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Isoenzyme Frequencies in Long-Term Selection Lines of *Drosophila melanogaster*: IV. Isoenzyme Frequencies of the Leucine Aminopeptidases (LAP) in Lines Selected for Short and Long Developmental Rate*

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Summary. 1) Selection lines derived from a reference line, the continuation of an initial population which were founded by a double cross of four laboratory stocks, were selected for short (line KS and K) and long (line LS and L) developmental rate for up to 183 generations.

2) Frequencies of the linkage groups, $A^{O}D^{F}$, $A^{F}D^{F}$ and $A^{S}D^{S}$, of two closely linked loci, LAP-A and LAP-D, were estimated by frequencies of the isoenzymes controlled by them.

3) The reference line RE had maintained a balanced allele polymorphism for all three linkage groups with the frequencies $f(A^{O}D^{F}) = 0,145$; $f(A^{F}D^{F}) = 0,605$; and $f(A^{S}D^{S}) = 0,250$. The reference line differs from the four laboratory stocks in which two further linkage groups ($A^{O}D^{S}$ and $A^{S}D^{F}$) occur.

4) Both lines selected for short developmental rate are different from each other and from the reference line. While in line K the linkage group $A^{O}D^{F}$ was fixed, in line KS the linkage groups $A^{F}D^{F}$ and $A^{S}D^{S}$ maintained a balanced polymorphism.

5) The lines selected for long developmental rate LS and L are distinct from the reference line, too. In both lines the linkage groups $A^{O}D^{F}$ and $A^{F}D^{F}$ are present. They differ from each other by a higher frequency of linkage group $A^{O}D^{F}$ and a smaller one of linkage group $A^{F}D^{F}$ in line LS.

6) The discussion mainly deals with the influence of the three following aspects: the response of the selection lines to selection; the mechanisms maintaining allele polymorphism; and the genetic drift.

Introduction

Selection lines were derived from an initial population which had been established by a double cross of four laboratory stocks. Two lines were selected for long and short developmental rate, respectively, for about 88 to 183 generations. Previous papers dealt with the same selection lines but with the isoenzymes controlled by the Est-6-locus and Aph-D-locus (Muhs, 1975c) or with lines selected under different temperature conditions which had been derived from the same initial population and were analysed for the isoenzymes controlled by the Est-6-locus, Aph-D-locus, LAP-A-locus and the LAP-D-locus (Muhs, 1975 a,b). In this paper the frequencies of different alleles of the LAP-A- and LAP-D-locus are described.

Materials and Methods

The general experimental technique, the *Drosophila* stocks and the foundation of the initial population (Muhs, 1975 a), selection lines and sampling (Muhs, 1975 c) and the isoenzymes (Muhs 1975 b) have been described elsewhere. Homogenizing and electrophoresis methods will be given in more detail in a further paper (Muhs, 1975 d).

In this study two lines had been selected for short developmental rate (lines KS and K) and two for long developmental rate (lines LS and L). The lines KS and LS had been established about 3 generations after founding the initial population, lines K and L about 13 to 15 generations after.

Results

The isoenzyme technique allowed investigation of the isoenzymes controlled by the closely linked LAP-A-locus and LAP-D-locus in the same zymogram. Thus it was possible to identify each linkage group. The linkage groups $A^{O}D^{F}$, $A^{F}D^{F}$, and $A^{S}D^{S}$ were found in the selection lines. Only in the reference line RE were two heterozygotes ($D^{F}D^{X}$) observed containing the allele D^{X}. This allele will not be considered here.

The three linkage groups can form six genotypes. Their corresponding phenotypes can be arranged in four groups:

I : AOAO/DFDF

II : AFAF/DFDF and AOAF/DFDF

III : ASAS/DSDS

IV : AOAS/DFDS and AFAS/DFDS

In the phenotype groups II and IV two phenotypes each are listed which can not be distinguished safely by the isoenzyme technique used here (Muhs, 1975b).

In the four laboratory stocks used for foundation of the selection lines all three linkage groups are present, $A^{O}D^{F}$

* This study is a part of a thesis (Faculty of Forestry, University Freiburg).

Table 1. Observed and Expected Numbers of Phenotypes

Mode of Selection	Selection Line	Observed Numbers in Phenotype Group I	II	III	IV	Expected Numbers in Phenotype Group I	II	III	IV	χ_1^2	df	χ_2^2	df
25° C	RE	5	132	14	103	5,33	137,54	15,88	95,25	1,097	1	-	
short	KS	-	182	2	72	-	185,83	5,61	64,56	2,259	1	-	
short	KS rep.	-	177	4	42	-	175,84	2,81	44,35	0,647	1	6,388*	2
short	K	256	-	-	-	-	-	-	-	-		-	
short	K rep.	256	-	-	-	-	-	-	-	-		-	
long	LS	29	226	-	-	28,97	226,03	-	-	-		-	
long	L	5	251	-	-	5,02	250,98	-	-	-		-	

The χ_1^2-test is a goodness of fit test, table value is 3,84 for one degree of freedom (df) and 95% probability. The χ_2^2-test is a heterogeneity test KS versus KS rep. (replication of KS), the table value is 5,99 for 2 df and 95% probability

Table 2. Estimates of the Frequencies of Linkage Groups and the Variances

Mode of Selection	Selection Line	Frequencies of Linkage Group $A^O D^F$	$A^F D^F$	$A^S D^S$	Variances $A^O D^F$	$A^F D^F$	$A^S D^S$
25° C	RE	0,145	0,605	0,250	0,00056	0,00171	0,00097
short	KS	-	0,852	0,148	-	0,00025	-
short	KS rep.	-	0,888	0,112	-	0,00022	-
short	K	1,000	-	-	-	-	-
short	K rep.	1,000	-	-	-	-	-
long	LS	0,337	0,663	-	0,00044	-	-
long	L	0,140	0,860	-	0,00024	-	-

The variances of the estimates of the linkage group $A^F D^F$ and $A^S D^S$ are identical in selection line KS and those of $A^O D^F$ and $A^F D^F$ are identical in selection lines LS and L. They are listed once.

being the most frequent. In addition, two linkage groups, $A^O D^S$ and $A^S D^F$, occurred which had never been observed in the selection lines (Muhs, 1975b).

The reference line RE is the continuation of the initial population which had been founded by a double cross of the four laboratory stocks. All three linkage groups are present in the reference line with the following frequencies $f(A^O D^F) = 0,145$; $f(A^F D^F) = 0,605$; and $f(A^S D^S) = 0,250$. We can assume that the frequencies of these linkage groups are maintained by a balanced allele polymorphism (Muhs, 1975b).

Distribution of Phenotypes and Linkage Groups in the Selection Lines

In Table 1 the observed and expected frequencies are given, together with the goodness of fit tests as far as they can be applied. The lines KS and K had been analysed twice. The replications of the examinations are designated by KS rep. or K rep. and had been done in the following generation.

The selection lines show clear cut differences. In line KS phenotype I was missing, but phenotype group II occurred most frequently. Phenotype III was observed only at a very low frequency and phenotype group IV at a frequency of about 0,25. In the replication (KS rep.) the frequencies were different from those of KS. In particular, the number in phenotype group IV decreased from 72 in line KS to 42 for the replication KS rep. This difference can be attributed at least partially to the smaller number of observations in KS rep. (224 instead of 256) but this difference is significant at the 5% level (see Table 1). Thus both estimates of the frequencies of KS and KS rep. are not homogeneous. This fact can only be explained by strong shifting of the allele frequencies from generation to generation. The goodness of fit tests show no significant differences, so we can assume that sampling had been done without bias and that random mating had occurred in the tested lines. The frequencies of the linkage groups and the variance are given in Table 2. Here, in KS rep., the frequency of the most frequent linkage group $A^F D^F$ is 0,888, about 0,036 higher than in KS. The corresponding frequencies of the linkage group $A^S D^S$ are 0,148 in KS and 0,112 in KS rep.

Only individuals of the phenotype I have been observed in line K as well as in the replication of line K (K rep.). This line is the only monomorphic line concern-

ing both LAP-A- and LAP-D-loci. The linkage group $A^{O}D^{F}$ had been fixed.

The lines LS and L contained only individuals of the phenotype groups I and II, so differ from KS as well as from K. Compared with line L the line LS showed more individuals of phenotype I, namely 29 of the total of 256 pupae analysed. This is also shown by the frequencies of the linkage groups (see Table 2). The frequency of the linkage group $A^{O}D^{F}$ in line LS reached 0,337, that of line L only 0,140. For the linkage group $A^{F}D^{F}$ the frequencies were reversed: here line L showed the higher frequency with 0,860 and line LS the lower one with 0,663.

Differences in Variability between Different Steps and Modes of Selection

As reported in the previous paper (Muhs, 1975 b) the four laboratory stocks still have two more linkage groups which do not occur in the reference line RE. This means that variability of the reference line is restricted compared with the variability of the initial population, which was founded by a double cross of the four laboratory stocks.

Selection for short or long developmental rate caused a further reduction of variability. In none of the selection lines did all three linkage groups occur together which were maintained by the reference line. Line KS lacked the linkage group $A^{O}D^{F}$, line K the linkage groups $A^{F}D^{F}$ and $A^{S}D^{S}$, and both lines LS and L lacked the linkage group $A^{S}D^{S}$. Generally it can be assumed that elimination of linkage groups and a reduction in the degree of heterozygosity had occurred in the first step of selection at the foundation of the initial population.

The second step of selection started with the establishment of the selection lines derived from the reference line and lasted during the whole time of artificial selection. The effect of selection consisted of a further elimination of linkage groups and a further reduction of the degree of heterozygosity in some cases.

The lines selected for short developmental rate had different linkage groups. While in line KS the linkage groups $A^{F}D^{F}$ and $A^{S}D^{S}$ were maintained, in line K the linkage group $A^{O}D^{F}$ was fixed. Thus the same mode of selection did not show the same results in this case. By selection for long developmental rate, both lines LS and L maintained the linkage groups $A^{O}D^{F}$ and $A^{F}D^{F}$, but at differing frequencies. In this case the same mode of selection resulted in a significant difference in allele frequencies.

Discussion

In previous papers the mode of selection (Muhs, 1975 c) and the physiological importance of the leucine aminopeptidases (Muhs, 1975 b) were discussed. In this study very different responses to selection were observed, so that an intensive discussion of these responses would seem to be necessary.

The Reaction upon Selection

The initial population arose from a double cross of four laboratory stocks which had been held under constant environmental conditions in the laboratory before the initial population was founded. We may take it for granted that during that time the laboratory stocks had adapted to the laboratory environment. Obviously each population had reached an equilibrium as it was not influenced by any pressure of selection caused by environmental changes. The double cross brought four gene pools together. Thus a high heterogeneity was reached and the population showed heterosis effects alternating with partial breakdowns. The fluctuations in the population size of the initial population, which disappeared after some 10 generations, can be regarded as the consequence of these effects. Increased competitive ability of a generation caused an extremely high density of the population which may have influenced the mating behaviour. Thus in the following generations many far fewer descendents were produced. We can conclude that the gene pools of the four laboratory stocks were different and had to integrate during a process lasting several generations.

The lines KS and LS were derived before this process of integration had been completed, so that these lines stem from an extremely fluctuating, unbalanced population. In contrast to this, all the other lines were derived from the line RE at the time when this line had found its equilibrium. As a matter of fact the lines KS and LS showed other reactions than the lines K and L which were selected according to the same mode. As far as both investigated loci (LAP-A- and LAP-D) are concerned, the line KS had maintained a certain heterogeneity, while in line K this was not the case because of the fixation of a linkage group. Since the line RE had also maintained heterogeneity, here an effect of selection must be present.

The initial population, called reference line RE in later generations, could not be founded under natural conditions. This very heterogeneous "hybrid population", however, will probably show a higher proportion of additive

genetic variance by distintegration of the coadapted chromosomes and gene complexes (Band, 1964; Spiess and Spiess, 1964, 1966). This variance can be used during mass selection (Kojima and Kelleher, 1963). Thus the initial population should react intensively and quickly upon selection (Tigerstedt, 1969). In the end the disintegration and change of the gene complexes would probably have a devastating effect on the population. Usually at first a decrease of fitness is connected with disintegration (Wallace and Vetukhiv, 1955). If during this time the pressure of selection is high and the population can not reproduce new adaptive gene complexes by recombination, fitness may decrease still further until the population dies out. In order to prevent this in the lines selected for developmental rate, 480 flies of each generation were used to found the next generation. By this method the populations had a chance to organize new coadapted gene pools.

After 45 generations (for line L), 55 generations (for line LS), 85 generations (for line K), and 105 generations (for line KS), Tigerstedt (1969) demonstrated that the reactions had been partly different even in lines selected for the same mode: "In the lines KS and K the developmental rate shortened from an average 13 to 11,3 days, the fitness increased continuously and the genetic variance was mostly additive. The lines LS and L reacted differently. In the line LS the average developmental rate increased from 13 to 13,5 days. Fitness increased slightly but most of the genetic variance had not been additive. In line L the average developmental rate increased from 13 to 15,5 days. This happened discontinuously after the 30 th generation. Fitness decreased continuously, the phenotypical variance was high and the additive genetic variance extremely small". From these results obtained by Tigerstedt (1969) we can conclude that the lines KS, K, LS and L had changed their gene pools fundamentally. The lines KS and K are obviously better adapted than the lines LS and L. The line L seems even to show a disintegration and a reduction of the genetic variability.

These findings of Tigerstedt (1969) do not agree with the results obtained here in every detail: there exists a very great difference between the lines KS and K. While the line KS has maintained a balanced polymorphism of the two linkage groups A^FD^F and A^SD^S, these linkage groups have been eliminated in the line K. Both lines differ from the reference line which could maintain polymorphism with all three linkage groups A^OD^F, A^FD^F and A^SD^S. The lines LS and L show the same linkage groups A^OD^F and A^FD^F, differing only in frequency. From this we can not conclude that in line L the gene pool is disintegrated. Both lines are different from the lines KS and K and from the reference line.

The differences between the lines selected for short or long developmental rate can be caused by selection up to a certain degree. This may not be the only explanation, since the same selection modes favoured the linkage group A^OD^F in the line K but the linkage groups A^FD^F and A^SD^S in the line KS. Two different modes of selection, however, enriched the same linkage group, A^FD^F, in the lines KS, LS and L. So far the responses to selection can not be shown by allele frequencies of the LAP-loci as marker genes.

These results demonstrate that in the case of the LAP-loci the alleles are not directly influenced by the modes of selection used here. On the other hand this is an advantage which allows observation of changes in the gene pool which are caused by reaction of the population to selection rather than by selection itself. Since isoenzymes are controlled by genes, changes in the gene pool can be observed. In particular, those mechanisms become obvious which play an important role in the distribution of the alleles and maintenance of allele polymorphism. From the extensive changes in the allele frequencies of the LAP-loci we may assume that similar shifts had occurred at other polymorphic loci, too, which were not directly exposed to selection.

To sum up, we conclude that alleles of which the distribution is determined directly by selection are obviously not appropriate for demonstrating a shift in the gene pool, since the response to selection covered, for example, the mechanisms maintaining allele polymorphism. The alleles examined here are more suitable for showing changes in the gene pool by shifting of the allele frequencies. They are influenced by selection as well as by mechanisms maintaining allele polymorphism.

Mechanisms maintaining Allele Polymorphism

In some selection lines allele polymorphism has been found. Despite intensive and lengthy selection, this polymorphism could be maintained nearly unchanged, e.g. in the temperature selected lines (Muhs, 1975b). The mechanisms responsible for this polymorphism are not known. There are, however, some explanations which may be considered.

On principle the allele polymorphism observed here can be explained by overdominance. Fitness values of the six genotypes which can be formed by the three linkage

groups have not been calculated, but investigations are in progress with the alleles D^F and D^S of the LAP-D-locus which allow the estimation of fitness at different frequencies of the alleles. First results show no overdominance of the herozygotes D^FD^S for normal crowding conditions and for egg-to-adult period.

At the frequency of 0.5, slight dominance was shown by the homozygotes D^FD^F, but this was not the case in all experiments. We conclude that overdominance does not exist or is of secondary importance, if at other frequencies any overdominance should be present.

During the first 20 to 30 generations the reaction of the selection lines on selection was weak (Tigerstedt, 1969). This may point to high interactions of the genes which led to an unbalance of the gene pool, if selection occurred. These interactions can maintain existing polymorphism (Mather and Harrison, 1949). In the selection lines these interactions play an important role which can be demonstrated by the lines selected for long developmental rate LS and L. While line L showed disintegration and a high response to selection, line LS had maintained fitness and responses to selection were weak. Here the interactions had stabilized the gene pool in line LS.

Taking the selection lines for different temperature conditions (Muhs, 1975 b) into consideration, this effect of high gene interactions can be shown more clearly. All lines had maintained the same allele polymorphism for the LAP-A- and LAP-D-locus in nearly equal frequencies. Selection had only small effects in this case. This shows that epistasis stabilized the existing integrated gene pool (Levins, 1965; Franklin and Lewontin, 1970) without favouring the recombinants (Lewontin, 1971).

The lines KS and K had increased fitness and at the same time responded to selection, which points to high genetic variability. The exception is the line K: here one linkage group had been fixed for the LAP-A- and LAP-D-locus. In the case of line KS the above mechanisms are not sufficient to explain the existence of a balanced allele polymorphism. Here a frequency dependence is assumed. Experiments on this topic showed frequency dependent selection with an equilibrium of about 0,6 for the allele D^F. We can assume that the linkage groups as well as the alleles D^F and D^S are frequency dependent.

Only in populations with high densities can frequency dependence be observed (Kojima and Huang, 1972; Huang et al., 1971). For the selection lines we can conclude that the frequency dependence had greater effects in temperature selected lines than in lines selected for developmental rate, since the temperature selected lines had the highest crowding conditions because they were held in population cages permanently. The temperature selected lines had maintained allele polymorphisms which can be well explained by frequency dependence.

An indispensable precondition for frequency dependent selection is the existence of selective values for the alleles, otherwise the equilibrium of the alleles becomes a by-product of linked gene complexes which have high selective values (McIntryre and Wright, 1966; Sved, 1968). In the selection lines a linkage of the LAP-A- and LAP-D-locus with such gene complexes can not be wholly excluded, but the population sizes were big enough to produce suitable recombinations even in the lines selected for developmental rate. Thus we may assume that the equilibrium is balanced by the selective values of the alleles.

The existence of selective values for both alleles D^F and D^S of the LAP-D-locus has been found in the first results of a series of experiments which were started to estimate fitness in relation to different frequencies and developmental stages. The results of these experiments will contribute detailed information on this topic (Muhs, in preparation).

Genetic Drift

Up to now the results have been discussed from the aspect of maintaining genetic polymorphism. The lines selected for developmental rate have lost a part of their variability, especially line K for the studied loci. In a previous chapter it was shown that the distribution of the linkage groups in this line is a product of selection only to a certain degree. Above all the fixation of the linkage group A^OD^F in line K and, on the other hand, the maintenance of the balanced polymorphism in the parallel line KS with both linkage groups A^FD^F and A^SD^S, remained unexplained.

Artificial or natural selection can reduce genetic variability. Because of the extensive genetic homeostasis, especially of the frequency dependence, fixation of a linkage group in line K should not take place. Therefore another factor has to be considered which can decrease the variability: the genetic drift.

If the fixation probability for every generation is $1/2\,N_e$ (N_e being the effective population size), we can expect that this fraction amounts to less than 1/480 each generation. Up to 183 generations had been selected. The

probability that an allele should be fixed during this time by drift alone is not high. In permanent populations (RE, 1a, 1b, 3a, and 3b) (Muhs, 1975b) the drift will certainly not be important because population sizes are big and generations overlap extensively.

As soon as selection takes place the fixation probability changes. In the cases involving selection and overdominance a decrease in fixation probability is expected. If selection, frequency dependence, and selective neutrality at the equilibrium frequency exist, a balanced polymorphism can be maintained effectively. If in the same case overdominance instead of selective neutrality is assumed, this seems to be the most effective way to maintain allele polymorphism (Nassar, 1970).

We may conclude that selection connected with mechanisms maintaining allele polymorphism does not lead to a higher probability of fixation than the genetic drift alone. In big populations, mechanisms maintaining allele polymorphism are more effective than drift; it is just the reverse in small populations (Dobzhansky and Spassky, 1962). The population size used here (480 individuals in line KS and K) and the duration of selection (up to 183 generations) had caused drift to be more effective in one line (K) than in the other line (KS). The fixation of one linkage group in line K can only be explained by the cooperation of drift and artificial selection.

In these investigations it is very difficult to distinguish between the effects of drift and selection. This is obvious for the studies, too, dealing with the alleles of the Est-6-locus and the Aph-D-locus (Muhs, 1975a,c). Except for the Aph-D^0-alleles, the alleles Est-6^S and Aph-D^1 had been fixed largely or completely in all lines. The effect of selection in these lines is evident, but drift may not have been without influence.

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