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Genetic analysis of the mutation *Female-lethal* in *Drosophila melanogaster*

BY TERRI MARSHALL* AND J. R. S. WHITTLE
School of Biological Sciences, University of Sussex, Falmer, Brighton BN1 9QG, Sussex

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SUMMARY

A genetic analysis was made of the *Female-lethal* (*Fl*) locus of *Drosophila melanogaster*. This is an *X*-linked mutation which causes lethality only in females. Other alleles do not complement *Fl* and are either lethal or sterile when homozygous in females. Complementation studies on *Fl* alleles demonstrate that there is no simple ranking of these alleles in terms of severity of phenotypic effect. Dosage manipulation of *Fl* alleles indicates that the sex-specificity is not a consequence of gene dosage effects. Viability studies on males carrying *Fl* alleles show that *Fl* alleles have no effect on viability regardless of the presence or absence of a *Y* chromosome. The *Fl* locus is therefore sex-specific. The hypothesis that Fl^+ is involved in the establishment of imaginal phenotypic sex cannot be substantiated on the basis of experiments utilizing sex-change mutations.

1. INTRODUCTION

The *Fl* locus is situated at 19·1 cMs on the *X* chromosome. The allele *Fl* is a fully penetrant recessive lethal in females, which die during embryogenesis; no effect in hemizygous males has been observed. *Fl* can act as a dominant lethal in females, this expression being dependent upon the maternal genotype, and showing variable penetrance. A second allele, *Female-lethal-sterile* (Fl^s), differs from *Fl* in that homozygotes are female-sterile rather than lethal, although Fl/Fl^s is lethal (Muller & Zimmering, 1960; Zimmering & Muller, 1961).

We have examined the possibility that this locus may code for a sex-specific gene product required only in females, and the alternative possibility that *Fl* mutations may be without effect in males because of some protecting effect of the *Y* chromosome. The four alleles of *Fl* available have permitted an examination of the range of female-lethal and sterile phenotypes produced by mutation at this locus. Muller & Zimmering (1960) showed that the mutation *transformer* (*tra*), which causes *XX* individuals to develop as sterile pseudomales (Sturtevant, 1945), failed to alter the lethal action of *Fl* in *XX* zygotes and we have extended this investigation to the other mutations which affect adult morphological sex. The hypothesis

* Present address: Genetics Laboratory, Department of Biochemistry, University of Oxford, South Parks Road, Oxford.

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was investigated that the sex-limited effects of *Fl* mutations were due to gene dosage rather than a manifestation of sex difference.

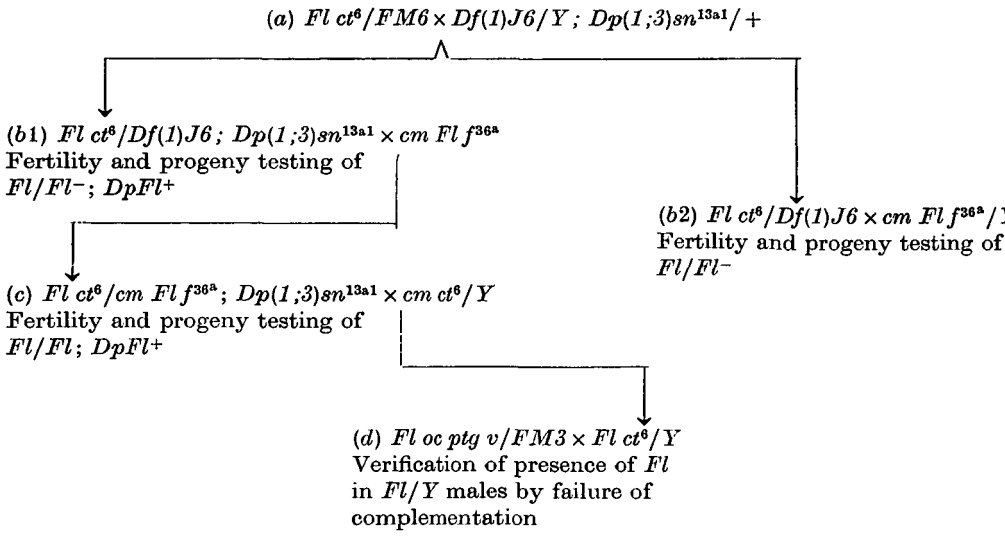
2. MATERIALS AND METHODS

Stocks

Fl alleles were maintained as balanced stocks. *X*-linked mutations (for description of mutations see Lindsley & Grell, 1968) were used to distinguish different *X* chromosome genotypes. For the male viability studies stocks with *Fl* alleles

Table 1. *Dosage manipulation of* Fl

(Mating scheme used to test the viability and fertility of females carrying a varying number of copies of *Fl* and *Fl*+.)



(*b*1) Single-pair testcross of females carrying a third chromosome duplication of *Fl*+ and an *X* chromosome deficient for *Fl*+. Phenotypically distinguishable as *Bar*+, *cut*+ females.

(*b*2) Single-pair testcross of females deficient for *Fl*+ but without third chromosome duplication. Phenotypically distinguishable as *Bar*+, *cut* females.

(*c*) Fertility and progeny testing of females homozygous for *Fl* but carrying third chromosome duplication for *Fl*+. Phenotypically *forked*+, *carmine*+.

(*d*) Complementation test to verify the presence of *Fl* in males, which are phenotypically *cut*.

were constructed from common original stocks to minimize other genotypic differences. The Fl^{2593} allele was kindly supplied by Dr E. Vyse of Montana State University, U.S.A. The translocation stock involving the *Fl* locus; $\widehat{XX}$, *y mf*/*Y* females and *Df*(*1*)*J6*/*Y*; *Dp*(*1*;*3*)sn^{13a1} males; which was used to manipulate the number of copies of *Fl* alleles was provided by Professor G. Lefevre of California State University, U.S.A. The *Df*(*1*)*J6* *X* chromosome consists of a short deficiency induced by irradiation in an *In*(*1*)*dl-49* chromosome marked with *forked* (Lefevre & Johnson, 1973). This chromosome is deficient for bands 6E1-7C1 including the

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carmine, *Fl* and *cut* loci and is mutant for *forked*. The third chromosome $Dp(1;3)sn^{13a1}$ has bands 6C12-7C9 inserted at band 79E of 3L. It is duplicated for the $carmine^+$, Fl^+ and cut^+ loci and is mutant for *singed* (Lindsley & Grell, 1968).

Crosses

Flies were raised at 25 °C on a standard yeast, maize, sugar medium supplemented by live yeast. The crosses used to investigate male viability were of the general form $\widehat{XX}$, yf/Y females $\times$ Fl^n/Y males or $\widehat{XX}$, $y\,w^a\,B$ females $\times$ Fl^n/Y males, where Fl^n represents the alleles *Fl*, Fl^s or Fl^+. In each experimental group, ten to fifteen females were placed in a 10 ml food vial with an equal number of males and were transferred every 2 or 3 days. The full progenies of five or six broods were scored. Similar conditions were used in the complementation studies.

Combinations of *Fl* and the sex-change mutations *transformer-dominant* (tra^D), *Masculinizer* (*Mas*), *doublesex* (*dsx*) and *intersex* (*ix*) were synthesized by balancer chromosome substitution, and linked markers were used to identify these genotypes. The mating scheme used to vary the dosage of the *Fl* allele is shown in Table 1. Similar schemes were used for the other alleles.

3. RESULTS

(i) *Complementation tests*

Table 2 shows that, although each mutant allele is either lethal or sterile when homozygous, the phenotypes produced by heterozygous combinations are more complex. The lethality observed in crosses two, three and four indicates that Fl^s, Fl^{s1} and Fl^{2593} are allelic to *Fl*. Homozygosity for Fl^{2593} also results in lethality (cross eight) in contrast to homozygous (crosses six and seven) and heterozygous (crosses nine and ten) combinations of Fl^s and Fl^{s1} which produce sterile females. The low viability of these Fl^s and Fl^{s1} combinations indicates a semi-lethal effect of these alleles. However, complementation does occur when Fl^{2593} is heterozygous with either Fl^s (cross eleven) or Fl^{s1} (cross twelve). The viability of these heterozygous females is high and they are fertile. Thus it appears that these alleles represent one complementation group but that intra-allelic complementation may occur.

The $Fl^s\,sn^3$ chromosome appears to be completely lethal when homozygous (cross five) although homozygous $y\,w^a\,Fl^s\,sn^3$ females may survive (cross six). Such a result was unexpected as the latter chromosome was synthesized from the $Fl^s\,sn^3$ stock. From these results there is no simple way to rank these alleles in order of severity of phenotypic effect.

(ii) *Viability effects of* Fl *alleles in males*

It was important to distinguish a sex-specific from a sex-differential action of *Fl* alleles. A sex-specific action of *Fl* implies that a normal Fl^+ gene product is required specifically in females and not in males. A sex-differential action of *Fl* would indicate that Fl^+ is required by both males and females, but that males either

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Table 2. *Complementation of* Fl *alleles. Frequencies of genotypes produced in combinations of various* Fl *alleles*

Maternal genotype	Paternal genotype	*Fl* combination	% Regular progeny*				Total progeny size
			Fl^1/Fl^2	Fl^2/Fl^+	Fl^1/Y	Fl^+/Y	
1. *Fl oc ptg v/FM6*	*Fl oc ptg v/Y*	*Fl/Fl*	0	37	38	25	368
2. *Fl oc ptg v/FM6*	$Fl^s\ sn^3/Y$	Fl/Fl^s	0	47	33	20	583
3. *Fl oc ptg v/FM6*	$Fl^{s1}\ ct^6/Y$	Fl/Fl^{s1}	0	48	35	16	382‡
4. *Fl oc ptg v/FM3*	$y\ Fl^{2593}/Y$	Fl/Fl^{2593}	0	48	52	0†	397
5. $Fl^s\ sn^3/y\ ClBv$	$Fl^s\ sn^3/Y$	Fl^s/Fl^s	0	56	44	0†	1015
6. $y\ w^a\ Fl^s\ sn^3/FM6$	$y\ w^a\ Fl^s\ sn^3/Y$	Fl^s/Fl^s	6	52	40	3	875
7. $Fl^{s1}\ ct^6/y\ ClBv$	$Fl^{s1}\ ct^6/Y$	Fl^{s1}/Fl^{s1}	0·4	52	47	0	1120
8. $y\ Fl^{2593}/M\text{-}5$	$y\ Fl^{2593}/Y$	Fl^{2593}/Fl^{2593}	0	37	42	20	339
9. $y\ w^a\ Fl^s\ sn^3/FM6$	$Fl^{s1}\ ct^6/Y$	Fl^s/Fl^{s1}	8	45	35	4	609‡
10. $Fl^{s1}\ ct^6/y\ ClBv$	$Fl^s\ sn^3/Y$	Fl^s/Fl^{s1}	1	48	51	0†	1218‡
11. $y\ w^a\ Fl^s\ sn^3/FM6$	$y\ Fl^{2593}/Y$	Fl^s/Fl^{2593}	39	35	19	6	421
12. $Fl^{s1}\ ct^6/y\ ClBv$	$y\ Fl^{2593}/Y$	Fl^{s1}/Fl^{2593}	26	34	40	0†	308

* Superscript 1 refers to the maternally inherited allele, superscript 2 to paternally inherited allele.

† Fl^+ chromosome carries a recessive lethal mutation.

‡ Exceptional progeny produced by these crosses. Produced because female parents carried a *Y* chromosome.

tolerate an imperfect gene product better than females or possess other mechanisms to achieve the same developmental goal. Table 3 records the results of experiments designed to test the viability of males carrying *Fl* alleles. The use of attached-*X* female parents ensured that the male progeny inherited the Fl^n chromosome from their father. A decrease in the survival of males carrying *Fl* and/or Fl^s can be detected by comparing the relative segregations of male and female progeny in the experimental groups to the Fl^+ control. χ^2 tests performed on the data in Table 3(*a*) showed no significant differences in Fl/Y or Fl^s/Y male viability compared to Fl^+/Y male viability.

Table 3. *Viability of* Fl *and* Fl^s *males*

(*a*) XY male viability

$\widehat{XX}$, $y\,f/Y \times Fl^n/Y$*

Genotype of progeny	Numbers of progeny produced		
	Fl^+ experiment	*Fl* experiment	Fl^s experiment
$\widehat{XX}/Y$ females	475	530	608
Fl^n/Y males	472	612	587

(*b*) *X/O* male viability

$\widehat{XX}$, $y\,w^a\,B/O \times Fl^n/Y$*

Genotype of progeny	Numbers of progeny produced		
	Fl^+ experiment	*Fl* experiment	Fl^s experiment
$\widehat{XX}/Y$ females	620	359	528
Fl^n/O males	725	473	583

* Fl^n represents the alleles Fl^+, *Fl* or Fl^s.

The possibility was also examined that males carrying *Fl* alleles survive because of the presence of the *Y* chromosome. Partial suppression of *X*-linked lethal mutations by the *Y* chromosome is one of many examples of position-effect variegation (Lindsley, Edington & Von Halle, 1960). On the basis of their interaction with heterochromatin the mutations *abnormal oocyte* (Sandler, 1970) and *daughterless* (Sandler, 1972) have been implicated in the regulation or synthesis of rDNA. Table 3(*b*) indicates that the removal of the *Y* chromosome does not affect the survival of males carrying *Fl* alleles. The attached-*X* females used were obtained from a stock of $\widehat{XX}$, $y^2\,w^a\,B$ females and $\widehat{XY}$, *v cv/O* males and possess no free *Y* chromosome. The *X/O* constitution of male progeny was verified by crossing 50 males from each experimental group *en masse* to approximately 100 virgin females. In no case were progenies produced by such crosses. Comparison of the relative segregations of *XO* males to their female sibs in each group by χ^2 tests in no case yielded a significant value. Therefore the presence of a *Y* chromosome has no effect on the survival of males carrying these *Fl* alleles.

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(iii) *Interactions between* Fl *alleles and sex-change mutations*

The normal function of the *Fl* locus may relate to the differentiation of female phenotypic sex. This hypothesis was investigated by altering the phenotypic sex in *Fl/Fl* females using various sex-transforming mutations and determining whether lethality was suppressed. The dominant mutations *transformer-dominant* (tra^D), *Masculinizer* (*Mas*) and the recessive mutation *intersex* (*ix*) exclusively affect chromosomal (*X/X*) females, causing them to develop as sterile intersexes. *Double-sex* (*dsx*) causes both genetic females and males to develop as intersexes. Analyses of large progenies in which *Fl* and these mutations were segregating are given in Table 4. In every cross transformed *Fl/Fl* individuals, should they be produced, would be easily distinguished by virtue of the *X*-linked markers present. The interaction of tra^D and Fl/Fl^s was also investigated as the lethal phase of Fl/Fl^s is later than *Fl/Fl* (Marshall, 1977 and in preparation), and might overlap a later period of activity of the sex-transforming mutations. None of these sex-transforming mutations suppressed the lethal phenotype of *Fl/Fl* or Fl/Fl^s, although in each cross other progeny classes showed the expected transformed phenotype. Large progenies were examined to detect any poorly viable classes.

The mutation *dsx* also transforms males to intersexes. Cross (*e*) indicates that transformed *Fl/Y* genotypes are viable. Comparison of the relative segregations of *Fl/Y; dsx/dsx*$^+$ and *Fl/Y; dsx/dsx* progeny to Fl^+/Y; *dsx/dsx*$^+$ and Fl^+/Y; *dsx/dsx* male progeny, or to the appropriate Fl/Fl^+ progeny, did not give significant χ^2 values. Therefore transformation of *Fl* males by *dsx* does not reduce their viability.

The presence of a free *Y* chromosome in the *FM6* maternal genome led to a high proportion of exceptional progeny in cross (*e*). Were they viable, *Fl/Fl/Y* genotypes would have been found in these crosses but such females were never observed, further indicating that the *Y* chromosome has no influence on the expression of *Fl*.

(iv) *Dosage manipulation of the* Fl *locus*

The resultant phenotype of a mutation will depend upon both the normal function of that gene and the type of mutation (Muller, 1932). The lethality and/or sterility of *Fl* alleles exclusively in homozygous females is possibly a consequence of gene dosage rather than physiological sex. One dose of *Fl* may be tolerated in *Fl/Y* individuals but two doses (assuming no dosage compensation at this locus) may result in an increased amount of an abnormal gene product with lethal consequences. *Fl* could even be a dose-dependent neomorph or a hypermorph. This was examined by dosage manipulation of *Fl* alleles. Should the phenotype of *Fl* be related to gene dose then *Fl/Fl* should have the same phenotype as *Fl/Fl; DpFl*$^+$ as lethality depends solely on the number of copies of *Fl*.

The translocation stock available, *ymf-* × *Df(1)J6/Y; Dp(1;3)sn*^{13a1}/+ (see Methods and Table 1), carries a deficiency for the Fl^+ locus in males, which can only survive if they also carry the duplication for this region of the *X* in their third chromosome. By crossing females heterozygous for an *Fl* allele to *Df(1)J6/Y;*

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Dp(1;3)sn^{13a1} males it is possible to construct females with heterozygous deficiencies (*Fl*$^{-}$) and/or an additional copy of *Fl*$^{+}$ (*DpFl*$^{+}$) in chromosome 3L. Table 1 shows the series of crosses used to investigate the viability and fertility of *Fl/Fl*$^{-}$, *Fl/Fl*$^{-}$; *DpFl*$^{+}$ and *Fl/Fl; DpFl*$^{+}$ female genotypes. A similar procedure was used

Table 4. *Frequencies of distinguishable genotypes in crosses combining* Fl *alleles with* tra^{D}, Mas, ix *and* dsx

(*a*) *Fl oc ptg v/FM3* × *Fl f*^{36a}*/Y; tra*^{D} *Sb e/TM3*

Genotypes	*Fl/Fl*; +/+	*Fl/Fl*; *tra*^{D}/+	*Fl/Fl*$^{+}$; +/+	*Fl/Fl*$^{+}$; *tra*^{D}/+	*Fl/Y*; +/+	*Fl/Y*;* *tra*^{D}/+
No. observed	0	0	244	211	176	222
%	0	0	29	25	21	26

* FM3 males are lethal.

(*b*) *y w*^{a} *Fl*^{s} *sn*^{3}*/FM6* × *Fl f*^{36a}*/Y; tra*^{D} *Sb e/TM3*

Genotypes	*Fl/Fl*^{s}; +/+	*Fl/Fl*^{s}; *tra*^{D}/+	*Fl/Fl*$^{+}$; +/+	*Fl/Fl*$^{+}$; *tra*^{D}/+	*Fl*^{s}*/Y*; +/+	*Fl*^{s}*/Y*; *tra*^{D}/+	*Fl*$^{+}$*/Y*; +/+	*Fl*$^{+}$*/Y*; *tra*^{D}/+
No. observed	0	0	113	151	112	128	51	78
%	0	0	18	24	18	20	8	12

(*c*) *Fl oc ptg v/FM3* × *Fl ct*^{6}*/Y; Mas/+*

Genotypes	*Fl/Fl*; +/+	*Fl/Fl*; *Mas*/+	*Fl/Fl*$^{+}$; +/+	*Fl/Fl*$^{+}$; *Mas*/+	*Fl/Y*
No. observed	0	0	241	227	413
%	0	0	27	26	46

(*d*) *Fl f*^{36a}*/FM3; ix pr cn/SM5* × *Fl oc ptg v/Y; ix pr cn/SM5**

Genotypes	*Fl/Fl*; *ix*/+	*Fl/Fl*; *ix/ix*	*Fl/Fl*$^{+}$; *ix*/+	*Fl/Fl*$^{+}$; *ix/ix*	*Fl/Y*; *ix*/+	*Fl/Y*; *ix/ix*
No. observed	0	0	584	137	659	230
%	0	0	36	8	41	14

* Eight exceptional progeny produced by this cross.

(*e*) *y w*^{a} *Fl sn*^{3} *f*^{36a}*/FM6; p*^{p} *dsx/TM6* × *Fl oc ptg v/Y; p*^{p} *dsx/TM6**

Genotypes	*Fl/Fl*; *dsx*/+	*Fl/Fl*; *dsx/dsx*	*Fl/Fl*$^{+}$; *dsx*/+	*Fl/Fl*$^{+}$; *dsx/dsx*	*Fl/Y*; *dsx*/+	*Fl/Y*; *dsx/dsx*	*Fl*$^{+}$*/Y*; *dsx*/+	*Fl*$^{+}$*/Y*; *dsx/dsx*
No. observed	0	0	398	193	334	154	180	79
%	0	0	25	12	21	10	11	5

* 15 % exceptional progeny genotypes produced by this cross.

to investigate the dosage of *Fl*$^{+}$, *Fl*^{s} and *Fl*^{s1}; in these cases *cm ct*^{6}*/cm ct*^{6}, *Fl*^{s} *sn*^{3}*/FM6* or *Fl*^{s1} *ct*^{6}*/y ClB v* females were initially crossed to *Df(1)J6/Y; Dp(1;3)sn*^{13a1} males. In each programme, several of the genotypes could only be identified by progeny tests for recessive linked markers on the *X* chromosome. At least 31 females of each necessary genotype were progeny tested. The results

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showed that the genotypes Fl^+/Fl^- and Fl^+/Fl^-; $DpFl^+$ were viable and fully fertile in contrast to Fl/Fl^- and Fl^{s1}/Fl^- which were completely lethal. Female genotypes Fl/Fl^-; $DpFl^+$, Fl/Fl; $DpFl^+$, Fl^{s1}/Fl^-; $DpFl^+$, Fl^{s1}/Fl; $DpFl^+$ and Fl^{s1}/Fl^{s1}; $DpFl^+$ were all viable and fertile. As the duplication of Fl^+ ($Dp(1;3)sn^{13a1}$) was mutant for *singed*, problems arose in identifying Fl^s females. *Singed* females which could only have been Fl^s/Fl^s; $DpFl^+$ or Fl^s/Fl^s were fertile. It was concluded that the fertility was due to the presence of Fl^+.

These results show that females homozygous for Fl are lethal, but even two copies of Fl produce neither lethality nor sterility when Fl^+ is also present. Thus these alleles are unlikely to be dose-dependent neomorphs or hypermorphs.

4. DISCUSSION

The range of phenotypes shown by the various Fl alleles confirms that this gene has an essential role in females. The most extreme allele in this series is Fl but the other alleles do not form a clear linear series in the extent and severity of their effects. The later lethal phase of Fl/Fl^{2593} and Fl/Fl^s compared to Fl/Fl zygotes also indicates that Fl is more severe in its effects than the other alleles (Marshall, 1977 and in preparation). No confirming evidence exists to suggest that Fl is neomorphic so Fl could be either an amorph or a hypomorph whilst the other less severe alleles may be hypomorphs.

The evidence from the viability studies shows that no effect of Fl alleles can be detected in males. This conclusion is reinforced by experiments to determine the effective lethal phase of Fl (Marshall, in preparation). Only 25% of zygotes, accounting only for homozygous Fl embryos, die when $Flf^{36^a}/++$ females are crossed to Fl males, when compared to control series. Thus Fl is the second example of a sex-specific mutation affecting only one sex, the other being *maleless* (Fukunaga, Tanaka & Oishi, 1975). All other sex-limited lethal mutations are sex-differential in action. The viability studies on X/O males, reinforced by the failure to recover viable $Fl/Fl/Y$ genotypes in the sex-change experiments, indicate that male survival is not influenced by the presence of a Y chromosome.

Alteration of imaginal phenotypic sex by the action of sex-transforming mutations neither suppresses the lethality of Fl/Fl and Fl/Fl^s in females nor induces lethality in Fl males, indicating that Fl^+ is not involved in the establishment of the adult sexual phenotype. In this respect Fl behaves similarly to *daughterless* (Colainne & Bell, 1968), *maleless* (Fukunga *et al.* 1975) and the maternal sex-ratio condition (Sakaguchi & Poulson, 1963; Miyamoto & Oishi, 1975). The only sex-limited lethal known to respond to the action of sex-change mutations is *sonless* (Colainne & Bell, 1972) which has a lethal phase extending to 48 h after hatching (Colainne & Bell, 1970). The lethal phase of Fl occurs during embryogenesis and may precede the action of the sex-transforming mutations. The mutation *transformer* is the most extreme of the sex-change mutations, XX; *tra/tra* individuals being almost indistinguishable from normal males, yet these pseudomales still possess some female characteristics (Brown & King, 1961); Fl^+

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may function in some female-specific process which persists in these intersexes. The expression of sex-transforming mutations involves imaginal disk derivatives but the embryonic lethality of *Fl* may reflect a quite separate developmental response to chromosomal sex from the differentiation of adult morphological sex. Alternatively the selective action of *Fl* might reflect differences between the *XX* and *XY* chromosomal constitution in terms of the amount or type of chromatin and associated proteins. Survival of homozygous *Fl* clones induced by mitotic recombination (Marshall, 1977 and in preparation) makes it unlikely that Fl^+ is involved in any cell-autonomous function.

It is concluded that Fl^+ codes for a product required specifically in *X/X* females. The evidence is consistent with *Fl* being an amorph or hypomorph, other alleles being hypomorphs. A role for Fl^+ in the establishment of female phenotypic sex has not been substantiated. Fl^+ may be required for a female specific process not directly related to the external sexual dimorphism of the adult.

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