EUR 701.e
REPRINT

EUROPEAN ATOMIC ENERGY COMMUNITY - EURATOM

A PROCEDURE FOR ANALYZING THREE-POINT TEST DATA WHEN ONE GENE SHOWS LOW PENETRANCE

by

K. KOJIMA
(Department of Genetics, North Carolina University)
and
M. DALEBROUX
(Euratom) (*)

1965

(*) **Directorate-General for Research and Training**
Biology Department

Reprinted from
DROSOPHILA INFORMATION SERVICE
January 1965

EUR 701.e

REPRINT

A PROCEDURE FOR ANALYZING THREE-POINT TEST DATA WHEN ONE GENE SHOWS LOW PENETRANCE by K. KOJIMA (Department of Genetics, North Carolina University) and M. DALEBROUX (Euratom) (*)

European Atomic Energy Community - EURATOM.
(*) Directorate-General for Research and Training.
Biology Department.
Reprinted from "Drosophila Information Service"
January 1965, pp. 49-52

Summary not available.

EUR 701.e

REPRINT

A PROCEDURE FOR ANALYZING THREE-POINT TEST DATA WHEN ONE GENE SHOWS LOW PENETRANCE by K. KOJIMA (Department of Genetics, North Carolina University) and M. DALEBROUX (Euratom) (*)

European Atomic Energy Community - EURATOM.
(*) Directorate-General for Research and Training.
Biology Department.
Reprinted from "Drosophila Information Service"
January 1965, pp. 49-52

Summary not available.

Kojima, K. and M. Dalebroux. North Carolina State. A procedure for analyzing three-point test data when one gene shows low penetrance.

During the Drosophila Research Conference at Madison, Wisconsin (1964), Dr. R. Hillman of Temple University called Kojima's attention to an article in DIS (Tsukamoto; DIS No. 38:91-93). The article deals with an estimation procedure of recombination fractions in three-point test with a low penetrance gene. Dr. R. Hillman applied Tsukamoto's method to his data, and obtained an uninterpretable result.

An algebraic examination starting from the tables in Tsukamoto's article leads his four formulae to the following results:

$$\text{Formula (1)} = \frac{100}{1 + \sqrt{\frac{R_1}{100-R_1}}}, \text{ instead of } R_1,$$

$$\text{Formula (2)} = \frac{100}{1 + \sqrt{\frac{R_2}{100-R_2}}}, \text{ instead of } R_2,$$

$$\text{Formula (3)} = 50\%, \text{ instead of } R_1,$$

and

$$\text{Formula (4)} = \frac{100}{1 + \sqrt{\frac{(100-R_1)\ (100-R_1 + yR_1)}{R_1\ (100y + R_1 - yR_1)}}}, \text{ instead of } R_2.$$

Thus, it seems that the four formulae by Tsukamoto do not give the estimates of recombination fractions as intended. The rest of this note will deal with a correct procedure for estimating two recombination fractions and one penetrance value in three-point test. The formulae for approximate sampling variances of the estimates will be given.

Consider a stock with mutants a, b, and x at three loci. The x is assumed to have a low penetrance. Denoting their wild-type alleles by +'s, an F_1 hybrid of this stock with a wild stock is a/+, b/+ and x/+, and its phenotype is of wild type. When the F_1 (the sex of this individual must be female in the case of Drosophila) is backcrossed to the triple mutant stock, segregation occurs at the three loci. There are eight phenotypic classes. The first problem is to determine whether locus x is located between the a and b loci or at the outside of the a-b segment. A test for this distinction can be performed by the following procedure.

As in Table 1, pool the observed numbers of animals according to four paired phenotypic classes. The difference, YU-ZX, is expected to be zero when the order of the loci is x-a-b and a positive value when the order is a-x-b. The magnitude of the latter value is given at the bottom of Table 1, and the symbols used will be defined later. The departure of YU-ZX may be tested by the following X^2 statistic with one degree of freedom:

$$X_1^2 = 4(YU - 1/2\ M)^2/M$$

where M = YU + ZX.

After the order of the three loci is determined, one can proceed to estimate the values of recombination fractions and penetrance. Symbols to be used are as follows:

p : the recombination fraction between the left-most and center loci.
q : the recombination fraction between the center and right-most loci.
y : the fraction of x/x individuals which appear as wild type (penetrance index).

x-a-b arrangement:

All phenotypic classes, their expected and observed numbers are given in Table 2. Compute the following;

$$A = \frac{n_1 + n_2 + n_3 + n_4}{N}, \quad B = \frac{n_1 + n_2 + n_5 + n_6}{N}, \quad Q = \frac{n_2 + n_4 + n_6 + n_8}{N}$$

The expected values of these quantities are

$$E(A) = p\,(1-y) + 1/2\ y$$

$$E(B) = q$$

$$E(Q) = 1/2\ (1 + y)$$

Thus, the estimates are given by

$$\hat{y} = 2Q - 1$$

$$\hat{p} = (2A-\hat{y})/2(1-\hat{y}) \text{ for the x-a segment}$$

$$\hat{q} = B \text{ for the a-b segment}$$

In other words, y and q can be estimated directly, and the estimate of p is compounded with the estimate of y. The sampling variances for the $\hat{q}$ and $\hat{y}$ are computed by

$$B(1-B)/N \quad \text{for } \hat{q}$$

$$4Q(1-Q)/N \quad \text{for } \hat{y}$$

The sampling variance for the p is more complicated, but approximately given by

$$\frac{1}{N(1-\hat{y})^2}\left[A(1-A) + \frac{(1-2A)^2}{(1-\hat{y})^2} \cdot Q(1-Q) - \frac{2(1-2A)}{(1-\hat{y})}\left\{\frac{(n_5+n_7)(n_2+n_4)}{N^2} - \frac{(n_6+n_8)(n_1+n_3)}{N^2}\right\}\right]$$

a-x-b arrangement:

As in the case of x-a-b, the phenotypic classes, their expected and observed numbers are given in Table 3 for this case. Compute the following;

$$A = \frac{n_1 + n_2 + n_3 + n_4}{N}, \quad B = \frac{n_1 + n_2 + n_5 + n_6}{N}, \quad Q = \frac{n_2 + n_4 + n_6 + n_8}{N}$$

Their expected values are

$$E(A) = p(1-y) + 1/2\ y$$

$$E(B) = q(1-y) + 1/2\ y$$

$$E(Q) = 1/2(1 + y)$$

In this case, the estimates of both p and q are compounded with the estimate of y, and they are

$$\hat{y} = 2Q-1$$

$$\hat{p} = (2A-\hat{y})/2(1-\hat{y}) \quad \text{for the a-x segment}$$

$$\hat{q} = (2B-\hat{y})/2(1-\hat{y}) \quad \text{for the x-b segment}$$

The sampling variance of $\hat{y}$ is given by 4Q(1-Q)/N, and the approximate sampling variances of $\hat{p}$ and $\hat{q}$ are

$$\frac{1}{N(1-\hat{y})^2}\left[A(1-A)+\frac{(1-2A)^2}{(1-\hat{y})^2}\cdot Q(1-Q)-\frac{2(1-2A)}{(1-\hat{y})}\left\{\frac{(n_5+n_7)(n_2+n_4)}{N^2}-\frac{(n_6+n_8)(n_1+n_3)}{N^2}\right\}\right]$$

and

$$\frac{1}{N(1-\hat{y})^2}\left[B(1-B)+\frac{(1-2B)^2}{(1-\hat{y})^2}\cdot Q(1-Q)-\frac{2(1-2B)}{(1-\hat{y})}\left\{\frac{(n_3+n_7)(n_2+n_6)}{N^2}-\frac{(n_4+n_8)(n_1+n_5)}{N^2}\right\}\right],$$

respectively.

(This work was partly supported by Public Health Research Grant GM 11546 from the Division of General Medical Sciences. The junior author is a member of the European Atomic Energy Community).

Table 1. x-a-b or a-x-b

Paired Phenotypes	x++ and +ab	x+b and +a+	xa+ and ++b	xab and +++	Total
observed numbers	X	Y	Z	U	N

$E(YU-ZX)=0$ for x-a-b

$E(YU-ZX)=p(1-p)(1-2q)(1-y)N^2$ for a-x-b

Table 2. x-a-b arrangement

Phenotypes	Expected Numbers	Observed Numbers
x + b	1/2 pq(1-y)N	n_1
+ a +	1/2 pq N + 1/2q(1-p)yN	n_2
x + +	1/2 p(1-q)(1-y)N	n_3
+ a b	1/2 p(1-q)N+1/2 (1-p)(1-q)yN	n_4
x a +	1/2 q(1-p)(1-y)N	n_5
+ + b	1/2 q(1-p)N+ 1/2pq yN	n_6
x a b	1/2(1-p)(1-q)(1-y)N	n_7
+ + +	1/2(1-p)(1-q)N+ 1/2 p(1-q)yN	n_8
Total	N	N

Table 3. a-x-b arrangement

Phenotypes	Expected Numbers	Observed Numbers
+ x +	1/2 pq(1-y)N	n_1
a + b	1/2 pq N + 1/2(1-p)(1-q)yN	n_2
+ x b	1/2 p(1-q)(1-y)N	n_3
a + +	1/2 p(1-q)N + 1/2 q(1-p)yN	n_4
a x +	1/2 q(1-p)(1-y)N	n_5
+ + b	1/2 q(1-p)N + 1/2 p(1-q)yN	n_6
a x b	1/2 (1-p)(1-q)(1-y)N	n_7
+ + +	1/2 (1-p)(1-q)N + 1/2 pq yN	n_8
Total	N	N

Spiess, E. B. University of Pittsburgh. D. persimilis from Humboldt County, Calif.

During July, 1964, persimilis was collected from the Redwoods Forest of Humboldt County, California (town of Weott). With 188 chromosomes identified the frequencies of arrangements from chromosome III are as follows: Klamath 78.2%, Mendocino 13.8%, Humboldt* 3.8%, Standard 1.1%, Cowichan 1.5%, Whitney 1.1%, and Unknown* 0.5%. We are tentatively designating the more common arrangement of two heretofore rare or unknown arrangements as "Humboldt" since we discovered it first in our cultures, took photographs with its heterozygote KL/HU*, and corresponded with Professor Dobzhansky (Rockefeller Institute) as to the arrangement's identity with that described by him (with C. Epling, 1944, Carnegie Institute Washington Publ. #554). Professor Dobzhansky agreed that this arrangement was likely to be his Humboldt arrangement. The exact banding pattern will be reported soon, but briefly it is an independent inversion of the Standard sequence of approximately the same length as the well known KL but displaced more proximally by about 15 bands than KL. The "Unknown*" arrangement however is a single step inversion from KL (overlapping) and had not been observed at the time of our correspondence with Dobzhansky, so that the correct naming may be decided later. In fact this latter "Unknown" may well be identical with Dobzhansky's Humboldt and the arrangement we designated above as "Humboldt*" may be a new arrangement. In either case, the frequency of the latter is much higher than observed before (3.8%); if it is truly a newly formed arrangement, it can hardly be ephemeral to the population.

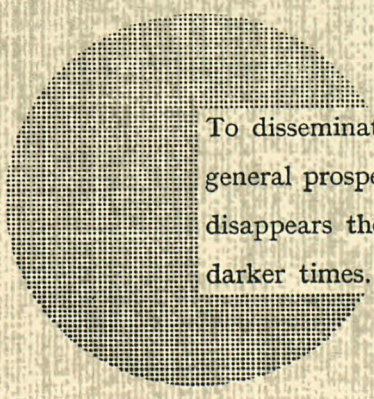
Whitten, M. J. University of Tasmania. Factors affecting penetrance of an eye mutant in D. melanogaster.

Penetrance of witty (DIS 38:31) in the homozygous state depends both on background modifiers and the environment. A novel method, involving the truncated normal distribution, and utilizing the fact that asymmetric flies are produced, has been applied to measure the genetic and environmental contributions to penetrance.

Initially it was thought that wi arose spontaneously in a Cy j stock. However the evidence suggests that all individuals in the stock were homozygous for wi and that penetrance was reduced to near zero by the large complement of modifiers reducing the activity of wi.

Removal of certain modifiers on the same linkage group as wi results in the dominant form. Penetrance of this form is then dependent on modifiers on Chromosome 3 and 1 and (or) 4.

It is believed that wi first occurred as a dominant in a natural population and a system of modifiers (dominance modifiers) was selected to reduce it to recessivity. Subsequently the penetrance of wi was reduced to near zero by the accumulation of further modifiers (penetrance modifiers). It has not yet been determined whether the two classes of modifiers are mutally exclusive.



To disseminate knowledge is to disseminate prosperity — I mean general prosperity and not individual riches — and with prosperity disappears the greater part of the evil which is our heritage from darker times.

Alfred Nobel