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The use of retrotransposons as markers for mapping genes responsible for fitness differences between related *Drosophila melanogaster* strains

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Summary

Hitch-hiking of dispersed mobile elements serving as molecular markers was used as a new tool for mapping quantitative trait loci in *Drosophila melanogaster*. Two *Drosophila* strains with high fitness (HA) were backcrossed repeatedly to a closely related strain with low fitness (LA) to initiate experimental populations with expected HA gene frequencies of 1/32. The frequencies of 19 insertion sites of the retrotransposons *mdg1* and *copia* were analyzed after 11 to 17 generations. Frequencies of sites from the HA line increased substantially in the pericentromeric region, indicating that one or more loci responsible for the fitness difference between the strains were located there. A maximum likelihood (ML) procedure was applied to estimate selection coefficients associated with the markers, and this indicated a broad, strongly selected region of the chromosome. At least one additional locus was localized in the middle of the 2L arm. Possible applications of this method are discussed.

1. Introduction

Elucidation of the nature of the genetic factors responsible for variation of quantitative traits represents one of the major challenges in genetics (see Sax, 1923; Mather & Jinks, 1982). A necessary first step is to map the loci that determine the variability of various quantitative characters, for which several methods have been proposed. Loci controlling quantitative traits (QTLs) have been localized relative to visible phenotypic markers, and in *Drosophila melanogaster* approximate locations of QTLs affecting bristle number on chromosomes have been determined (Thoday, 1979; Mather & Jinks, 1982; Shrimpton & Robertson, 1988*a*, *b*). The technique is limited by the density and phenotypic effects of morphological markers and erroneous map position assignments are possible (McMillan & Robertson, 1974). Only a small set of data have been obtained in this way (Thoday 1979; Shrimpton & Robertson, 1988*a*, *b*).

More recently, molecular methods for QTL mapping have been proposed (Beckman & Soller, 1983). Progress in recent years has been mostly due to the application of isoenzyme or restriction fragment length polymorphic markers (Tanksley *et al.* 1982; Paterson *et al.* 1988; Lander & Botstein, 1989). In this case the correlations between quantitative trait values and presence of molecular markers are analysed in progenies of crosses between different lines (Marker based – MB analysis). Alternatively, the presence or absence of molecular markers (presumably neutral during the experiment) may be determined in lines derived from the cross selected for high or low values of the quantitative trait considered (trait based – TB analysis, Stuber *et al.* 1980; Lebowitz *et al.* 1987). Selection changes the frequencies of the molecular markers because of hitch-hiking (Thompson, 1977) allowing inference of the linkage between the markers and QTLs. TB analysis is more robust than MB analysis when the same number of markers and

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individuals are analysed for molecular markers, especially if selection goes on for several generations (Lebowitz *et al.* 1987). Unfortunately, there is little experimental data obtained from TB analysis based on a sufficient number of molecular markers (but see Nuzhdin & Pasyukova, 1991; Keightley & Bulfield, submitted).

Previously, mobile elements (ME) have been used to induce mutations affecting quantitative traits (Mackay *et al.* 1992), but these elements can also be used as Mendelian markers because their transposition rates are usually very low (Tchurikov *et al.* 1981; Charlesworth *et al.* 1992), and most lines of *Drosophila melanogaster* have a unique pattern of ME insertion sites (Ananiev *et al.* 1979; Belyaeva *et al.* 1984; Charlesworth *et al.* 1992). The dense distribution of ME sites along the chromosomes also makes them suitable molecular markers for TB analysis, because associations between QTLs and at least some sites are expected to be preserved during the course of selection over several generations.

Here we report the results of a TB analysis on differences in fitness between closely related *Drosophila melanogaster* strains with low and high fitness. The sites of insertion of the retrotransposons *mdg1* and *copia* on the second chromosome revealed by *in situ* hybridization were used as molecular markers for the QTLs that influence fitness. The selection pressure for TB analysis was obtained through natural selection.

2. Materials and methods

Fitness measurements. The competition index of Hartl & Haymer (1983) was used to characterize fitness. Five females and five males from the tested line were placed in a tube together with fifteen females and fifteen males of the tester line carrying the marked compound arms of the second chromosome: *C(2L)RM, dp; C(2R)RM,px*. Interstrain progeny of this cross are inviable. The ratio of the number of offspring of the tested strain to the total number of offspring (competition index) from 9 to 28 replicates was used to characterize the fitness of the tested strain.

Description of strains. A low fitness line (LA; Table 1) was obtained by long (more than 600 generations) selection for decreased sexual activity of males under close inbreeding (see Kaidanov, 1980 for details). This line is characterized by a complex of maladaptive features, for example, low viability, fecundity, mobility and thermostability.

High fitness lines (HA) were closely related to LA line. HA1 is distinguished from LA by the second chromosome, which controls the higher fitness; the X and third chromosomes of this strain are identical to LA. HA2 has the same second chromosome as HA1, but the X and third chromosomes are from a different inbred strain unrelated to LA. See Pasyukova *et al.* 1989; Belyaeva *et al.* 1989 for details of the construction of these stocks. We have chosen them to illustrate the mapping methodology because of clear fitness differences between the second chromosome of the HA strains compared to LA.

Sites of retrotransposon location in the original strains. Radioactive probes for *in situ* hybridization on polytene chromosomes were obtained as described elsewhere (Pasyukova *et al.* 1986) using the plasmids with the full copies of *mdg1* (Georgiev *et al.* 1981) or *copia* (Dunsmuir *et al.* 1980). Only sites on the second chromosome were studied.

The locations of *mdg1* and *copia* insertion sites in the LA strain were stable for many years. There were *mdg1* insertion sites at 23A, 30A, 33C, 34DE, 35CD, 56F, 57A, 59DE and *copia* insertion sites at 23A, 26C, 33A, 36AB, 39CD, 42B, 53E in the second chromosome of the LA strain (Pasyukova *et al.* 1989).

HA1 and HA2 had second chromosome fixed (*mdg1* insertion sites 23A, 56F, 57A, 59DE; *copia* insertion sites 42B, 47B, 53E) or unfixed (*copia* insertion sites 23A, 39CD) sites coinciding with the LA sites (Pasyukova *et al.* 1989; Belyaeva, unpublished). These HA1 and HA2 sites are not informative for mapping and have been excluded from analyses.

The sites that were fixed in the HA1 and HA2 lines but absent in the LA line are termed 'HA sites' (*mdg1* insertion sites 25A, 26C, 39CD, 41A, 42A; *copia* insertion sites 33F, 34F, 35CD, 38A, 41A, 42A, 52D). The sites that were fixed in the LA line but absent in the HA1 and HA2 lines are termed 'LA sites' (*mdg1* insertion sites 30A, 33C, 34DE, 35CD; *copia* insertion sites 26C, 33A, 36AB; Table 2). There are a total of 19 molecular markers on the second chromosome useful for mapping the fitness differences between the LA and HA strains.

Experimental population. To initiate the HA1 experimental populations one HA1 male was mated with three LA females (F0 generation, Fig. 1). Eight F1 males were crossed individually to LA females to start eight subpopulations. Females of each subpopulation were mated with LA males for three generations. After these five generations of backcrossing the frequency of HA sites was expected to be 1/32, provided that selection was absent. From this point (referred to as G1, fig. 1) each subpopulation was maintained in mass culture. High density (50–100 individuals per tube) was used to decrease the influence of random drift. The flies were placed in new medium 5–10 days after emergence. Finally, the frequencies of molecular markers from 82 individuals were analysed at G11.

The same procedure was used with the HA2 line, but nine subpopulations were started and the frequencies of molecular markers were analysed in G13 and G17 (approximately equal quantities of larvae were analysed in each generation, 36 individuals were studied in total).

Estimation of selection coefficients associated with markers. Selection coefficients associated with the marker loci were estimated by maximizing the

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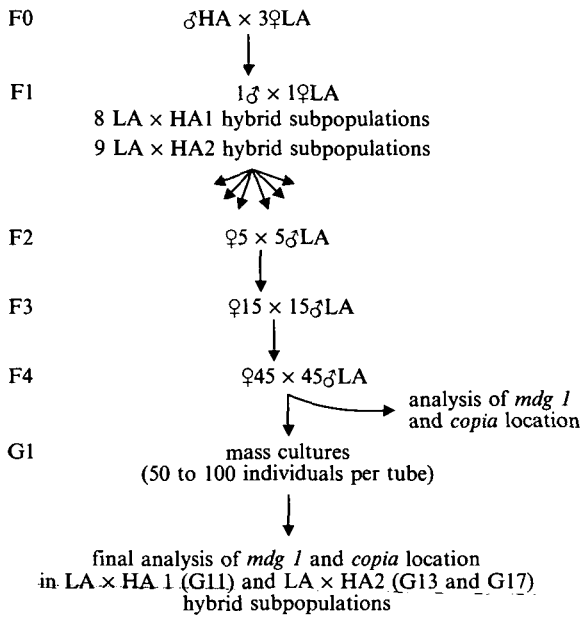

Fig. 1. Design of the experiment.

likelihood of the observed genotype frequencies under the assumption of complete linkage between a marker and a dominant gene affecting fitness. The experiment was simulated by Monte Carlo methods with a gene of selective value *s* in the F0, and with the mating structure and population sizes according to Fig. 1. Fertility selection occurred from the F2 onwards, and 50 progeny were simulated from G1 onwards. The likelihood of the data is the frequency of occurrence of the observed phenotype frequencies (Table 3) among many replicates (10^5) of the simulation, where the marker was either dominant (i.e. those transposable elements present in HA-'HA sites'), or recessive (i.e. elements absent in HA-'LA sites'). The overal log likelihood was the sum of log likelihoods of the data for independent experimental replicates, and this was maximized with respect to *s*. This method has been used to infer magnitudes of gene effects on body size in selected lines of mice (Keightley & Bulfield, submitted).

3. Results and discussion

Frequencies of the molecular markers in G1. To estimate selection in generations F0–F4 the molecular markers were studied in G1 (*mdg1* sites in most of the subpopulations, and *copia* sites in some of them, Table 2). On average, each HA site was found in roughly 1/5 of G1 individuals, i.e. their mean frequency was about 1/10 because the presence of a site is a dominant character and all the HA sites in G1 had to be heterozygous. The discrepancy with the expected value of 1/32 (see above) was probably due to the action of selection of dominant HA alleles affecting fitness during the F0–F4 generations. The data on fitness of F1 progeny from the cross LAxHA1 confirm that the high fitness is a dominant character (Table 1).

Fitness and frequencies of the molecular markers in G11, G13 and G17. In generations G1–G17 both dominant and recessive alleles which increased fitness could be selected for. As a result, the mean fitness of subpopulations was expected to increase at least to initial level of HA lines, which was confirmed by the data on the first subpopulation obtained from the HA1 strain (Table 1).

In situ hybridization does not allow homozygous and heterozygous sites to be distinguished. Data on the frequencies (*f*'s) of individuals with a given site averaged by subpopulations are shown in Table 3. No new *mdg1* or *copia* sites were found during the experiment, while all the original sites were found in the final analysis, so the transposition rate during the experiment was very low or zero. The patterns of change of marker frequency in the HA1 and HA2 lines were similar, as were the distributions of *f* values for *mdg1* and *copia* elements. The *f* values of HA sites varied from 0·2 to 0·95, and increased from low values in the distal part of the left arm (*mdg1* sites 25A and 26C) to high values in the pericentromeric region (*mdg1* sites 39CD, 41A, 42A; *copia* sites 33F, 34F, 35CD, 38A, 41A, 42A) and decreased to low values in the distal part of the right arm (*copia* site 52D). Therefore the pericentromeric region of the second

Table 1. *Competition index of LA and HA1 stocks, and their hybrids*

Stock or hybrid	Total number of progeny	Number of replicates	Competition index (%)
LA	1297	13	4·1 ± 1·5
HA1	797	10	17·9 ± 2·8
F1 LAxHA1	1195	12	36·0 ± 5·8
G11 LAxHA1 no.1*	1037	9	41·8 ± 7·1
G11 LAxHA1 no.4*	2503	28	10·3 ± 2·4
G11 LAxHA1 no.4L*	851	10	5·1 ± 2·1

* G11 LAxHA1 no.1 and no.4 are two of the eight subpopulations derived from the LAxHA1 cross. G11 LAxHA1 no.4L is the subline extracted from the LAxHA1 no.4 subpopulation (see text for details). The determination of the competition indexes was done at G11 (Fig. 1).

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Table 2. *Sites of* mdg1 *and* copia *location in the second chromosome of initial stocks and hybrid populations*

				LAxHA1(G1) Subpopulation no.							LAxHA2(G1) Subpopulation no.								
Sites*	LA	HA1	HA2	1	2	3	4	5	6	7	1	2	3	4	5	6	7	8	9
mdg1 25A	—	9	6	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26C	—	9	6	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30A	+	—	—	3	2	2	1	1	5	3	4	4	3	1	2	2	2	5	1
33C	+	—	—	3	2	2	1	1	5	3	4	4	3	1	2	2	2	5	1
34DE	+	—	—	3	2	2	1	1	5	3	4	4	3	1	2	2	2	5	1
35CD	+	—	—	3	2	2	1	1	5	3	4	4	3	1	2	2	2	5	1
39CD	—	9	6	1	1	0	0	0	3	1	2	1	2	0	0	0	0	4	0
41A	—	9	6	1	1	0	0	0	3	1	2	1	2	0	0	0	0	4	0
42A	—	9	6	1	1	0	0	0	3	1	2	1	2	0	0	0	0	4	0
Number analysed		9	6	3	2	2	1	1	5	3	4	4	3	1	2	2	2	5	1
copia 26C	+	—	—	1	1	0	0	0	1	3	0	3	1	0	0	0	1	1	0
33A	+	—	—	1	1	0	0	0	1	3	0	3	1	0	0	0	1	1	0
33F	—	9	6	1	1	0	0	0	0	1	0	1	1	0	0	0	0	1	0
34F	—	9	6	1	1	0	0	0	0	1	0	1	1	0	0	0	0	1	0
35CD	—	9	6	1	1	0	0	0	0	1	0	0	1	0	0	0	0	1	0
36AB	+	—	—	1	1	0	0	0	1	3	0	3	1	0	0	0	1	1	0
38A	—	9	6	1	1	0	0	0	1	3	0	3	1	0	0	0	1	1	0
41A	—	9	6	0	0	0	0	0	0	1	0	1	1	0	0	0	0	1	0
42A	—	9	6	0	0	0	0	0	0	1	0	1	1	0	0	0	1	0	0
52D	—	9	6	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0
Number analysed		9	6	1	1	0	0	0	1	3	0	3	1	0	0	0	1	1	0

Figures correspond to the number of individuals which had mobile element at a given site.
* Sites *mdg1* 23A, 56F, 57A, 59DE; *copia* 23A, 39CD, 42B, 47B, 53E are uninformative for mapping (see text for details) and were excluded from the table.

chromosome was probably most strongly associated with the fitness differences between the lines. The data on the LA sites support this conclusion. The frequencies of HA and LA sites in the final generations were in good agreement: the pericentromeric regions of the second chromosome with the maximal frequency of HA sites had minimal frequency of LA sites and *vice versa*.

ML estimates of selection coefficients associated with marker loci are plotted in Fig. 2. An area of 10–15 cM is associated with an effect with a selective advantage of about 0·6. The effect associated with the markers declines on either side, but selection is still evident 15–20 cM away from this region. If selection occurs solely from fertility differences, Hardy–Weinberg ratios can be expected in the progeny. The inferred gene frequencies at marker loci under this assumption are shown in Fig. 3. The gene frequencies of all markers are greater than 1/32, and HA alleles are close to fixation over a large area near the pericentromere. Also shown in Fig. 3 is a curve obtained by Monte Carlo simulation for the expected gene frequency at G11 at markers linked to a gene of selective advantage 0·6 at map position 42. This suggests a rather sharper peak than observed in the experiment if a single gene is responsible for the fitness differences. If selection occurs by viability differences, Hardy–Weinberg proportions are not expected, but under this assumption quadratic formulae for marker gene frequencies can be derived in terms of genotype frequencies and s, and ML estimates of s obtained above can be used in the formulae. Under this assumption, the estimated gene frequency at markers in the pericentromeric region is about 0·8 (i.e. higher than for fertility selection), but is little different from that shown in Fig. 3 in flanking regions.

Additional loci controlling fitness. We cannot exclude the possibility that the intense selection associated with the pericentromeric region of the HA second chromosome concealed less intense selection in other regions which also contributed to the increased fitness of the HA lines. Some additional information was obtained due to the fact that in subpopulation 4 from the HA1 line the pericentromeric region and the 2R arm of the second HA chromosome were lost in the first five generations, probably because of random drift. In the final G11 generation the fitness of this subpopulation was much lower than in the subpopulation 1 (Table 1) where all the HA second chromosome was preserved. However, the fitness value of the fourth subpopulation is significantly higher than that of the original LA line (Table 1). Therefore, the regions of HA second chromosome which remained in subpopulation 4 also made some

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Table 3. *Sites of* mdg *and* copia *location in the second chromosome after natural selection of hybrid populations (G11, G13 and G17)*

	LAxHA1(G11) subpopulation no.									LAxHA2(G13 and G17) subpopulation no.									
Sites*	1	2	3	4	5	6	7	8	*f* (%)	1	2	3	4	5	6	7	8	9	*f* (%)
mdg1 25A†	5	3	1	3	0	1	2	1	22	1	0	2	1	0	2	0	0	1	31
26C†	6	3	2	3	0	1	2	3	30	1	1	2	2	2	2	2	0	1	56
30A‡	4	7	3	16	6	7	7	7	85	1	2	0	2	0	0	2	2	3	63
33C‡	5	7	2	20	6	7	7	2	76	1	2	0	2	0	0	0	1	3	44
34DE‡	5	7	2	20	6	6	3	2	73	1	2	0	2	0	0	0	1	3	44
35CD‡	5	7	3	20	6	4	3	3	74	1	2	0	2	0	0	0	1	3	44
39CD†	7	8	2	0	4	7	6	6	69	2	2	4	1	3	2	4	2	3	89
41A†	7	8	2	0	4	7	5	7	69	2	2	4	1	3	2	4	2	3	86
42A†	7	8	2	0	4	7	6	7	71	2	2	4	1	3	2	4	2	3	89
Number analysed	9	9	4	22	6	7	7	7		2	2	4	2	3	2	4	2	3	
26C‡	3	4	1	19	3	5	4	3	92	4	2	2	1	2	1	2	1	0	73
33A‡	1	4	0	16	3	5	5	2	71	0	2	0	2	0	0	2	1	0	44
33F†	4	3	1	8	0	5	1	3	67	3	1	2	2	2	2	2	1	2	86
34F†	4	3	1	5	0	4	5	3	72	5	1	2	2	2	2	2	1	2	91
35CD†	4	4	1	5	2	5	4	3	83	5	1	2	2	2	2	2	1	2	91
36AB‡	1	4	1	10	2	2	1	2	60	1	1	0	1	1	1	1	1	1	45
38A†	4	4	1	3	2	2	1	3	86	4	2	2	2	2	2	2	1	2	94
41A†	4	2	1	0	3	5	5	3	80	4	2	2	2	2	2	2	1	2	94
42A†	4	3	1	0	3	5	5	3	82	4	2	2	2	2	2	2	1	2	94
52D†	3	1	1	0	1	2	3	3	54	2	0	0	1	2	1	1	0	0	33
Number analysed	4	5	1	20	3	5	5	3		5	2	2	2	2	2	2	1	2	

Figures correspond to the number of individuals which had mobile element at a given site; *f*: mean frequency of individuals which had mobile element at a given site.
* See caption to the Table 2.
† HA sites.
‡ LA sites.

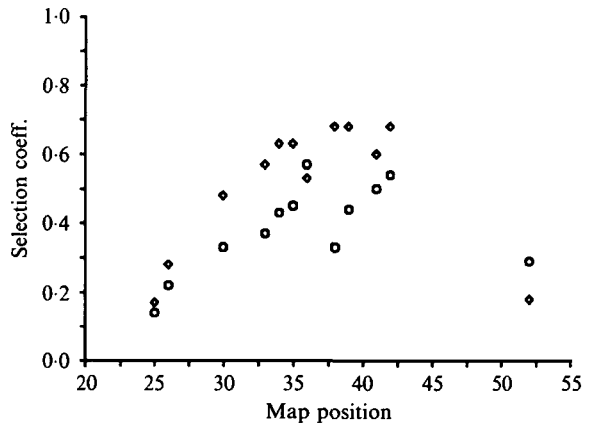

Fig. 2. ML estimates of selection coefficients associated with marker loci plotted against map position. Data on markers at G11(○), and G13-G17(◇) (G15 was simulated) are shown. Average values are shown for markers at the same map position. Standard errors of s were estimated from the curvature of the likelihood about the maximum, and are between 16% and 38% of the mean.

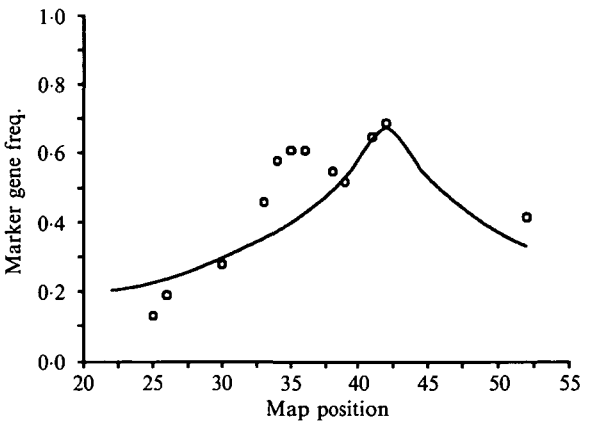

Fig. 3. Gene frequencies at marker loci at G11 under the assumption of Hardy–Weinberg frequencies. Average frequencies are shown for markers at the same map position. The curve is the expected gene frequency at G11 for markers linked to a gene of selective advantage 0·6 at map position 42.

contribution, albeit not a major one, to increased fitness of the HA1 line. The sites of retrotransposon location were studied in 30 individuals of this subpopulation. Although these data are insufficient for a definitive conclusion, they suggest that the increase in fitness of HA1 subpopulation 4 was mainly associated with sections 30 to 33 of the HA chromo-

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some. Moreover, the inbred subline which did not have any HA sites was extracted from HA1 subpopulation 4. It had at least not statistically different fitness (N4LA in Table 1) from the original LA line.

A novel mapping technique. In this study an analysis based on hitch-hiking of stable mobile elements *mdg1* and *copia* serving as molecular markers for QTL mapping was used to identify regions of the second chromosome responsible for an increase of fitness in high lines compared to their ancestral low fitness line. The frequencies of all the HA-specific sites of the retrotransposons *mdg1* and *copia* in the second chromosome increased in mass cultures submitted to natural selection in the laboratory, suggesting hitchhiking with loci responsible for the increased fitness of the HA lines. Two independent experiments with TB analysis gave similar results for the same chromosome from two different lines. The maximal final frequencies of HA sites were observed in the pericentromeric region, which indicates that QTLs responsible for the increase in fitness were located in this region. Additionally, at least one locus with a smaller contribution to fitness is probably located in sections 30–33.

A similar procedure to ours can be used for mapping *Drosophila* QTLs determining the variation of morphological quantitative traits, provided that the lines with different values of the trait under study have different locations of transposable elements or some other marker system. Several generations without selection would be useful to destroy associations between loosely linked QTLs and molecular markers before starting selection on the trait. The copy number of several transposable element families is large enough to allow high resolution for mapping purposes. Mobile elements inserted very closely to a QTL can be later used for cloning the QTL.

MB analysis is probably preferable than TB analysis if QTLs controlling several characters are mapped simultaneously. However, for precise mapping of QTLs controlling individual traits, TB analysis can be more powerful (Leibovitz *et al.* 1987) and with the ease of isolation of molecular markers (e.g. microsatellites), it can be utilized for any type of organism. We believe that our approach can be a useful implementation of the TB method.

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