ males). Each population was founded by the progeny of a single *bb*^{2}/*B*^{s}*Y* male. Each generation produced 100–200 male progeny; 30 of these males were selected at random and used to sire the next generation, and the remainder were frozen in groups of 10 for DNA extraction. For each experiment, one-tenth of the DNA was digested with either *Eco*RI or *Bam*HI or was doubly digested with *Eco*RI and *Bam*HI (see Fig. 1). DNA was blotted onto nitrocellulose and probed with an 11.5-kb uninterrupted rDNA repeat.

The *bb*^{2} *Eco*RI restriction pattern reveals no qualitative changes over five generations (Fig. 2*A*) despite the fact that by G_4, 100% of the males were *bb*$^+$. The rDNA restriction pattern also remained constant in the lines bearing *mei-9, mei-41*, or *mus-101*^{D1} (data not shown). Although no *bb*$^+$ revertants were observed in the *mus-108* cultures, the *mus-108 Eco*RI restriction pattern reveals an increase in intensity of the 17-kb band compared to the band at 11 kb. The 17-kb repeat differs from the 11-kb repeat as a result of a 5-kb insert (see Fig. 1), known as type I, located within the 28S rRNA gene (21). The autoradiographs were scanned and the ratio of the intensity of the 17-kb band relative to the intensity of the 11-kb band was determined (Fig. 3). Although in the control the ratio of these bands was constant over several generations of magnification, in *mus-108* males the intensity of the 17-kb band relative to the 11-kb band increased 4-fold.

Table 2. Single-pair magnification experiments using *mei-41*- and *mus-108*-bearing males

Male genotype	*X*/*sc*^{4}*sc*^{8} progeny: *bb*$^+$	*X*/*sc*^{4}*sc*^{8} progeny: *bb*	No. of males producing 0, 1, 2, or >2 *bb*$^+$ revertants: 0	1	2	>2	Frequency of *bb*$^+$ revertants
Experiment A							
bb^2/*Ybb*$^-$	206	928	14	8	4	23	0.182
mei-41 bb^2/*Ybb*$^-$	9	502	15	5	2	0	0.018
mus-108 bb^2/*Ybb*$^-$	0	314	48	0	0	0	≤0.003
Experiment B							
bb^2/y$^+$*bbYbb*$^-$	5	846	68	5	0	0	0.006
mei-41							
bb^2/y$^+$*bbYbb*$^-$	6	932	71	4	1	0	0.006
mus-108							
bb^2/y$^+$*bbYbb*$^-$	7	451	61	0	0	1	0.018

Males were crossed to *sc*^{4}*sc*^{8}/*dl-49* females and the *X*/*sc*^{4}*sc*^{8} female progeny were scored for *bb*. All *bb*$^+$ daughters were retested by crossing to *sc*^{4}*sc*^{8}/*B*^{s}*Y* males.

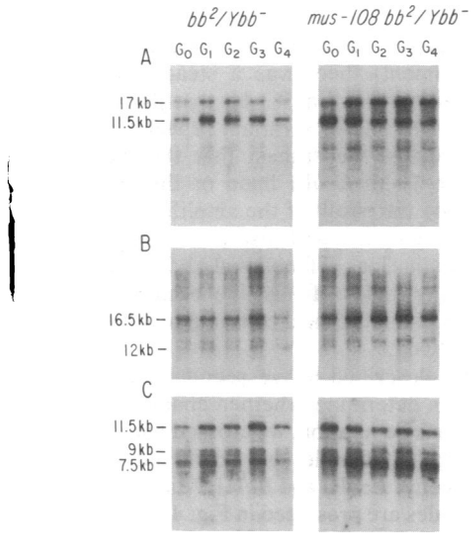

FIG. 2. The restriction pattern of *mus-108 bb*^{2}/*Ybb*$^-$ changes over four generations of magnification. DNA was isolated from males of the indicated genotype at G_0, G_1, G_2, G_3, and G_4; digested with *Eco*RI (*A*), with *Bam*HI (*B*), or with *Eco*RI and *Bam*HI (*C*); electrophoresed in a 0.7% agarose gel; and blotted onto nitrocellulose. The probe was an 11.5-kb noninserted rDNA repeat, nick-translated with [α-^{32}P]dCTP to ≈10^8 cpm/μg.

Amplification of an insert-bearing repeat was also observed in *Bam*HI digests (Fig. 2*B*) as an increase in the intensity of the 16.5-kb band in *mus-108* males undergoing magnification. This band corresponds to adjacent insert-bearing repeats. We also observed the simultaneous disappearance of a band at ≈12 kb. *Bam*HI fragments of this size represent partial deletions of the type I insert (22).

Analysis of these DNA samples after a *Bam*HI/*Eco*RI double digestion again revealed no qualitative change in the

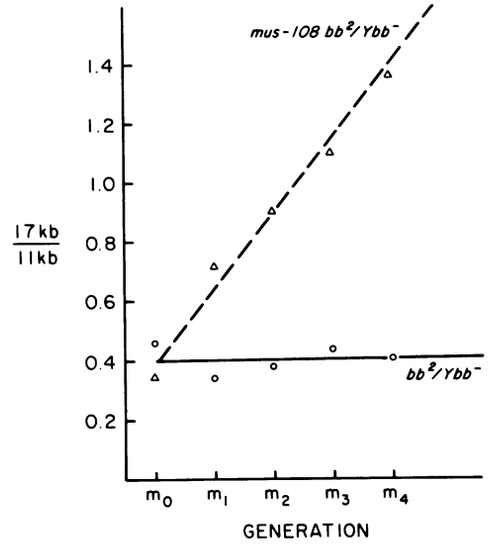

FIG. 3. The ratio of 17-kb repeats to 11-kb repeats increases over several generations in *mus-108 bb*^{2}/*Ybb*$^-$ males. The intensities of the 17-kb and 11-kb bands in Fig. 2*A* were measured using a Joyce–Loebl densitometer. The ratio is plotted here against the generation for both *mus-108 bb*^{2}/*Ybb*$^-$ (△) and *bb*^{2}/*Ybb*$^-$ (○) males.

control experiment (Fig. 2*C*) or in the lines bearing *mei-9*, *mei-41*, or *mus-101* (data not shown). However, in the *mus-108* experiment, there was a steady increase in the intensity of a minor band at 7.3 kb that presumably corresponds to the right end of a variant repeat class carrying a type I insert. Thus, we suggest that the increase in the intensity of the 17-kb *Eco*RI band or the 16.5-kb *Bam*HI fragment may be the result of the amplification of a variant repeat class carrying a type I insert. As might be expected from the continuous loss of functional 11.5-kb rDNA repeats, the Ybb^--bearing males of this line became progressively more bobbed in phenotype and consequently the line died out at generation seven.

The variants described above accumulated over several generations. To determine whether changes could be observed in only one generation, we crossed *mus-108* bb^2/Ybb^- males to $sc^4sc^8/dl\text{-}49$ females and recovered single *mus-108* bb^2/sc^4sc^8 progeny. *Eco*RI and *Bam*HI digests of DNA from 31 of these females are presented in Fig. 4. At least 6 of these isolates show changes in the rDNA restriction pattern. In sample 2 there is a new band (a) at 13 kb. In sample 22 there is a new band at 10 kb (b). Sample 23 reveals a marked increase in the intensity of a doublet at 9–10 kb (c). Samples 28 and 29 show an increase in intensity of a 9- to 10 kb-doublet (d, e) and a decrease in the intensity of the 7.5-kb bands. Finally, sample 30 lacks the band at 9 kb (f). In all, we examined 77 individuals and observed 6 clear cases of restriction-pattern variation. Our ability to assay only the appearance or disappearance of major bands may underestimate the rate and extent of variation.

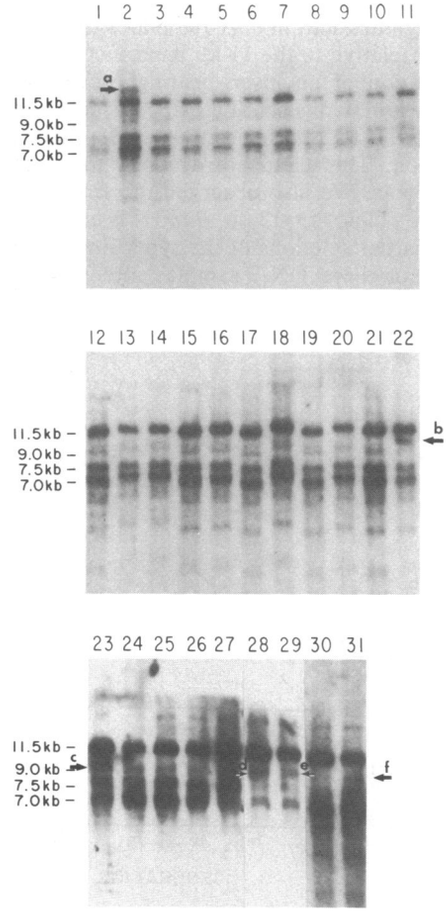

FIG. 4. *Bam*HI/*Eco*RI double digests of DNA from single X/sc^4sc^8 progeny of *mus-108* bb^2/Ybb^- males crossed to $sc^4sc^8/dl\text{-}49$ females. DNA was electrophoresed, blotted, and probed as described for Fig. 2. Bands a–f are described in the text.

No such variants were observed among 50 tested progeny of nonmagnifying *mus-108* bb^2/B^sY males (data not shown), even though these samples were prepared in exactly the same manner. This suggests that the restriction-pattern changes seen in Fig. 4 are not the consequence of problems in extraction, digestion, or blotting. Moreover, in the case of sample 2 (Fig. 4), a variant rDNA restriction pattern was also observed after digestion with *Eco*RI and *Hin*dIII. Fig. 5 displays the *Eco*RI/*Hin*dIII rDNA restriction patterns of both sample 2 and of an X/sc^4sc^8 female obtained from a nonmagnifying *mus-108* bb^2/B^sY male. These two samples differ both in the position and intensities of bands at >5.6 kb and in the relative intensities of the two bands comprising the doublet at 4.4 kb. This suggests that the variant restriction pattern observed for sample 2 in Fig. 4 is not a consequence of partial digestion. Nonetheless, in the absence of the molecular isolation and characterization of one or more of these variant repeat classes, we can say only that the passage of an X chromosome *bb* locus through a *mus-108*/Ybb^- germ line results in changes in the relative abundance of certain repeat classes and that these changes are not observed in controls.

Each of the bands that are amplified in the samples presented above can be seen as a faint band in the other non-variant digests. Thus, we suggest that the changes in restriction pattern observed among the progeny of *mus-108* bb^2/Ybb^- males do not reflect the generation of new classes of rDNA repeats but rather the amplification of one class of repeat, perhaps as a consequence of homogenization events.

DISCUSSION

Previous work has shown that magnification results in stable increases and decreases in rDNA that maintain the qualitative stability of the rDNA array (8). However, several major questions regarding rDNA magnification remain unanswered. First, although there is considerable evidence that meiotic magnification results from unequal sister-chromatid exchange, little is known about the mechanism of the premeiotic events. Second, despite numerous genetic studies (8, 9), the mechanism by which Ybb^- induces magnification is still unclear. This is of particular significance for premeiotic magnification, where we must relate the induction of magnification to the bobbed phenotype. Third, it is still unclear what role rDNA magnification plays in the normal maintenance of rDNA redundancy.

The data presented above show that premeiotic magnification requires the product of the $mei\text{-}41^+$ locus, whereas

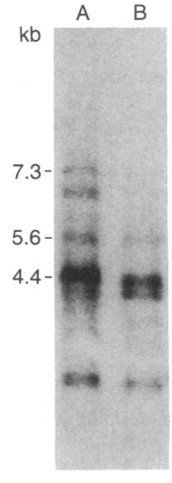

FIG. 5. *Hin*dIII/*Eco*RI double digests of DNA from X/sc^4sc^8 female number 2 (*A*) and from an X/sc^4sc^8 daughter of a nonmagnifying *mus-108* bb^2/Ybb^- male (*B*). After electrophoresis in 0.7% agarose and blotting onto nitrocellulose, the DNA was probed as described for Fig. 2.

meiotic magnification is independent of *mei-41*. Screening of ethyl methanesulfonate-treated bb^2 X chromosomes yielded three additional magnification-defective chromosomes that also inhibit only premeiotic events (unpublished observations). This demonstrates that early and late magnification do not require identical genetic functions. Early and late events also differ in that early events require the bobbed phenotype (9). This suggests that they occur by different mechanisms.

Given that rDNA amplification (compensation) occurs in the soma (23, 24) and testes (25) of X/Ybb^- males, we propose that bb^+ chromosomes arise premeiotically by the exchange-mediated resolution of amplified rRNA genes. According to this model, genes like *mei-41* are involved in the initial amplification events and genes like *mus-108* are required for the resolution of amplified "onion-skin" structures by successive exchanges to generate a unineme chromosome with increased rDNA redundancy. A similar mechanism has been proposed to explain the generation of stable gene amplification in mammalian cells (26). We propose that meiotic events occur by unequal sister-chromatid exchange and that this requires only exchange functions such as those presumably supplied by *mus-108*.

Although heterodox, this hypothesis explains the failures of premeiotic events to produce reciprocal products and provides a basis to explain the restriction-pattern changes in *mus-108*-bearing males undergoing magnification (see below). The failure to recover reciprocal products of premeiotic magnification has been attributed to their cellular lethality (8). Although this explanation is plausible prior to stem-cell formation, the subsequent divisions are syncytial and thus would not be subject to selection (27). Events occurring in this later phase would give rise to clusters of reduced lethal chromosomes. Such clusters have not been observed (8, 9). We propose that lethal chromosomes rarely occur premeiotically because such exchanges would occur between two or more duplicated copies of the rDNA on the same chromatid.

Any hypothesis that postulates different mechanisms for early and late events must account for the ability of *mus-108* to block both processes and the complete inability of ring X chromosomes to magnify (8, 10). Although the *mus-108* data can be explained simply by postulating a component common to two different processes, the total absence of bb^+ progeny from $R(1)\ bb/Ybb^-$ males suggests that sister-chromatid exchange is part of both the premeiotic and the meiotic mechanisms. However, other X chromosome aberrations, such as inversions, also magnify poorly if at all (ref. 28 and unpublished observations), so the ability of a ring X chromosome to block premeiotic magnification may be spurious.

Our data demonstrate that magnification events require functions defined by the wild-type alleles of *mei-41*, *mus-101*, and *mus-108* mutations. Because of their inability to synthesize normal-length DNA on a UV-damaged template (11–13, 18), these mutants have been defined as postreplication-repair defective. Although the mechanism of postreplication repair in eukaryotes is unclear, in prokaryotes this process is dependent on recombination between sister strands (29, 30). If a similar mechanism operates in eukaryotic cells, it might explain the effect of repair-defective mutations on the magnification process. However, alleles of *mus-108*, *mei-41*, and *mus-101* are pleiotropic and also affect such processes as recombination and mitotic chromosome stability (18). Thus, although the correlation of the magnification defect with the repair phenotype is striking, the possibility that the inhibition of magnification is a consequence of a block in some other cellular process cannot be discounted.

In addition to their role in magnification, the gene products of *mei-41* and *mus-108* also play a role in the normal maintenance of rDNA. This was shown by the high frequency of aberrations involving the rDNA in otherwise normal males bearing *mei-41* (14). The analysis of *mus-108* demonstrates that these repair systems are also required for the stable maintenance of the rDNA under magnifying conditions. We speculate that the rDNA variants produced by *mus-108* bb^2/Ybb^- males represent the aberrant resolution of failed premeiotic magnification events.

Finally, our analysis of *mus-108* bears directly on the problem of the evolution of repetitive gene families. Our data indicate that under specific genetic conditions, the qualitative make-up of the rDNA can change within a single generation, apparently by the amplification or loss of a given repeat class rather than the creation of novel variants. Accordingly, these events may reveal a mechanism for amplifying or removing variant copies within a tandem array. Although such processes occur with a small number of generations in mammalian cell lines (26), we are not aware of a previous example of such rapid changes within the germ lines of whole organisms. We argue that the cell-line studies as well as our data provide support for a role of rapid homogenization events ("molecular drive") in the evolution of tandem arrays, as suggested by Dover (15).

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