PARALOG, A CONTROL MUTANT IN *DROSOPHILA MELANOGASTER*

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ABSTRACT

The genetic properties of a pleiotropic mutant mapping at 1.4 ± 0.1 in band 3B3 or its adjacent interbands on the *X* chromosome are described. The mutation is expressed autonomously in germ line cells, where it is recessive and has antimorphic properties. At 29°, the mutation blocks oocyte differentiation, causing female sterility. At lower temperatures, it disturbs the maternal information in the egg; as a result, the progeny lack germ line cells (grandchildless phenotype) and exhibit defects of the cuticular pattern. The mutation is also expressed in somatic cells through zygotic interactions with neighboring regions, including 3A2, 3A3 (zeste), 3C1–2, 3C4 and 3C6–8 (Notch). We interpret the data by postulating that the expression of sets of dispersed genes might be controlled by the local topology of the chromosome, itself constrained by pairing of dispersed repeated elements. We call the mutation paralog.

IN 1972, MADELEINE GANS induced maternal-effect mutants in *Drosophila melanogaster* in an attempt to determine what information for embryonic determination is supplied maternally. One of the mutants she isolated, X^{1122}, presented a complex pleiotropic phenotype, and many of its characteristics could be quantified. This analyzable complexity provided the impetus for the present study. The genetic analysis of this mutant revealed some puzzling interactions with nearby regions, suggesting a control of gene activity at the level of the global chromosomal structure. This article describes the genetics of X^{1122}; developmental studies will be published separately at a later date.

MATERIALS AND METHODS

Strains: The X^{1122} chromosome was recovered after EMS treatment of a v^{24} chromosome by M. GANS, AUDIT and MASSON (1975) in a screen for maternal-effect mutants. Common laboratory strains (v^{24}, *FM3/w v* l^{44ts} *C(1)RM/Y*) and media were described in the same paper.

For genetic analysis, we used the *sc ec cv* ct^6 *v* g^4 *f* and *y w spl* strains from Bowling Green; the *y v f* mal^{bz} strain from Zürich; *sc z ec* ct^6 from Pasadena, and *y* z^a w^a (mislabeled *y z* w^{aE}) from Paris.

For complementation analysis, we used the *z* and the z^{11Gs} homozygous strains from Paris, *fs(1)Nas* from Pasadena, and a collection of mutants in the zeste-white region kindly supplied by B. H. JUDD. They included alleles of *l(1)zw1* (62b22); *l(1)zw6* (63e5, 63e13); *l(1)zw12* (64k1, 64k3, 64k9); *l(1)zw7* (62e3); *l(1)zw5* (62j1); *l(1)zw11* (64g3); *l(1)zw9* (*z 63k18 spl* sn^3), all kept in males carrying a w^+Y chromosome crossed to *C(1)RM y f*/w^+Y females;

and one allele of each of the female sterile loci *fs(1)Ya* and *b* kept in y^2 w^+/Y males crossed to *C(1)RM*, *y w f/Y* females.

Gene-dosage effects were investigated using chromosomes whose origins and short descriptions are given in Table 1. For a more complete description, see LINDSLEY and GRELL (1968), JUDD, SHEN and KAUFMAN (1972), LIM and SNYDER (1974), LIU and LIM (1975) and YOUNG and JUDD (1978). A relatively good correspondence appears between the genetical and cytological maps, and we give the genetic description of the rearrangements.

General method used for the study of fecundity, fertility and progeny analysis: Two samples of about 100 females each of the same age to within two days are placed in "pondoirs." These are glass bottles fitted with small, easily changed boats containing Zalokar medium (fresh baker's yeast + wine vinegar + saccharose + neutral red + agar) (GANS, AUDIT and MASSON 1975). Females kept this way can stay healthy for more than one month at 23°. Eggs are removed and counted, at least daily; this gives the fecundity (number of eggs per female per day) as a function of the age of the females. Consecutive egg batches, after sampling for measurements of the frequency of hatching, are put in bottles containing standard medium (dried brewer's yeast, corn meal, agar and Moldex). Dead pupae and empty pupal cases are counted; adults of different genotypes are counted, examined under a dissecting microscope (× 25) for the detection of morphological abnormalities and then dissected in water + 1% detergent Mucasol (Polylabo). This treatment renders fatty tissue transparent in a few seconds, allowing flies to be easily classified according to the number of agametic gonads present.

For any particular cross, this procedure measures, as a function of maternal age, the fecundity, the stage of lethality of any inviable zygotes, the viability of the different progeny genotypes and the frequency among surviving adults of morphological abnormalities and agametic gonads.

Presentation of the results: Measurements in replicate experiments were somewhat variable, partly because of group behavior for laying and humidity. Each test was therefore done in two pondoirs, and the experimental and control crosses were always done in parallel. All experiments were repeated at least twice.

Confidence limits given correspond to the 95% significance level. Limits were not calculated for parameters that are particularly subject to nonstatistical fluctuations, such as fecundity. In these cases, only raw data are given.

For those crosses in which a known lethal class is produced, the total number of eggs has been appropriately corrected to allow direct comparison.

RESULTS

The X^{1122} *phenotype: Maternal and zygotic effects*

We shall present only the elements necessary for understanding the genetic analysis. A more detailed description will be published later.

As will be shown, all the defects described are associated with a single mutation, located at *1*–1.4; band 3B3. We call it paralog (*par*), from the Greek παρα λογοσ, which means against reason and logic, also against expectation, and refers to the everyday surprises the mutation produces by its effects in combination with a group of seven other loci. It is also meant to recall the paralogous, or ectopic, pairing that occurs between dispersed repeated sequences and that provides a possible explanation for the phenomena involving paralog described in this article.

The mutant appeared in an EMS screen for sex-linked maternal-effect mutants and was described as a recessive female sterile at 29° (GANS, AUDIT and MASSON 1975). EMS induction of X^{1122} may be questioned, however, since another chromosome (X^{1103}) with a similar phenotype, and not complementing X^{1122}, was simultaneously recovered. Although the *X* chromosome used was made isogenic just prior to mutagenesis, the two mutants might actually both derive from a spontaneous mutation pre-existing in the mutagenized stock.

TABLE 1

Origin and description of the strains used in dosage studies

Chromosome	Strain and origin	Description of rearrangement	According to
Deficiencies *Df(1)*			
62g18	$:=y\ f/w^+Y \times Df/w^+Y$ (TX)	[*gt-zw1*]	JUDD
64c4	$:=y\ f/w^+Y \times Df/w^+Y$ (TX)	[*z-w*]	JUDD
64f1	$:=y\ f/w^+Y \times Df/w^+Y$ (TX)	[*zw3-zw12*]	JUDD
64j4	$:=y\ f/w^+Y \times Df/w^+Y$ (TX)	[*zw2-zw3*]	JUDD
65j26	$:=y\ f/w^+Y \times Df/w^+Y$ (TX)	[*gt-zw1*]	JUDD
K95	$:=y\ f/w^+Y \times y^2Df/w^+Y$ (TX)	[*zw1-zw3*]	JUDD
N^8	*FM1/Df* × *FM1/Y* (CT)	*3B4-C1*; *3D6-E1*	SLIZYNSKA
N264–39	$FM4/w^{ch}\ Df \times FM4/Y$ (CT)	(point mutant)	WELSHONS
N264–105	*In(1)dl-49/Df* × *dl-49/Y* (BG)	*3C6–7*; *3D2–3*	SUTTON
TEM7	$FM6l^{69a}/Df \times Df/w^+Y$ (W)	[*zw1-zw12*]	LIM
TEM202	$FM6l^{69a}/Df \times Df/w^+Y$ (W)	[*zw6, w . . .*]	LIM
w258–11	*In(1)dl-49/yDf* × *dl-49/Y* (CT)	[*z, w . . .*]	SLIZYNSKA
w258–42	*FM1/y Df* × *FM1/Y* (CT)	[*zw8, w . . .*]	JUDD
w258–45	*FM4/y Df* × *FM4/Y* (CT)	[*zw2-zw3*] + [*zw12, w*]	JUDD
"*w258–45*"	$:=y\ f/w^+Y \times y^2Df/w^+Y$ (TX)	[*zw12-w*]	JUDD
w^{rJ1}	$:=y\ f/w^+Y \times y^2Df\ spl\ ec\ sn^3/w^+Y$ (TX)	[*tko-w*]	JUDD
w N^{71a}	*In(1)dl-49/y Df* × *dl-49/Y* (CT)	*3A6–7*; *3C9–10*	LEFEVRE
X12	$:=y\ f/w^+Y \times y\ sc\ Df/w^+Y$ (TX)	[. . . *gt, zw11*]	JUDD
Duplications			
w^+Y	$:=y\ f/w^+Y \times Df(1)64f1/w^+Y$ (TX)	[*zw10-w*]	JUDD
$Dp(1,2)w^{+70h31}$	$:=y\ w\ f/Y \times Df(1)w258\text{–}45(64)/Y$; *Dp* (TX)	*2D1–2*; *3D3–4*	JUDD

Loci are ordered from left to right: *gt tko z zw1 zw8 zw4 zw10 zw13 zw2 zw3 per zw6 zw12 zw7 fs(1)Yb fs(1)Ya zw5 zw11 zw9 w rst vt N.* Strains were kindly provided in 1975 (except wN^{71a}) by B. H. JUDD (TX, Texas), J. K. LIM (W, Wisconsin), L. CRAYMER (CT, Caltech) and I. OSTER (BG, Bowling Green).

As may be seen in Table 2, *FM3/par* v^{24} females are fertile at 28.5° and give fully viable *FM3/par* v^{24}, *par* v^{24}/*par* v^{24} and *par* v^{24}/Y progeny that have no external morphological defects or agametic gonads. However, the ovaries of homozygous females are reduced in size, a result of abnormal egg chamber development; many chambers contain more than the normal number of sixteen cells and more than one oocyte. Few of them reach the vitellogenic stages; the fecundity of *par/par* females is therefore very low at 28.5°; the few eggs that are laid die before hatching, regardless of their genotype. The pattern of embryonic lethality was briefly described by ZALOKAR, AUDIT and ERK (1975).

At 23°, homozygous females are fully viable and fecund, but some 60% of their progeny, due to asynchrony of mitosis and defective nuclear migration in the late cleavage stage, fail to cellularize a complete blastoderm and die soon afterward. The other 40% form complete blastoderms, but lack pole cells. All the embryos in this class complete development, but the resulting adults show

TABLE 2

Effects of X^{1122} *in the germ line cells: influence of temperature and paternal genotype*

Breeding temperature	Characteristics measured	$\varphi \frac{FM3}{X^{1122}} \times \frac{X^{1122}}{Y} \sigma$	$\varphi \frac{X^{1122}}{X^{1122}} \times \frac{X^{1122}}{Y} \sigma$	$\varphi \frac{X^{1122}}{X^{1122}} \times \frac{+}{Y} \sigma$
	Fecundity	25 ; 20	1 ; 0.4	1 ; 0.4
28.5° ± 0.5°	Hatching	95 — 100	0 — 2	0 — 2
	Emergence	90 — 100	0 — 0.01	0 — 0.1
	Defects in progeny:	0 — 0.1	—	—
	Fecundity	30 ; 25	30 ; 25	30 ; 25
	Hatching	95 — 100	35 — 45	35 — 45
	Emergence	95 — 100	39 — 43	38 — 42
	Defects in progeny:			
23° ± 0.5°	agametic	0 — 0.3	98 — 100	99 — 100
	abdominal	0 — 0.3	47 — 53	46 — 54
	thoracic	0 — 0.3	18 — 23	17 — 24
	cephalic	0 — 0.3	ε — 3	0 — 1
	Fecundity	8 ; 6	8 ; 6	
	Emergence	70 — 80	30 — 40	
	Defects in progeny:			
16° ± 1°	agametic	0 — 0.5	19 — 27	
	abdominal	0 — 0.5	1 — 5	
	thoracic	0 — 0.5	ε — 3	
	cephalic	0 — 0.5	ε — 3	

Age of the mothers has no measurable influence. Progeny with different genotypes develop at the same rate, are recovered equally, and present the same frequencies of defects.

Results in the first column are identical to those obtained in a cross of *FM3*/$v^{24} \times v^{24}/Y$ (not shown); thus, no dominant effect of X^{1122} in the germ line appears.

The maximal, then mean fecundities over 7 days at 29°, 10 days at 23° and 15 days at 16° are expressed as the number of eggs laid per female and per day.

The frequencies of hatching (from the chorion) and emergence (from the pupal case) corrected for embryonic lethality of *FM3/Y*, and the rate of specific defects in the progeny, are given at the 95% confidence level.

An interval of 0 — 3/n denotes an experiment with 0 cases observed among n, whereas an interval ε — *x* denotes an experiment where at least two cases were observed.

a number of defects. As a result of the lack of pole cells, all have agametic gonads and are sterile. Also, probably as a result of local discrete defects in the blastoderm, most of them show a number of cuticular defects, which are graded postero-anteriorly in frequency. Abdominal structures (genital apparatus, tergites and sternites) are absent or modified in their pattern in 50% to 80% of the flies; thoracic structures are modified in 20% to 30% of the flies, cephalic ones in 1% to 5% of the flies (THIERRY-MIEG, unpublished). Among these defects, agametic gonads and local duplications of the wing margin are used as reliable parameters to characterize the mutant, since they do not occur in common laboratory strains.

At 16°, homozygous *par* v^{24} females are partially fertile, 20% to 30% of their progeny are agametic and few cuticular defects are observed.

At all temperatures, the frequency of defects in the progeny of homozygous paralog mothers is independent of the genotype of the zygote itself: the effects so far described are under strict maternal control. This correlates with the extent of the temperature-sensitive period, restricted to the mother's lifespan (THIERRY-MIEG, unpublished). We demonstrated by clonal germline analysis and pole-cell transplants that all of the features just described are simple autonomous recessive effects of the *par* v^{24} chromosome in the germ line cells (THIERRY-MIEG, unpublished).

Several lines of evidence indicate that paralog also acts in somatic cells. First, homozygous or hemizygous flies from any mother have, when raised at 16°, wing veins broadened into regular deltas at the junction with the margin. This zygotic phenotype segregates with the maternal effects of the *par* v^{24} chromosome and seems to be another manifestation of paralog. Second, recombination and dosage analysis have uncovered a number of surprising zygotic interactions of paralog with regions close to it (3A2 to 3C8), in particular with the zeste and Notch loci. These will be detailed in the next sections.

Recombinational analysis of the recessive effects of X^{1122} *in the germ-line*

Five marker strains were used. The general scheme is described in Figure 1. The phenotype of flies containing the recombinant (*rec*) chromosome was examined in order to detect zygotic effects. The maternal effects were studied in three types of females, *FM3/rec*, *rec/rec* and *rec*/X^{1122}; four vials were tested per cross, 2 females per vial for *FM3/rec*, both 2 and 10 females per vial for the others. For the two generations preceding the test, the flies were raised at two temperatures, 23° and 29°, in order to take into account the early start and long extent of the temperature-sensitive period. Quantitative data on the fecundity, fertility, presence and nature of defects in the progeny were then gathered. This was done at 29°, where female sterility predominates, at 23°, mostly for gametic and abdominal defects in the progeny, and after a shift from 23° to 29°, a treatment known to give a high incidence of cephalic and thoracic defects in the progeny of the shifted females (THIERRY-MIEG, unpublished). At least 150 progeny flies were examined and dissected per chromosome tested, in order to detect quantitative variants.

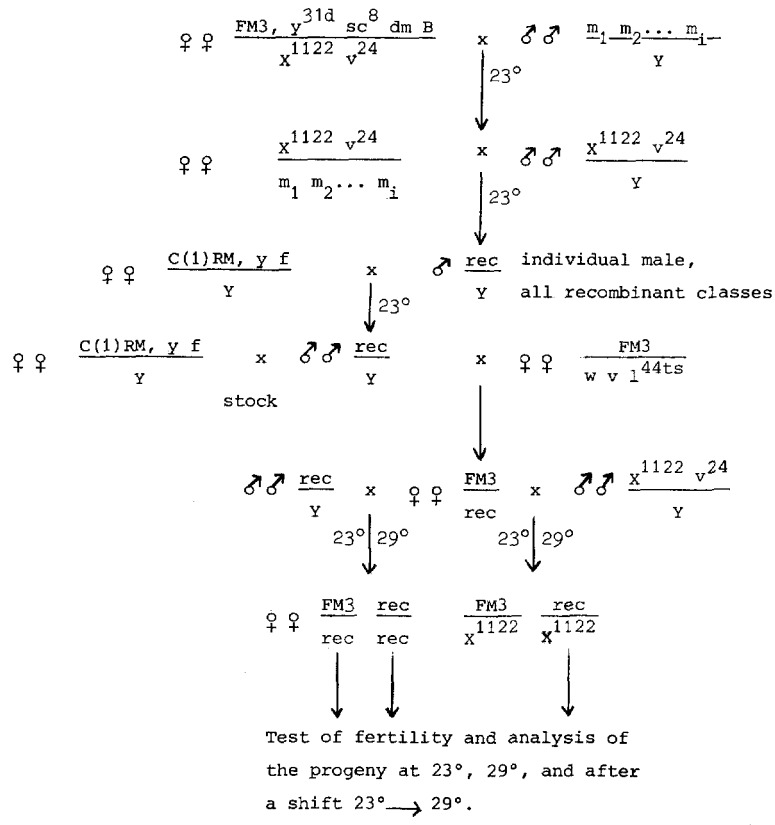


FIGURE 1.—Protocol for mapping the mutant zygotic and maternal effect characters in the original $X^{1122}v^{24}$ chromosome.

The chromosome designation "$m_1m_2 \ldots m_i$" stands for *sc ec cv* ct^6g^4f, *y w spl*, $y\ z^aw^a$ or *y v f mal*. The temperature at which each cross is performed is indicated along the arrow. The last three steps are effected at 23° and 29°; this allows mapping of the characteristics that appear at high temperature (female sterility and maternal effect embryonic lethality) and of those confined to low temperature (maternally affected morphological defects or the grandchildless phenotype).

The results are summarized for the *y w spl* strain in Tables 3 and 4, and for *y* z^a w^a in Table 5; less extensive data (not shown) obtained with the other strains (*sc ec cv* ct^6 g^4 *f*, *sc z ec* ct^6 and *y v f* mal^{bz}) confirm the conclusions.

The most striking feature is that all of the effects of X^{1122} in the germ line segregate together in each of the 113 chromosomes studied, among which 84 recombined in the *y–w* interval. Since a small region of 0.25 cM in the proximal half of the zeste-white region on the *X* chromosome is responsible for the complete set of defects, we assume that they all result from a single mutation, paralog, located at $1.5 \times 35/38 = 1.38$ (1.20 to 1.49 at 95% confidence) according to the *y w spl* experiment, and at $1.5 - 3/26 \times 0.84 = 1.40$ (1.25 to 1.48) according to the *y* z^a w^a experiment (the map position of z^a is 0.66 and w^a 1.5 in that strain).

TABLE 3

Segregation of X^{1122} *characters in recombinant chromosomes from* y w spl/X^{1122} v^{24} *females*

Genotype	Number of chromosomes studied	Fertility and progeny at 29°	Fertility at 23°	Frequency of defects in the progeny: Agametic (23°)	Abdominal (23°)	Thoracic or cephalic (23°→29°)	Conclusion
y w spl v+	5	15–20(+)	15–20	0	0	0	*par+*
y+ w+ spl+ v	5	0	5–10	90–100	30–40	20–30	*par*
y w/spl+ v	7	15–20(+)	15–20	0	0	0	*par+*
y+ w+/spl v+	8	0	5–10	40–70	5–20	20–30	*par Su*
y/w+ spl+ v	11	0	5–10	9:90–100	30–40	20–30	9 *par*
				2:40–70	5–20		2 *par Su*
	1	15–20(+)	15–20	0	0	0	1 *par+*
y+/w spl v+	23	15–20(+)	15–20	0	0	0	23 *par+*
	2	0	5–10	40–70	5–20	20–30	2 *par Su*
y+/w spl/v	1	15–20(+)	15–20	0	0	0	*par+*

Results summarized here concern *rec/rec* females; *rec/*X^{1122} females have the same general characteristics, except for quantitative variations explained in the text.

Fertility is expressed as the number of adult progeny per female and per day. When its level is wild type (15–20), the progeny have a wild-type phenotype [+] also.

Intervals displayed in this table are not statistical, but represent the extreme values observed with the various chromosomes.

In both mapping experiments (*y w spl* and *y* z^a w^a), fecundity at 23° and 29°, and the stage of embryonic death at 29°, depend on the genetic background. For example, the four test vials of *rec/rec* females gave consistent results, but were frequently less fertile at 23° than were the *rec/*X^{1122} females. This difference was observed in about half of the recombinants (19 out of 31 in the *y* z^a w^a experiment) but did not obviously depend upon the particular *X*-chromosome combination, and is thus probably associated with the most proximal region of the *X* chromosome.

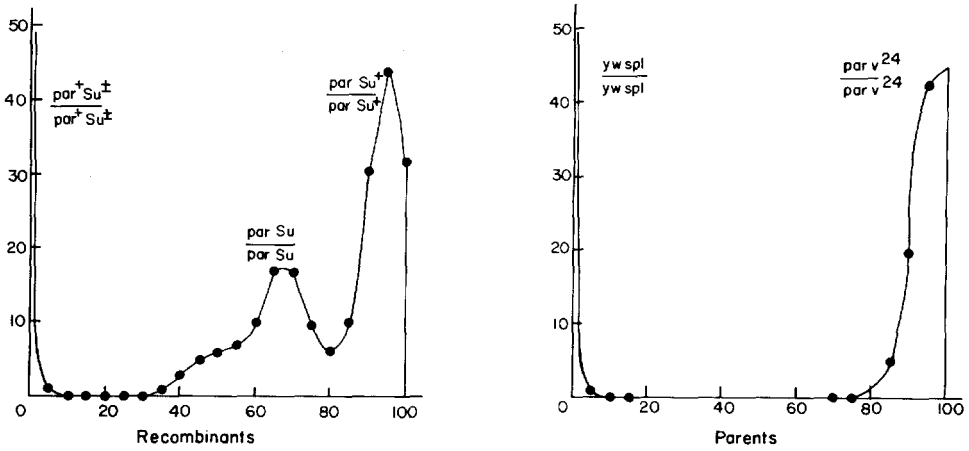
Two secondary observations relate to the *y w spl* experiment. First, *par spl/FM3*, *y* sc^8 *dm B* females have rough and reduced eyes, resembling the split phenotype. Second, as may be seen in Table 4, the *y w spl* strain contains a modifier gene, which we call *Su(par)*, that maps to the right of *v* on the *X* chromosome, and decreases in a semidominant way the frequency of agametic flies from 95–100% to 51–61% and that of abdominal defects from 26–49% to 5–14%. No effect on fecundity at 29° or the frequency of thoracic or cephalic defects was observed. *Su(par)/Su(par)* females are indistinguishable from wild type.

Four secondary observations arise from the *y* z^a w^a experiment. The results are shown in Table 5. First, an effect on the eye color of interactions between z^a and *par* in the presence or absence of w^a appears in the third column. When aged, z^a *par* flies have brown eyes and z^a *par* v^{24} orange, while z^a *par* w^a flies are white eyed throughout their life. This effect is temperature sensitive, with more

TABLE 4

Level of expression of paralog in recombinant chromosomes from y w spl/X^{1122} v^{24} *females*

Histograms†



Properties of *Su(par)*‡

Genotype of females	Fecundity at 29° (eggs/♀/day)	Rate of defects in the progeny: Agametic (23°)	Abdominal (23°)	Thoracic (23°→ 29°)
par Su+/par Su+	0.5 to 2	100(98–100)	32(26–40)	27(20–35)
par Su+/par Su		77(71–82)		
par Su/par Su	0.5 to 2	56(51–61)	9(5–14)	27(20–35)
par+ Su/par+ Su	20 to 25	0(0–2)	0(0–2)	0(0–2)

† Smoothed histograms of the frequency of agametic progeny from individual x^{1122} or *y w spl* flies (right) and from *rec/rec* or *rec/*x^{1122} flies (left). Each individual cross contributes to the histogram by a likelihood binomial distribution of total weight unity. A new class appears between 40% and 80% agametic flies.

‡ Properties of *Su(par)*, a quantitative modifier of paralog, pre-existing on the *X* chromosome of the *y w spl* strain. Mean results at 95% confidence level.

eye pigment at 29° than at 23°. Also more pigment is produced in males than females, probably because the z^a lightening effect itself is not dosage-compensated. At 23°, the following gradation was observed:

$$\frac{w^a}{Y}\,\delta = \frac{par\ w^a}{Y}\,\delta = \frac{w^a}{w^a}\,\varphi = \frac{par\ w^a}{par\ w^a}\,\varphi > \frac{z^a\ w^a}{Y}\,\delta > \frac{z^a\ w^a}{z^a\ w^a}\,\varphi \geqslant$$

[dark apricot] [light apricot]

$$\geqslant \frac{z^a\ par\ w^a}{z^a\ w^a}\,\varphi > \frac{z^a\ par\ w^a}{Y}\,\delta > \frac{z^a\ par\ w^a}{z^a\ par\ w^a}\,\varphi$$

[very dilute light apricot] [quasi-white]

These color variations might allow easy selection for modifications at either the z^a or the *par* locus. They have already made possible the recovery of two

TABLE 5

Properties of recombinant chromosomes from y z^a w^a–par v^{24} *females*

	Genotype	Number of chromosomes tested	Eye color of homozygous females at 23°	Progeny of *FM3/rec* at 29° Relative viability of *rec/rec**	Pseudo-gametes†	Properties of *rec/rec* at 29° Fecundity and embryo development‡	Fertility and progeny§	Defects in progeny of *rec/rec* at 23° Agametic	Abdominal	Thoracic and cephalic
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
(a)										
	y z^a *par*+ w^a *v*+	5	light apricot	1	2% (0–6)	++	+	0	0	0
	y+ *z*+ *par w*+ *v*	5	vermilion	1	0	+	—	95–100	20–30	15–25
(b)										
	y z^a *par*+/*w*+ *v*	2	somewhat light vermilion	1		++	++	0	0	0
	y+ *z*+ *par*/w^a *v*+	1	dark apricot	1		+	—	90–100	20–30	15–25
	y z^a/*par w*+ *v*	5	orange in old ♀	1	1% (0–5)	—	—	80–100	20–30	15–25
	y z^a/*par w*+/*v*+	1	brown in old ♀	1	1% (0–5)	—	—	95–100	20–30	15–25
	y+ *z*+/*par*+ w^a *v*+	14	dark apricot	1		++	++	0	0	0
	y+ *z*+/*par*+ w^a/*v*	3	light apricot	1		++	++	0	0	0
	y/*z*+ *par w*+ *v*	4	vermilion	1	1% (0–5)	+	—	90–96	20–30	15–25
	y/*z*+ *par w*+/*v*+	3	wild type	1		+	—	83–100	20–30	15–25
	y+/z^a *par*+ w^a *v*+	13	light apricot	1		++	++	0	0	0
(c)										
	y z^a/*par*/w^a *v*+	2	white	0.5	2% (0–15)	—	—	98–100	30–40	
	y/*z*+ *par*/w^a *v*+	3	dark apricot	1	2% (0–5)	1—;2+	—	85–95	30–40	

(a) 10 random chromosomes of the parental types.
(b) All chromosomes that recombined in the *y*–w^a region.
(c) Synthetic chromosomes, where the *par* or *z*+ *par* region of the original strain has been inserted into a *y* z^a w^a *v*+ chromosome of different origin by recombination in *y*+ *z*+ *par* w^a *v*+/*y* z^a *par*+ w^a *v* females.

* The viability of *rec/rec* females relative to their *FM3/rec* sisters.

† The mean frequency and, within parentheses, the observed variations over six generations are quoted. Pseudogametes appear in females of both genotypes, but males are not affected.

‡ A strong correlation between the number of eggs laid per female per day and the stage reached by the embryos appeared. ++ stands for a mean fecundity of 25–30 eggs and a development of 80–85% of the embryos up to segmentation (16 hr after oviposition). + stands for a fecundity of 8–10 eggs and a development of 35–45% of the embryos up to segments. — stands for a fecundity of 1–2 eggs per female day and less than 5% development after the undivided gut stage (8–12 hr).

§ The fertility is graded ++ = 20–25 progeny/female/day; + = 8–12 progeny/female/day; — = 0 progeny/female/day.

We noticed reduced longevity of *y* z^a w^a and *y* z^a *par* w^a adults; the other combinations are wild type.

independent spontaneous light apricot clones from a very dilute light apricot stock (*y* z^a *par* w^a #7). A concommitant loss of the germinal expression of paralog was demonstrated in the first clone and apparently corresponded to a reversion toward wild type; the second was not studied as it was unstable for eye color.

A second interaction appears at 29° between paralog, z^a (or its close neighborhood) and at least one other region of the *y* z^a w^a chromosome to the right of paralog. As appears in column 4, this leads to a reduced fertility of *FM3/y* z^a *par* w^a females, whose sons and homozygous daughters are poorly viable. This appears to be a dominant maternal effect of the z^a *par* w^a combination, since *y* z^a *par* w^a/*Y* males from an attached-*X* stock are as viable as their *y* z^a w^a/*Y* cousins.

A third interaction involving paralog and a region $iso^{0.9}$ of the *y* z^a w^a chromosome, closely linked to z^a but more distal (approximate map position is 0.9), appears in the sixth column. Combination between *par* and the isoallele $iso^{0.9}$ leads both to a reduction by a factor of 5 to 10 of the fecundity of $iso^{0.9}$ *par* homozygous females and to a diminution of the lifetime of their progeny. These die before or during gastrulation (8–12hr), whereas, half the progeny of *par* homozygous mothers survive until segmentation (16hr).

The fourth observation relates to a feature of the *y* z^a w^a Paris strain. When we cross, at 29°, males from this stock to *FM3/y w v l* ^{44ts} females (Gif), we observe in the progeny, and then in the *FM3/y* z^a w^a constituted stock, a number of "pseudoagametic" females with underdeveloped ovaries: germ line cells are present but blocked in previtellogenic stages. This phenotype of gonadal atrophy resembles agamety. Male genitalia have a normal morphology. Of several factors apparently involved, at least one seems sex linked. The frequency of this character decreases while the stock is kept; for example, it decreases from 42% in the first generation of homozygous *y* z^a w^a females to less than 2% in the sixth. The appearance of a few pseudoagametic flies among the progeny of *FM3/ rec* at 29° (Column 5) is probably part of the same phenomenon and also decreases, in some cases, from 15% (first generation) to 0.5% (sixth generation). In no case do true agametic flies appear among the progeny of *FM3/ rec* females. The occurrence of pseudoagametes, in both the presence and absence of paralog, mostly in females, might result from the same factors causing the described interactions and instability in segregants from crosses with the *y* z^a w^a stock. A high frequency of aberrant disjunction is observed in such segregants (results not shown). These facts make us suspect a relationship with the phenomenon of hybrid dysgenesis (KIDWELL, KIDWELL and SVED 1977; BREGLIANO *et al.* 1980).

Complementation analysis

Fortunately, paralog happens to lie between zeste and white in a region that has been a battleground for workers with various interests and aims. It must be close to being saturated with lethal (13 complementation groups), female sterile (2 groups) and visible (2 groups) mutations; one behavioral locus has also been described. According to recombination and deletion mapping (see next section), paralog lies in the rightmost part of the region, in the 3B3 band identified by

JUDD, SHEN and KAUFMAN (1972) as containing *l(1)zw12*. Allelism tests conducted at 23° and 29° demonstrate full complementation for all the characters between paralog and the lethal alleles of *l(1)zw1, 6, 12* (3 alleles), *7, 5, 11, 9*, listed in MATERIALS AND METHODS. Paralog also complements *z*, z^{11G3} and alleles of the female-sterile loci *fs(1)Y1,Y2*, mapped between *zw7* and *zw5* (3B4–3B5). Thus, paralog appears to represent a new complementation group in the zeste-white region.

Cytological location and gene-dosage effect

In this section, the results of complementation tests of *par* with various deficiencies in the zeste-white region (Table 1) are described. They indicate that paralog (*1*–1.4) lies in the 3B3 band or adjacent interbands, that it has antimorphic properties and that it interacts with neighboring regions.

Df/par females were constructed by introducing the deficiency chromosome either through $Df/w^{+}Y$ fathers or through *Df/Balancer* mothers. The sisters, *Df/FM3* and *par/Bal*, have the same autosomal background; they were studied in parallel as controls. Whenever an interaction between the deficiency and the *par* v^{24} chromosome appeared (that is, *Df/par* differed from *Df/FM3* or *par/Bal*), the regions of the *X* chromosome responsible for the effect were ascertained by repeating the crosses, with both a *y* z^{a} *par* w^{a} strain—in which a segment containing paralog, of maximal length 0.5 cM, was transferred by recombination into a *y* z^{a} w^{a} chromosome of different origin—and the original v^{24} chromosome, from which X^{1122} = par v^{24} was derived. Two-day-old flies (within one day) were followed for ten days in pondoirs, in order to detect any maternal age effect. The deficiencies can be grouped into three major classes, according to their interactions with the paralog chromosome.

The first class, *DfI*, (Figure 2 and Table 6) is composed of five strains, *w258-42*, *w258-45*, "*w258-45*", *64f1* and *TEM7* that, when heterozygous with the *par* v^{24} chromosome, show some paralog characteristics. Since only one band is uncovered by all five deficiencies, we conclude that *par* probably maps in this band, namely, 3B3. However, the phenotype of females *DfI/par* is much less extreme than that of *par/par*; at 29°, where *par/par* lay very few eggs that never hatch, *DfI/par* females lay a normal number of eggs, of which 50% to 80% hatch, and 1% to 50%, depending on the strain, give rise to adults. Whatever their sex and genotype, a large majority of these are agametic (70% to 100%), have abdominal defects (20% to 40%) and specific wing alterations (5% to 20%). The degree of expression of the paralog characteristics in *DfI/par* females depends partly on the way that they were constructed: paralog is slightly better expressed when it is transmitted by the father. Of course, the various strains are not isogenic, so that the genetic background may also have an influence.

Only one deficiency of this class, *w258–42*, was tested at low temperature; at 23° the expression of paralog is weak, the rate of emergence is wild type, only 14% of the progeny are agametic and less than 10% have morphological defects. Females were then shifted from 23° to 29° in order to determine the temperature-sensitive period. It took about twice as long to reach the control value at 29° in *Df/par* females as compared to *par/par* females. The effect of tempera-

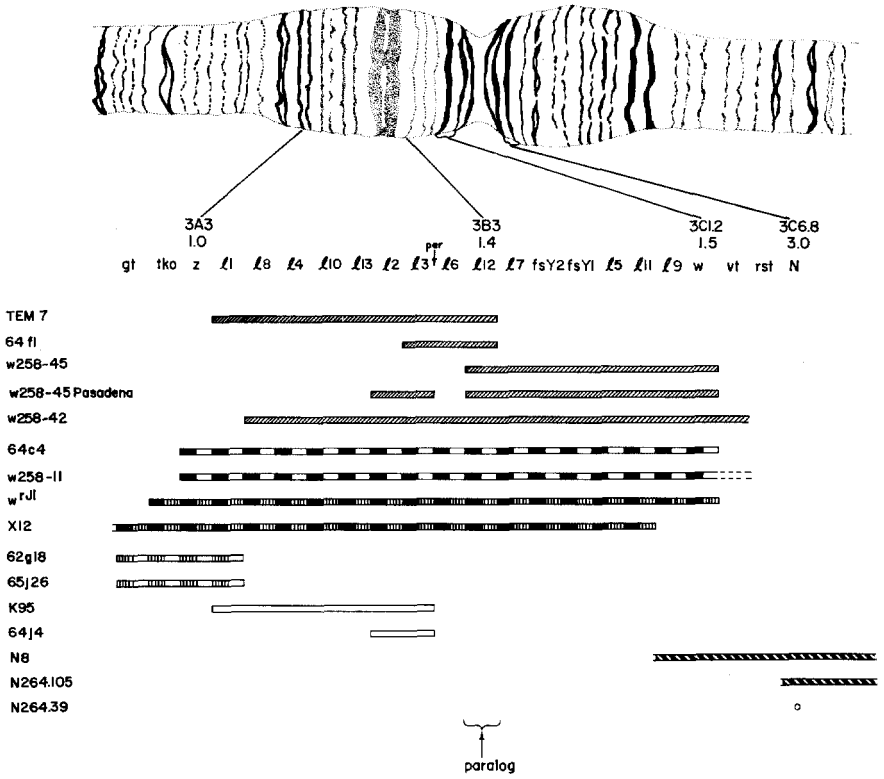


FIGURE 2.—Cytogenetics of section 3, and results of dosage analysis of paralog. The diagram presents the banding pattern of salivary gland chromosomes in sections 2 to 4 at the distal end of the *X* chromosome. Specific bands and their allocated genes are indicated; map positions are in centimorgans. The order of the complementation groups evidenced after saturation of the region with lethal—and possibly visible and female-sterile mutations—is indicated (from Judd).

Deficiencies that define the dosage effects of paralog are drawn according to data in Table 1. Selective complementation of a given deficiency with two adjacent complementation units allows exact definition of the deficiency breakpoint. The rare instances of uncertainty are indicated with an open-ended bar, in which cases the deficiency may uncover additional complementation groups.

The pattern shading in the bars reflects the results of dosage analysis. The five upper deficiencies (leftward hatched filling) are the class I deficiencies. They uncover paralog, and indicate that the nonamorphic *par* mutation lies in the *l(1)zw12*-3B3 band. The long-wave broken line characterizes the four deficiencies in class II. When combined with paralog, they express qualitative effects different and more extreme than class I. This may relate to the absence, in addition to the 3B3-*par* + *l(1)zw12*, of the 3A3-zeste band.

The remaining six deficiencies are class III. While they do not uncover paralog, they indicate dominant interactions of paralog possibly with 3A2 (interspersed clusters of vertical fine lines, in *62g18* and *65j26*, but also in two of the class II deficiencies, *X12* and w^{rJ1}), and also the Notch locus-3C6-8 (heavy rightward hatching).

ture is more rapid on two doses than on one, indicating again that the paralog mutation is not the amorphous condition of the gene.

The *w258–45* strain from Pasadena and "*w258–45*" from JUDD deserve special mention. The latter had been extracted from the former by recombination: *w258–45* = "*w258–45*" + *64j4*. Only in those two strains are the characteristics

TABLE 6

Characteristics of the Class I deficiencies

t°	Tested females	From mothers	Maximal fecundity	Rates of* Adult emergence	Rates of* Pupal lethality	*par* defects in progeny† Agametic	*par* defects in progeny† Abdominal	*par* defects in progeny† Thoracic	Special features	Nondisjunction‡
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
29°	*FM1/w258-42(/Y)*	*FM1/w258-42/(Y)*	55	34	15,	0(0-1)	(0-1)	(0-1)		+
	par v/w258-42(/Y)		60	19	14	94(92-98)	(23-26)	(2-9)		
	FM4/w258-45(/Y)	*FM4/w258-45/(Y)*	30	63	5	0(0-1)	(0-1)	(0-1)		+
	par v/w258-45(/Y)		35	27	7	50 → 100(m̄79-87)	m̄(26-39)	(11-22)	age effect	
	FM3/"w258-45"	*FM3/par v*	25	100	0	0(0-1)	(0-3)	(0-3)		
	par v/"w258-45"		22	47 → 3	2 → 28	10 → 77(m̄20-32)	0 → 20	(1-5)	age effect	
	FM3/64f1	*FM3/par v*	30	100	0	0(0-1)	(0-1)	(0-1)		0
	par v/64f1		30	7	55	69(59-78)	(18-38)	(17-37)		
	FM6/TEM7	*FM6/TEM7*	30	28	20	0(0-3)	(0-3)	(0-3)		0
	par v/TEM7		30	1	5 + 80 larv.	100(70-100)	(15-78)	(3-56)		0
	FM3/par v	*FM3/par v*	35	70	0	0(0-1)	(0-1)	(0-1)		0
	par v/par v		2	0	0	—	—	—		
23°	*FM1/w258-42(/Y)*	*FM1/w258-42/(Y)*	22	50	0	0(0-1)	0	0		+
	par v/w258-42(/Y)		33	53	0	14(10-18)	(0-5)	(3-7)		
	FM3/par v	*FM3/par v*	30	95	0	0(0-0.1)	0	0		0
	par v/par v		30	40	0	100(98-100)	(46-54)	(15-26)		

Whatever their origin, the tested females are fully viable and do not exhibit any morphological defects, nor do *par/0 or Y* nondisjunction males (sample > 200). The females were generally mated to *par* $v^{24}/w+Y$ males; no effect of their age was noticed, unless otherwise specified.

* Experimental values eventually corrected for the lethal classes are given. The sample size, 2000 to 7000 embryos each, makes the statistical errors much lower than the experimental variations.

† 95% confidence limits are given in parentheses.

‡ Nondisjunction is estimated by the presence of two or more *par* v^{24} males in a sample of 1000 progeny flies from *Df/Bal* × *par* v^{24}/Y.

of paralog better expressed in aging females. Indeed, 46% of the eggs laid by two-day-old "*w258–45*"*par* females give rise to adults, of which 12% are agametic; whereas, only 3% of the eggs laid by five-day-old females give adults, of which 74% are agametic. The rate of abdominal defects continuously increases from 15–20% to 40–45% over this same time period. Similar effects are found with *w258–45*. We would like to correlate this age dependence with the position of the left breakpoint common to those strains, *i.e.*, between *zw6* and *zw12* (*3B2–3B3*). We would then be in a particularly interesting situation where the deletion would not completely uncover the functional unit of paralog, so that it would require a longer time to get the full expression of the mutation. The hypothesis that the wild-type part of paralog still present in the deficiency chromosomes controls the temporal expression of the paralog mutation in *trans* is testable by mutagenesis, selection and fine-structure analysis of dominant suppressors of *par* with age effects.

The expression of the *par* maternal effects in combinations of *par* v^{24} with the class I deficiencies leads to the conclusion that *par* is located between *zw6* and *zw7* (3B2 and 3B4), around *zw12*, the only lethal uncovered by each of the five deletions. However, it has already been shown that paralog fully complements three alleles of *zw12*. Moreover, in *par/DfI* females, the expression of paralog is consistently lower than in *par* homozygotes, which implies that the mutation is neither the amorphic, nor hypomorphic condition of the gene.

The second class, *DfII* (Figure 2 and Table 7), is composed of four strains (*w258–11*, *64c4*, w^{rJ1} and X^{12}) that are large deficiencies uncovering most of the zeste-white region, including the 3B3 paralog band. The results obtained with this class appear complex. The new properties are probably related to the 3A3 band, assigned to the zeste locus, since it is the only one uncovered by all class II deficiencies, but by no class I deficiency.

The main characteristic of this class is the complete sterility of *DfII/par* females, irrespective of the temperature, the origin of the chromosomes or the age of the females. At 23° and 16°, they are as viable and fecund as their control sisters *Df/+* or *par/+*, but the eggs mostly die in embryonic stages and never develop into adults. At 29°, even the viability (Table 7, column 3) and the fecundity (column 7) of *par/DfII* females are affected. These effects depend on three factors: maternal or paternal origin of the chromosomes, the left breakpoint of the deficiency and the age of the females.

If the left breakpoint is between 3A2 and 3A3 (*64c4* and *w258–11*), then *Df/par* females from *FM3/par* mothers are 80% as viable and 50% as fecund as their control *FM3/Df* sisters. If born from *Balancer/Df* mothers, these same females have viabilities and fecundities around 60% and 30% of the *Balancer/par* controls, respectively. Eggs from both types of mothers appear normal, but seldom hatch and never survive to the third larval instar.

If the left breakpoint is distal to 3A2 (w^{rJ1} and X^{12}), the viability is affected in the same way as in the two more proximal deficiencies, but the fecundity is still more reduced, a number of eggs appear flaccid or frequently lack a chorion, and a strong age effect appears. Here, also, *Df/par* females from *Df/FM3*

TABLE 7

Characteristics of the Class II deficiencies at 29°

Origin (♀ 0–4 days)	Genotypes tested	Phenotype				Fertility and progeny				
		Viability	% Gonadal atrophy	Specific wing and other thoracic defects	Confluens wings	Maximal fecundity	Flaccid eggs	Rate of emergence	Pupal lethality	Defects in progeny
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
$\frac{FM3}{64c4} \times \frac{par\ v^{24}}{Y,}$	*FM3/par v*	100	24(548)*	0+1(346)	0	42	0	100	0	No
	64c4/par v	58–68	20(552)*	4+20(206)	++	8	0	0	0	—
	♂ ND par/Y		30(12)		++					
$\frac{FM3}{64c4} \times \frac{y\ z^a\ par\ w^a}{Y}$	*FM3/y z^a par w^a*	100	18(278)*	0+1(146)	0	36	0	98	0	No
	64c4/y z^a par w^a	56–72	18(164)*	3+8(90)	++	14	0	0	0	—
$\frac{FM3}{64c4} \times \frac{v^{24}}{Y}$	*FM3/v^24*	100	3(154)	0+1(154)	0					
	64c4/v^24	120–140	8(210)	0+1(210)	0					
$\frac{FM3}{par\ v^{24}} \times \frac{64c4}{w+Y}$	*FM3/64c4*	100	0(1/246)	0+2(246)	0	39	0	31	30	Yes*
	par v/64c4	74–85	4(10/250)	4+17(200)	+	22	0	0	0	—
	par v/w+Y	110–130	1(2/305)	0+2(305)	(w+Y)					
$\frac{FM4}{\frac{w258\text{–}11}{(Y)}} \times \frac{par}{Y}$	*FM4/w258–11/Y*		4(50)	0+0(50)	0	22	0	24	12	Yes*
	FM4/(z^a)par/(Y)		19(80)*	0+0(89)	0	34	0	100	0	No
	w258–11/(z^a)par/(Y)		13(86)*	16+14(101)	++	10	0	0	0	—
	FM4/Y/(Y)		20(96)*	0+6(50)	0					
	*(z^a)par/(Y)*ND		21(70)*	5+5(70)	++					
$\frac{FM4}{\frac{w258\text{–}11}{(Y)}} \times \frac{FM4}{Y}$	*FM4/w258–11/(Y)*		1(80)	0+0(90)	0					
	FM4/Y/(Y)		2(49)	0+1(50)	0					

TABLE 7—Continued

Origin (♀ 0–4 days)	Genotypes tested	Phenotype: Viability	Phenotype: % Gonadal atrophy	Phenotype: Specific wing and other thoracic defects	Phenotype: Confluens wings	Fertility and progeny: Maximal fecundity	Fertility and progeny: Flaccid eggs	Fertility and progeny: Rate of emergence	Fertility and progeny: Pupal lethality	Fertility and progeny: Defects in progeny
$\frac{FM3}{w^{rJ1}} \times \frac{par}{Y}$	*FM3/(z^a)par*	100	4(277)	0+2(277)	0	38	0	100	0	No
	w^{rJ1}/(z^a)*par*	63–70	4(197)	7+20(210)	++	1	100	0	0	—
	par/O ND		0(8)		++					
$\frac{FM3}{par} \times \frac{w^{rJ1}}{w^+Y}$	*FM3*/w^{rJ1}	100	2(238)	0+2(249)	0	40	0	75	8	Yes
	par/w^{rJ1}	90–98	2(207)	10+16(212)	+	10→0*	10→100*	0	0	—
	par/w^+Y	100–120	2(196)	0+1(275)	(w^+Y)					
$\frac{FM3}{X12} \times \frac{par}{Y}$	*FM3/(z^a)par*	100	1(416)	0+1(414)	±	36	0	100	0	No
	X12/(z^a)par	51–58	4(292)	5+7(256)	+	1	100	0	0	—
$\frac{FM3}{par} \times \frac{X12}{w^+Y}$	*FM3/X12*	100	0(57)	0+4(57)	0	36	0	70	6	Yes
	par/X12	110–130	0(73)	8+14(73)	0	6→0*	0→100*	0	0	—
	par/w^+Y	85–98	0(39)	0+0(45)	(w^+Y)					

The flies tested came from mothers less than 4 days old. In each case, three paralog-bearing chromosomes were used: $X^{1122} = par\ v^{24}$, $y\ par\ v^{24}$ and $y\ z^a\ par\ w^a$; but since it has no effect on the results (see for example *64c4*), the data are further regrouped under the denomination "*par*."

Enumeration of the total progeny gives the viability of *par/Df* females relative to their sisters, at 95% confidence level (column 3). A sample, of size indicated in brackets, is dissected. The frequency of gonadal atrophy, agametes or pseudoagametes, is given (column 4). A sample is scored for defects; the frequency of duplication of the wing blade, characteristic of paralog, is given, followed by that of less specific thoracic defects (column 5). A Confluens wing-vein phenotype might be expressed very strongly (++: 50–90% of the flies; high expressivity), strongly (+ : 10 to 40% of the flies), weakly (±: less than 5%, low expressivity) or not at all (0) (column 6). As a matter of fact, *par*/w^+Y males are Confluens ++, but this is due to the duplication of 3C6-8 in w^+Y.

A sample of the females less than 2 days old was mated to *par*/w^+Y males, their fertility and progeny analyzed by the pondoir standard method (columns 7–11). The experiment lasted 15 days, and the asterisk (*) denotes an influence of the age on the expression of the character.

These four deficiencies give a high level of nondisjunction in females *Df*/+.

mothers are more affected, and their viability is around 60% and fecundity 3% of the control; all eggs laid are flaccid. On the other hand, those females from *FM3/par* mothers are 100% viable, and when two days old, lay 25% of the control number of eggs, all of which appear normal. However, the beneficial influence of their origin vanishes with age; when five days old, their fecundity drops to about 5% of the control, and all of their eggs appear flaccid.

To summarize the results obtained with the class II deficiencies, two types of interactions concerning viability and fertility have been described in hemizygous paralog females: a deficiency for 3A3 leads to sterility at any temperature, mostly due to embryonic lethality. At 29°, viability and fecundity are also reduced. A deficiency for 3A2–4 leads, at 29°, to a fecundity still lower and age-dependent; the few eggs laid are flaccid. Both these interactions are more extreme if the paralog chromosome is supplied by the father and the deficiency by the mother.

A second feature uniquely assigned to the class II deficiencies is the expression of paralog morphological defects, such as those on the wing blade, in *DfII/par* females. These defects never appear in the *DfII/+* or *par/+* sisters (Table 7, column 5). The penetrance varies slightly with the deficiency, but not with the parental origin of the chromosome. These characteristic *par* defects are thus expressed both in a strictly maternal way, in the progeny of *par/par* females, whatever the genotype of the zygote itself might be (*par/+* or *par*), and in a strict zygotic way, in the very *Df/par* flies, hemizygous for *par* and for 3A3, whatever the genotype of their mother might be (*Df/+* or *par/+*). It seems, formally, that a deficiency for 3A3 modifies the time of expression of paralog.

A third feature is the appearance in some females of gonadal atrophy. It is, however, difficult to distinguish agametic ovaries, as observed in paralog, from pseudoagametic ones, as observed at 29° in hybrid dysgenesis. The data shown in Table 7, column 4, and below, are best interpreted if both paralog and a dysgenic-like behavior of the deficiencies intervene. On the one hand, some 1% to 5% of "agametic" flies arise in the progeny of $FM3/par\ v^{24} \times Df/w^{+}Y$ (column 4) and none in the $FM3/v^{24} \times Df/w^{+}Y$ controls (results not shown). In the case where expressivity is highest, (*64c4*), *par/Df* flies are significantly more affected than their *FM3/Df* sisters; this might correspond, as in the case just described of the wing blade phenotype, to a weak zygotic expression of paralog in flies hemizygous for 3A3 and *par*. On the other hand, a high frequency of "agametic" flies is observed in the reciprocal crosses using *Bal/Df 64c4 or w258–11* females; but this time the distribution of "agametic" flies among the progeny classes is roughly uniform, *Bal/par* and *Df/par* being equally affected. Moreover, this dominant maternal effect of the deficiencies is expressed whatever the father might be, $par\ v^{24}$ (38%), $y\ z^{a}\ par\ w^{a}$ #3 (30%), $y\ z^{a}\ par\ w^{a}$ #7 (66%), but also v^{24} (9%), Chantelle (32%), Canton-S (40%), or Harwich (100%) (the numbers given are for *FM3/Df 64c4* mothers less than three days old; samples are around 200 flies each). As in some other cases related to hybrid dysgenesis, this effect strongly depends upon maternal age—for instance it decreases from 21% (19–24) for 0- to 5-day-old females to 11% (9–14) between

5 and 10 days and to 3% (3–9) over 10 days—but contrary to the KIDWELL description of gonadal atrophy, it affects males and females equally. These effects are interesting, but complex, and more experiments will be needed in order to determine the respective roles of paralog, the deficiencies and the genetic background in this system.

The last effect specific to some class II deficiencies is the appearance in *DfII/par* individuals of a wing-vein phenotype similar to that of Confluens, a phenotype characteristic of Notch$^+$ duplications. Here again, the penetrance is affected by the origin of the chromosomes; both the frequency and expressivity are higher if the mother is heterozygous for the deficiency and paralog is supplied by the father. The effect is observed at high frequency with *64c4*, *w258–11* and w^{rJ1}, but not with X^{12} and the class I deficiencies, pointing to the influence of the 3B5–3C2 region located between paralog and Notch, in conjunction with 3A3. A tentative interpretation is that the Confluens phenotype is caused by an overexpression of the Notch (3C7) locus in *cis* to paralog; this is further supported by the high level of phenotypically Confluens *par/O or Y* nondisjunction males from *Df/+/Y* mothers.

Finally, it was noticed that females heterozygous for any *DfII*, or for *w258–42* and *w258–45*—but for none of the other deficiencies used—show a high rate of nondisjunction, at least for the *X* chromosome. This effect has already been described by ROBBINS (1977) as resulting from haploidy for the *z-w* region. We now assign it to hemizygosity for part of the *zw12–zw9* region. Quantitative variations are evident among the deficiencies, but they may result from the immensely different genetic background, as well as from a dose-dependent modifier inside the *z-w* region.

The third class of deficiencies (Table 8) is composed of six strains that do not exhibit, when heterozygous with *par* v^{24}, any germinal features of paralog. These include *K95* and *64j4*, two Notch deficiencies (*N264–105* and N^8) and two deficiencies around the zeste band (*62g18* and *65j26*).

No interactions are seen with *K95* and *64j4*. However, one may notice in column 5 the poor fertility at 29° of *K95/FM3* or *par v/K95* females, partly due to the lethality of *K95/w*$^+$*Y* males, which occurs at all stages of development. The same effect, independent of paralog, is also observed with six of the 15 deficiencies tested. These are *TEM7*, *w258–42* (Table 6, columns 5 and 6), *w258–11*, *64c4*, w^{rJ1} and *X12* (Table 7, column 9); they all uncover the *zw1–zw2* region, suggesting the existence in this region of a gene that, when haploid, leads to a partial female sterility at 29°. These deficiencies are viable and fertile at 23° in heterozygous condition.

To study the interactions with the Notch deficiencies, females were constructed only one way (from *Df N/Bal* mothers) and compared to their cousins *Df N/Bal*, *Df N/y* z^a *par* w^a and *Df N/*v^{24}. Whatever the temperature (23° or 29°), *Df N/*(*par* v^{24} or *y* z^a *par* w^a) females show a much reduced penetrance of the Notch wing phenotype as compared to the complete penetrance of *N* observed in *Df N/Bal* and *Df N/*v^{24} females. Fifty percent of *Df N/par* flies have perfectly wild-type wings, while the remainder often show only one nick per

TABLE 8

Characteristics of the Class III deficiencies

t°	Tested females	From mothers	Maximal fecundity	Rate of emergence	Pupal lethality	Special features
29°	*FM1/N8*	*FM1/N8*	40	100	0	
	par v²⁴/N8		40	100	0	Notch suppression
	FM1/N264–105	*FM1/N264–105*	20	60	2	
	par v/N264–105		18	60	2	Notch suppression
	FM4/N264–39	*FM4/N264–39*	28	75	0	
	par v/N264–39		30	72	0	——
	FM3/K95	*FM3/par v*	27	31	20	
	par v/K95		22	12	15	——
	FM3/64j4	*FM3/par v*	50	100	0	
	par v/64j4		50	95	0	——
	FM3/62g18	*FM3/par v*	50	100	0	
	par v/62g18		30 → 2	13 → 0	0	Eggs normal to flaccid depending on age
	FM3/65j26	*FM3/par v* or	30	75	8	
	par/65j26	*FM3/y z^a par w^a*	15 → 0.2	35 → 0	12 → 2	Eggs normal to flaccid depending on age
	FM3/par v	*FM3/65j26*	28	82	0	
	65j26/par v		3	4	2	Flaccid eggs
23°	*FM3/65j26*	*FM3/par v*	27	98	2	
	par v/65j26		30	77	4	——

Df/par females do not exhibit any visible phenotype; they are as viable and fecund as *Df/Bal*; upon examination and dissection of 600 progeny, no defect was detected. Disjunction of the *X* chromosome is normal in all cases.

Data for the N^{264-39} point mutant are given here for comparison with the Notch deficiencies.

wing on one wing per fly. Thus, a mutation present in the *z w* region of the X^{1122} chromosome, and absent from the original v^{24} chromosome—most probably paralog itself—partially suppresses the Notch phenotype associated with two deficiencies of the Notch region. Interestingly, no suppression was observed with *N264–39*, which has been shown by WELSHONS (1975) to be a point mutation at the locus.

The behavior of the deficiencies around zeste, *65j26* and *62g18*, is somewhat special. They interact with paralog, since *Df/(par* v^{24} or *y* z^{a} *par* w^{a}) females differ from their *FM3/Df* and *FM3/par* sister controls (Table 8). However, none of the characteristic defects of paralog appear, which is consistent with *par* mapping outside this interval. *Df/par* females from the cross of *FM3/Df* ♀ × *par/*w^{+} *Y* ♂ lay only a few flaccid eggs, most of which die as embryos; they are thus nearly sterile, whatever their age. This effect is less drastic and becomes age-dependent if the deficiency is donated by the father (from the cross of *FM3/par* ♀ × *Df/*w^{+}*Y* ♂). When these *Df/par* daughters become older than three to five days at 29°, their fecundity drastically falls from 50% to less than 5% of the control value. During the same period, the ability of eggs to complete development falls gradually from 40% to 0%, at which point all eggs are flaccid and take color from the medium. Also, in the progeny, females from young mothers have normal ovaries, but those from 3- to 5- day-old mothers have very reduced ovaries because of defective vitellogenesis. None of them, however, is agametic. This description is reminiscent of similar age-dependent effects on fecundity and egg flaccidity observed at 29° with two class II deficiencies, X^{12} and w^{rJ1}, which uncover in common with *62g18* and *65j26* the three-band region from 3A2 to 3A4 (Table 7, columns 7 and 8). Comparison with the two class II deficiencies that do not show this effect (*64c4* and *w258–11*) indicates that haploidy for the 3A2 band is an active component of the interaction. One interesting feature of this interaction is that it appears identical in flies hemizygous for paralog (*DfII/par = Df(3A2–4 + 3B3)/+ par*) or heterozygous for it (*DfIII/par = Df(3A2–4)par*$^{+}$*/+par*). Thus, for these class III deficiencies, the paralog^{+} gene *cis* to the deficiency appears neutral. Unfortunately, attempts to construct a *Df65j26 par* chromosome have failed, so that it is not known if the *cis* and *trans* positions of *par* and the deficiency differ in any way.

Extra dose studies

The reduced expressivity of paralog when heterozygous with the class I deficiencies that uncover it (Table 6) contrasts with its recessive behavior, and led us to investigate the phenotype of *par/par/par*$^{+}$ flies. For this study, two duplications that do not variegate for the w^{+} locus are chosen. One of them also covers the zeste region ($w^{+}Y$: 2D1-2–3D3-4; Y^{L}); the other does not (*Dp(1,2)* w^{+70h31}: 3A6-8–3C2-3; 31). Sister females containing a variable number of doses of the *par* or *par*$^{+}$ alleles were tested in pondoirs. As may be seen in Table 9, both duplications give similar results: a slight expression of paralog is consistently seen in *par/par/par*$^{+}$ flies. At 23°, the only detectable effect is a tiny reduction in the rate of emergence of the progeny. At 29°, this factor is more reduced, due to a maternally affected lethality that occurs mainly during the

TABLE 9

Expression of paralog in par/par/par+ *flies*

Tested genotypes	Dosage of paralog	22°			29°			
		Maximal fecundity	Rate of emergence	Agametes among the progeny	Maximal fecundity	Rate of emergence	Pupal lethality	Agametes among the progeny
$\frac{y\ par\ w^a}{FM3}$ / $\frac{}{\frac{1}{2}Dp(1,2)w^{+70h31}}$	par / + / (+)	12	99 — 100	0/1145	25	83 — 85	0	0/735
$\frac{y\ par\ w^a}{y\ par\ w^a}$ / $\frac{}{Dp(1,2)w^{+70h31}}$	par / par / +	12	90 — 92	1/1181	20	36 — 38	2	59/1904
$\frac{y\ par\ w^a}{y\ par\ w^a}$	par / par	15	38 — 42	862/1051	2	0 — 0.1	0	—
$\frac{y\ par\ w^a}{FM3 \text{ or } Basc}$ / $\frac{}{w^+Y}$	par / + / +				9	13 — 15*	17	0/447
		20	71 — 75	0/231				
$\frac{y\ par\ w^a}{Basc}$	par / +				15	15 — 17*	26	0/393

TABLE 9—Continued

Tested genotypes	Dosage of paralog	22°			29°			
		Maximal fecundity	Rate of emergence	Agametes among the progeny	Maximal fecundity	Rate of emergence	Pupal lethality	Agametes among the progeny
$\frac{y\ par\ w^a}{y\ par\ w^a}$ $\frac{}{w^+Y}$	$\frac{par}{par}$ $\frac{}{+}$	20	62 — 66	$\frac{1}{945}$	14	27 — 29	9	$\frac{17}{794}$
$\frac{y\ par\ w^a}{y\ par\ w^a}$	$\frac{par}{par}$	20	10 — 12	$\frac{668}{814}$	15	0 — 0.2	0	—

In the case of $Dp(1,2)w^{+70h31}$, the tested females are sisters coming from the cross of *FM3/y par* w^a *#1* ♀♀ × *y par* w^a *#1/Y*; $Dp(1,2)w^{+70h31}$ ♂♂ at 23° and 29°. In the case of the w^+Y duplication, they come from *FM3/y par* w^a *#1*/w^+Y ♀ × *y par* w^a *#1*/w^+Y ♂♂ at 23°, and from *Basc/y par* w^a/w^+Y ♀♀ × *y par* w^a/w^+Y ♂♂ at 29°. Contrary to *FM3*, the *Basc* (w^a) chromosome allows a visual sorting of *par*/+ and *par*/+/+ females, but on the other hand, it appears to be responsible for semidominant sterility at 29° (*), due to maternal-effect lethality at any stage.

The sample size varied between 3,000 and 10,000 eggs, and the rate of emergence, corrected for the lethal classes, is given at the 95% confidence level. The proportion of pupae that died is also noted. In the case of $Dp(1,2)w^{+70h31}$, segregation of the markers in the progeny was not distorted; the reduction in the rate of emergence among the progeny of *par/par/+* females thus results from a strict maternal-effect lethality.

first larval instar and affects equally flies of the different genotypes. Moreover, some 2% to 3% agametic flies appear in th progeny.

This low but significant semi-dominant expression of paralog in *par/par/par*$^+$ females and the intermediate phenotype of *par/Df* females indicate that *par* is an antimorphic mutation, according to MULLER's (1932) terminology.

Advantage was also taken of these duplications to look for grandparental effects. Females of a given genotype (*par/par*, *par/par/par*$^+$ or *par/+*), but from mothers that carried different doses of *par*, were compared in parallel pondoirs at 23° and 29°. Apart from marginally significant effects, the number of eggs laid by *par/par* females and the ability of these eggs to develop are clearly affected by both the genotype and the age of their grandmothers (Table 10). The higher the proportion of paralog doses in the ancestors, the stronger the expressivity of paralog in the progeny. These results are in close agreement with the temperature-sensitive experiments (THIERRY-MIEG, unpublished) and suggest that toxic effects associated with the paralog mutation may accumulate in germ line cells.

DISCUSSION

We have demonstrated that a modification at a single chromosomal site leads to a variety of effects. Some of them are expressed in an autonomous and recessive way in the germ line cells, and lead to a complex pattern of defects (Table 2). This might result from the disturbance of a basic germ line property, such as cell polarity, autonomously transmitted along generations of flies (THIERRY-MIEG, unpublished). Other effects are expressed in somatic cells, either directly or through dominant or recessive interactions with other mutants or haploid regions. The mutation, called paralog, maps on the *X* chromosome in the zeste-white region, at 1.4 ± 0.1 according to recombinational analysis, and, consistently, between the polytene chromosome bands 3B2 and 3B4 according to

TABLE 10

Memory in an embryo of its grandmother's paralog dosage

Mothers of the females tested		Tested females: *y par* w^a/*y par* w^a		
			Frequencies of embryos	
Genotype	Age in days	Fecundity	Segmented	Hatched
par/+/+	0–2	4–5	45	20
	14–16	4–5		22
par/par/+	0–2	3–4		11
	8–10	0.7–1.5		3
	14–16	0.2–0.7	3	0

The fertility at 29° of *par/par* females 2 to 5 days old is analyzed as a function of the genotype and the age of their mothers, which may have an extra *par*$^+$ dose in the form of a w^+Y. Similar results are obtained with $Dp(1;2)w^{+70h31}$.

The mean fecundities over a 3-day period, then the maximum observed, are given (eggs/♀/day). Samples of 500 to 1,000 embryos each were examined.

cytogenetic analysis. The degree of expression of paralog defects in the germ line depends upon the dosage of the paralog region in these cells, and follows the gradation

$$\frac{+}{+} = \frac{par}{+} = \frac{Df}{+} < \frac{\frac{par}{par}}{par^+} < \frac{par}{Df} < \frac{par}{par} .$$

Thus, paralog is an antimorphic mutation in MULLER's (1932) terminology. This means that the mutation does not correspond to the loss of a wild-type function, but to the gain of a new one, apparently competing with others. Due to the lack of amorphic alleles, the function, if any, of the par^+ DNA is still unknown. But since the zeste-white region is probably saturated with zygotic recessive lethals, all of which perfectly complement paralog, it is likely that null alleles are not zygotic lethals. par^+ might perform a vital function, but be repeated in the genome, or it might be needed only for the differentiation of the germ line. Alternatively, its function might be just to provide a site for mutation.

The mutation appeared after EMS mutagenesis, but since two alleles were simultaneously recovered, we suspect that it is of spontaneous origin. The mutation is very stable. However, in a context ($y\ z^a\ w^a$, Paris) seemingly related with hybrid dysgenesis—a phenomenon variously interpreted as resulting from DNA transpositions—it becomes unstable; the mutation might thus be a DNA insertion.

A distinctive feature of paralog is its interactions with not one, but several, possibly many, other loci. These are revealed when *par* is associated with other genetic defects, deficiencies or mutations, or possibly in certain genetic backgrounds. This paper describes interactions only with close neighbors of *par*. We shall first recall some properties of the 3A-C region that might be of interest for the interpretation of the effects described. Region 3 of the *X* chromosome (Figure 2) contains a giant palindrome 3C1–8 (PANSHIN 1941). The white (3C1–2) and Notch (3C6–8) loci, as well as the roughest and vertical (3C3–5) loci occupy symmetrical positions in this palindrome. That this symmetry might have functional significance is indicated both by strikingly similar zest-suppressing properties of breakpoints in the 3B4–3C2 and 3C6–8 regions (GANS 1953) and by interactions between *vt* and *rst* indicating functional equivalence of deficiencies for the 3C3 and 3C5 bands (LEFEVRE and GREEN 1972). Moreover. attempts to select lethals in that 6- to 8-band region have failed, which again indicates redundancy. At the center of the palindrome lies the 3C4 constriction, a site of ectopic pairing, X-ray breakage and repetitive elements. Both the constriction and the 3A3 zeste band have been described as intercalary heterochromatin (HANNAH 1951; SLIZYNSKA, personal communication). The zeste band lies outside the palindrome, 13 bands distal from white. It might be structurally related to elements of the 3C region, as indicated both by direct observation of ectopic pairing, and by recovery of spontaneous deficiencies and duplications (GREEN 1961; LEFEVRE and GREEN 1972). At the functional level, the

expression of the neomorphic *z* mutation depends both on the dosage of the most proximal and probably regulative part of the white locus, and on the structural integrity of several sites proximal to zeste and scattered in the 3B–3C region. A possible set for them is 3A3, 3B2–5, 3C1–2, 3C6–8 (GANS 1953). The requirement on the topology of the 3B-C region seems most stringent: euchromatic as well as heterochromatic rearrangements suppress the zeste phenotype superdominantly, that is, almost regardless of the number of doses of the wild-type region and of their regular arrangement (GANS 1953).

JACK and JUDD (1979) suggested that the topological constraint might be the pairing of the w^+ genes in the nucleus. This hypothesis is elegant and simple, but must be taken in a very broad sense in order to account for all the results (THIERRY-MIEG, unpublished). In the same vein, two mutations in the zeste region have been isolated by E. B. LEWIS as mimicking a disruption of pairing between homologous chromosomes bearing the *Ubx* and bx^{34e} alleles, leading to a "transvection"-like phenomenon (LEWIS 1954). Further analysis indicated that they are hypomorphic alleles of zeste: z^a mutations enhance some alleles at the bithorax locus, all of which, interestingly, are spontaneous (KAUFMAN, TASAKA and SUZUKI 1973). Effects of z^a on other loci have not yet been investigated.

The presence of paralog in a zygote bearing mutations or deficiencies in *trans* leads to specific defects that have been described in detail, but with no interpretation, in the RESULTS. These were mostly side observations, and require further investigation in the future. However, we may try to group the results into suggestive phenotypical classes in order to generate a tentative, but testable, interpretation.

Four types of interactions of paralog recall phenotypes characteristic of the Notch complex locus (WELSHONS 1974; WELSHONS and KEPPY 1975; POULSON 1945). The first one is a zygotic and dominant partial suppression of the Notch wing phenotype in individuals *par* N^+/ *par*$^+$*Df N* (N^s and *N264–105*) (Table 8). The influence of the paternal *versus* maternal origin of the chromosomes, and of the *cis versus trans* configuration has not been checked. However, a Notch point mutant, *N264–39*, is not suppressed, indicating a structural requirement for this effect to occur; paralog seems selectively to suppress the Notch phenotype associated with deficiencies for at least a part of the 3C6–3D2 region.

The second interaction is the appearance of a Confluens wing phenotype characteristic of an overdose of the Notch$^+$ region in *Df(3A3–4) + (3B3) + (3B5–C3)* N^+/*par* N^+ (*w258–11*; *64c4*; w^{rJ1} flies but not X^{18}, *w258–42* or *TEM7* flies) (Table 7, column 6). This effect is strong only if the deficiency simultaneously takes out regions on both sides of paralog in 3A3–4 and 3B5–C3. Its penetrance and expressivity are much higher if the deficiency chromosome is maternal and the paralog paternal in origin. The following indirect observation gives an insight into the *cis* or *trans* effect of this interaction. Haploidy for a region (ROBBINS 1977) in 3B4–6 leads to frequent nondisjunction in *Df*/+ females. The *par*/*O* or *Y* sons recovered (but not v^{24} or +/*O* or *Y*) express on even stronger Confluens phenotype than do their *Df*/*par* sisters, indicating that the complete

information for this phenotype is contained in the *par* N^+ chromosome itself. The Notch suppression and Confluens phenotype could be commonly interpreted as resulting from an increased Notch$^+$ function in the *par* N^+ chromosome. The Notch$^+$ locus may be physically duplicated on this chromosome; paralog might, for instance, be an insertion of N^+ (3C6–8) in 3B3 not visible on the salivary chromosomes. Alternatively, the presence of paralog in 3B3 might lead to an increase in the expression of the Notch$^+$ locus in *cis* relative to the mutation. Both hypotheses correlate with the zygotic delta-like wing-vein phenotype of the various recombinant *par* N^+ flies raised at 16°, which somewhat resemble Confluens. Interaction of paralog and split, a pseudoallele of Notch, which leads to a dominant expression of *spl* in *par spl/Bal* flies, remains to be more extensively investigated.

Further indication of topological effects involving paralog are seen in its interaction with zeste at 3A3. When a z^a allele (isolated by GANS) giving a wild-type eye color is combined with paralog, a zygotic semidominant temperature-sensitive interaction occurs: z^a *par* flies are brown-eyed, and z^a *par* w^a, white (Table 5, column 3). Since paralog has no effect on the pigment pathway by itself, it seems likely that its presence in 3B3 is able to interfere dominantly with the normal zeste-white relationship. It would be of interest to compare more directly paralog and the breakpoints in 3B2–4 that act as dominant suppressors of zeste.

A dominant maternal effect of the z^a *par* w^a combination also appears (Table 5, column 4). It seems to result from an interaction of *par* with two factors, one on its left closely linked to z^a and one on its right; it causes a 50% decrease in viability of z^a *par* w^a flies from *FM3*/z^a *par* w^a mothers. This parallels, and may be related to the 50% decrease in viability observed in *DfII/par* flies from *Df/Bal* mothers, but less or not at all from *par/Bal* mothers (Table 7, column 3). Since paralog has no direct effect on the viability, and because of the maternal effect, we may hypothesize that, on a paralog chromosome contributed by the father, some vital functions uncovered by the class II deficiencies are inactivated, leading to the lethality of the *par/DfII* zygotes. Absence of the zeste locus (class II, but not I) and for at least another factor contained in the *l(1)zw8-l(1)zw11* interval (class II, but not III) seems required in this case.

Two other effects appear only when paralog is heterozygous with the class II deficiencies, and are also probably related to hemizygosity for the zeste band. Flies *Df*(z + *par*)/(*par* or z^a *par*) express in a strict zygotic way an usually maternal character of paralog, the iteration of the wing blade; some agametics are also recovered. Moreover, due to a maternal-effect embryonic lethality, females *Df*(z + *par*)/(*par* or z^a *par*, but not v^{24} or +) are completely sterile at all temperatures (16°, 23°, 25°, 29°). Both of these effects might be the result of an early activation of the paralog function in the presence of a deficiency for the zeste region. As in the case of Notch, however, a true deficiency seems needed, since none of these effects are reproduced with a supposedly amorphic z^a mutant at the locus.

A similar sterility appears in *par/Df(1)TEM202* and *par/Df(1)wN*^{71a} flies (Table 1; results not shown) indicating a possible interaction between paralog and a region between 3C3 and 3C9 symmetrical to the one with 3A3. More deficiencies must be studied, but it might be that intercalary heterochromatin sites, such as 3A3 and 3C4, act as clocks for the genes lying in a segment between two of them.

Aside from interactions involving the Notch and zeste loci, interactions between paralog and 3A2 have been described (Table 7, columns 7 and 8; Table 8, columns 4 and 6). *Df3A2/par* females lay very few eggs, most of which appear flaccid or lack a chorion and die as embryos. This effect, extreme if *par* is contributed by the father, is very slight in young females where *par* is contributed by the mother; it becomes however fully expressed in these aging females. The most peculiar property of this interaction is its nondependence on the dosage of the paralog region; it is identical in flies hemizygous or heterozygous for *par*. This again suggests a *cis*-dominant action of *par* that might be tested by construction of the appropriate rearrangements. The isoallele *iso*$^{9.9}$ present in the *y* *z*^{a} *w*^{a} strain (Table 5, column 6) might, by its position and phenotype, correspond to hypomorphic form of the 3A2 factor.

Interactions with more distant loci are just beginning to be investigated. For instance, in flies hemizygous for the vestigial region (chromosome *2*, 49EF) the maternal effects of paralog are expressed one generation earlier—as in the combinations *par/Df II*—but now dominantly: among *par/+*; *Df(2)vg*^{B} or ^{C}/+ flies, 5 to 15% show the characteristic iteration of the wing margin, and 7 to 16% are agametic. Preliminary results also indicate interactions with the *sc*, *Pc* and *su(Hw)* loci.

The degree of expression of most interactions described varies according to the paternal or maternal origin of the chromosomes involved. Such a maternal effect has two major interpretations: there might exist near *par* a region whose absence in the mother enhances the mutant phenotype, which itself will depend upon haploidy in the zygote for other regions, such as 3A2, 3A3–4, 3B4–C1, 3C4 and 3C6–D2. The determination of the region responsible is overconstrained by the data, since no single band is uncovered by all the deficiencies showing a maternal effect. Most of them, however, except for the class I deficiencies, lack the *3A3* (zeste) band: the absence of zeste might act as a maternal and zygotic enhancer of paralog, in a way similar to the bithorax system. However, *z*^{a} does not reproduce the effects of a deficiency for the locus, but rather leads to a new phenotype, namely a change in eye color.

An alternative is suggested by analogies with the phenomena of chromosomal inactivation and position-effect variegation, in which a memory of the origin of the chromosomes has been described (see for instance SPOFFORD 1959; YAMAUCHI and GOLDBERG 1974). For a given rearrangement, the degree of variegation at a given locus is higher if the rearranged chromosome is contributed by the father. We can thus imagine that the maternal effects described in combination of paralog and the deficiencies occur directly *via* a differential chromosomal

expression: the presence of structural deficiencies in the mother and of *par* in the zygote would allow the expression of the different local potentialities of the paternal and maternal genomes, themselves probably related to physically differentiated chromosomal states. By comparing with other cases of "position effects" in a broad sense, we shall further develop this hypothesis (THIERRY-MIEG, unpublished). A simple and consistent interpretation emerges, which is not unique, but extensively testable, and thus follows the rules of the game. We suppose that, above the control at the level of the transcription unit, there exists, at least for highly regulated functions, a control at the level of chromosomal segments. Interference with this control by means of structural rearrangements or spontaneous mutations shows its dependence on the topological integrity of regions scattered over some chromomeres. In the case of the 3ABC region, a subset appears to be 3A3 + 3B2–5 + 3C1–2 + 3C6–8 (from GANS 1953), and we visualize paralog as a DNA insertion in one of these sites (3B3) necessary for the global control of the region; this explains its interactions with loci on one side or the other and gives insight into the mechanisms underlying this type of regulation. In order to account for this multisite structure at the local level and the more global constructive interactions between these domains all over the genome, it is tempting for the nonbiochemist to involve somatic pairing of interspersed repeated elements—ectopic or paralogous pairing (KAUFMANN and IDDLES 1963)—that would lead to a generalized transvection phenomenon (LEWIS 1954).

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