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Environmental Change Uncovers Differences in Polygenic Effect of Chromosomes from a Natural Population of *Drosophila melanogaster*

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Polygenic variation of sternopleural bristle number was investigated at the whole chromosome level in a natural population of *Drosophila melanogaster*. Fifty pairs of second and third chromosomes were analyzed at 25℃. Since environmental factors such as temperature influence polygenic expression of quantitative traits, whole chromosomal effects of 28 pairs from the larger original sample were measured under cycling temperature, a 10 - 30℃ cycle in 24 hours, to reveal any polygenic alleles whose effects might be masked under the constant temperature. While third chromosomes typically showed a larger contribution to polygenic variation in both environments, second chromosomes showed greater sensitivity to environmental changes. Cluster analyses of second and third chromosomes produced a limited number of clusters. Such a small number of clusters implies that there may be a small number of genes, or quantitative trait loci (QTLs), having large effects on phenotypic variation. The genetic structure assessed under constant temperature, however, did not show any correlation with the structure under cycling temperature. The discrepancy could be caused by independent response of each polygenic allele to temperature changes. Thus, polygenic structure in natural populations should be thought of as a temporally changing profile of interactions between gene and ever-changing environment.

Most traits of an organism seem to be continuous, although Mendelian traits have been examined more extensively and have yielded more detailed information about the genes responsible for the traits. Unlike many Mendelian traits, quantitative traits are quite sensitive to environmental conditions and are often thought to be due to the segregation of many polygenes that, by definition, have small phenotypic effects (Mather, 1941; Mather and Jinks, 1982). Although such a definition of polygenes appears to rule out being able to study individual effects, attempts to isolate quantitative trait loci (QTLs) and investigate their effects have in fact been successful (Lander and Schork, 1994; Alpert et al., 1995; Long et al., 1995; see also references in Thompson, 1977 and Tanksley, 1993).

Stabilizing selection refers to a situation where those individuals whose phenotypes are around the mean or optimal phenotype are favored. Such stabilizing selection seems to act upon many quantitative traits (Endler, 1986). Under some theoretical models, stabilizing selection is predicted to deplete genetic variability (Fisher, 1930; Robertson, 1956; Bulmer, 1971; Kimura, 1981). This prediction is not, however, supported by observations, such as the ability of many natural populations to respond to artificial selection. The genetic capacity for these to vary seems to be maintained in nature in spite of apparent stabilizing selection.

The balanced linkage of polygenes (Mather, 1943) may explain the polygenic architecture of quantitative traits and help resolve the apparent contradiction between the expected effects of stabilizing selection and the maintenance of genetic variability. This hypothesis suggests that polygenic heterozygosity may be maintained by alternative configurations of alleles having increasing (+) and decreasing (-) effects on polygenic traits between paired chromosomes at a given locus (relational balance; + +/- - or + -/- +) and among loci relevant to the traits within a chromosome (internal or epistatic balance; + - + -). These are called balanced polymorphisms.

Thoday and Gibson (1972) expanded Mather's hypothesis to non-homologous chromosomes. Under stabilizing selection an individual having internally unbalanced chromosomes can obtain an optimal phenotype with balanced genomes (+ +/+ +; - -/- -). Non-homologous chromosomes under stabilizing selection, therefore, should show a negative correlation of polygenic effects.

Although there have been many attempts to analyze polygenic variation by solely statistical methods (Falconer,

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1981; Mather and Jinks, 1982; Becker, 1984) and to isolate quantitative trait loci using chromosomes from selected or laboratory strains (Thompson and Thoday, 1979; Shrimpton and Robertson, 1988a,b; Lander and Botstein, 1989; Lander and Schork, 1994; Alpert et al., 1995; Long et al., 1995; Doerge and Churchill, 1996; Jansen, 1996), few studies have investigated polygenic structure in natural populations (Thompson and Mascie-Taylor, 1985; Thompson et al., 1991). Understanding polygenic structure in natural populations would be one of the most desired prerequisites to unveil the mechanisms by which polygenic expressions are regulated and by which polygenic variation is maintained. Thus, we investigated the genetic structure in a quantitative trait, sternopleural bristle number, of *Drosophila melanogaster* in a natural population.

The expression of the polygenes affecting sternopleural bristle development depends upon environmental conditions such as temperature (Schnee and Thompson, 1984a). Some polygenes that do not have any effect in a specific environmental condition could be latent and play an important role in expressing an optimal phenotype when the environment changes, while others express themselves to an optimal phenotype in the current environment. Such conditional polygenic expression might help maintain genetic variability.

To see if any specific polygenic configurations, such as internally balanced chromosomes or balanced non-homologous chromosomes, have evolved in nature and if changing environment would help maintain genetic variability, the polygenic structure of a sample of chromosomes was first screened under a constant temperature and then under a cycling temperature. The cycling temperature mimics the environmental conditions under which the natural chromosomes have evolved. To assess the polygenic structure underlying variation in sternopleural bristle number, we estimated the whole chromosome effects of second and third chromosomes isolated from a natural population of *Drosophila melanogaster*. These two chromosomes carry approximately 80% of the *Drosophila* genome. The results do not show balancing between chromosome 2 and 3. The absence of interchromosomal balance between non-homologous chromosomes can be interpreted in either of two ways. Either balanced linkage is not a way to accomplish optimal phenotypes or each chromosome maintains internally (intrachromosomally) balanced polygenic combinations. The autosomes did, however, differ in the way their effects on bristle number changed when developmental temperature conditions were altered.

Materials and Methods

Quantitative trait

The sternopleural bristle number in *D. melanogaster* is a popular model system for quantitative geneticists. Sternopleural bristle number is sensitive to environmental conditions. There is an inverse relationship between bristle number and temperature (Rasmuson, 1958; Parsons, 1961; Caligari and Mather, 1975; Schnee and Thompson, 1984a). This system seems to be under stabilizing selection (Barnes, 1968; Parsons, 1973; Caligari and Mather, 1980). Stabilizing selection tends to reduce expressed variation by selecting against individuals with extreme phenotypes (Fisher, 1930; Robertson, 1956; Bulmer, 1971; Kimura, 1981). Despite the apparent stabilizing selection on the trait, variation appears to be maintained since the bristle number can respond to artificial selection. Also, only a small number of quantitative trait loci (QTLs) having relatively large effects appear to be responsible for the majority of variation in sternopleural bristle number (Gibson and Thoday, 1962; Wolstenholme and Thoday, 1963; Thoday et al., 1964; Spickett and Thoday, 1966; Schnee and Thompson, 1984a; Shrimpton and Robertson, 1988a,b; Long et al., 1995). The small number of QTLs allows us to investigate the polygenic structure in nature and the relationships between QTLs and environment in a more or less direct fashion as in Mendelian traits. Thus, the sternopleural bristle system is a good model system for the study of mechanisms by which polygenic expressions are regulated and by which polygenic variability is maintained.

Population

Drosophila melanogaster females were collected near Noble, Oklahoma, USA, from a fruit pile placed for a few days in a rural forest in summer, 1990. Each captured female fly was allowed to lay eggs in an 8-dram vial at 25±1℃ on cornmeal, molasses, and agar medium. Fifty isofemale lines were established. From the progeny in these isofemale lines, wild chromosomes were isolated for these studies.

Whole chromosome assay

The breeding program for the whole chromosome assay is diagrammed in Fig. 1. To see the effects of chromosome 2 and chromosome 3, a single male from each isofemale line was crossed to virgin females from the isogenic standard control strain that carries the recessive eye color mutants *brown* (*bw*, 2-104.5) and *scarlet* (*st*, 3-44.0). The mutants are described in more detail by Lindsley and Zimm (1992). Each F1 male from the cross carries a single chromosome 2 and a single chromosome 3 from the original isofemale line and chromosomes 2 and 3 and an X chromosome from the isogenic control line. A single F1 male was backcrossed to virgin females from the isogenic standard. All the F_2 flies carry the X chromosomes from the isogenic control line. Eye color classes of F_2 progeny are exactly matched with their chromosomal make-ups: scarlet-eyed flies (*+/bw*; *st/st*) carry a single chromosome 2 from the isofemale line with the

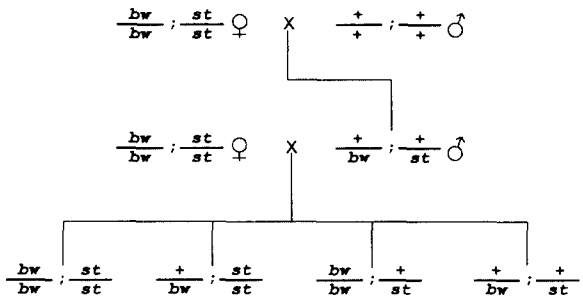

Fig. 1. Breeding program which isolates a pair of second and third chromosomes from a single male.

genetic background of the control line; brown-eyed flies (*bw*/*bw*; +/*st*) carry a single wild-type chromosome 3; red-eyed flies (+/*bw*; +/*st*) carry both a wild-type second and a wild-type third chromosome; white-eyed flies (*bw*/*bw*; *st*/*st*) carry no wild-type chromosomes. This makes it possible to quantify each chromosome effect and interaction on the bristle number compared with an internal control (white-eyed flies) developing in the same culture vial and, therefore, sharing the same environment. Each pair of autosomes isolated from a natural population can be replicated and retested by backcrossing heterozygous red-eyed males (+/*bw*; +/*st*) to white-eyed virgin females (*bw*; *st*) from the isogenic standard.

The assumption that there is no recombination in males of *D. melanogaster* makes it possible to estimate the effects of the intact chromosomes from the isofemale lines with the whole chromosome assay. Rare male recombination, if any, would be a conservative force in that it would substitute a QTL allele from the wild-type autosome with one from the standard line. Since the QTL effect is measured relative to expression in the standard (*i.e.*, the difference in phenotypic effect between the wild-type and standard chromosomes), this exchange would simply be seen as a loss of QTL phenotypic effect. There was no evidence that male recombination affected the expression of any line in this study.

Phenotypic effects of each chromosome were measured under constant temperature (25℃) and cycling temperature (10 to 30℃ in 24 h). In each temperature environment, six replicates of whole chromosome assay breeding were set up and the sternopleural bristle numbers of five flies for each sex of each class were scored. Effects of each chromosome and interaction between chromosome 2 and 3 were calculated as deviations from the average bristle number of the co-segregating standard sibs (*bw*; *st*). For example, to obtain the chromosome 2 effect, the average bristle number of the white-eyed flies was subtracted from the average bristle number of the scarlet-eyed sibs. The polygenic effects were analyzed by a four-factorial ANOVA in fixed model (Sokal and Rohlf, 1981).

$$Y_{ijklm}=\mu+II_i + III_j + Sex_k + Rep_l + (II\cdot III)_{ij} + (II\cdot Sex)_{ik} + (II\cdot Rep)_{il} + (III\cdot Sex)_{jk} + (III\cdot Rep)_{jl} + (Sex\cdot Rep)_{kl} + (II\cdot III\cdot Sex)_{ijk} + (II\cdot III\cdot Rep)_{ijl} + (II\cdot Sex\cdot Rep)_{ikl} + (III\cdot Sex\cdot Rep)_{jkl} + (II\cdot III\cdot Sex\cdot Rep)_{ijkl} + \varepsilon_{ijklm},$$

where μ equals the parametric mean bristle number. II_i, III_j, Sex_k and Rep_l are second chromosome effects, third chromosome effects, sex differences and replicates, respectively. Parentheses represent first, second and third-order interactions, and ε_{ijklm} is the error term. ANOVAs have been performed with MINITAB-pc statistical software release 7.2.

Mantel test

To investigate which chromosome contributes more to the polygenic structure of this trait, the similarity matrices in each chromosome and interaction were compared to the matrix of overall effect by the Mantel test.

The Mantel test is a nonparametric correlation test of associations based on two different sets of characteristics (Mantel, 1967). Mantel test statistic, Z, is calculated as

$$Z=\sum_{i,j}^{n} X_{ij}\, Y_{ij},$$

where X_{ij} and Y_{ij} are the off-diagonal elements of matrices X and Y. Significance tests are performed by comparing the observed Z value with the expected Z value based on random permutations of the rows and columns of matrix Y. A t value is calculated by subtracting the expected Z value from the observed Z value and then dividing the difference by the standard error of Z. The t value is compared to a standard normal distribution.

The Mantel test can measure the degree of relationship between two distribution-free patterns. Because polygenic structure might have a distribution-free or nonparametric association, we employed the test to find out which component or chromosome effect would contribute the largest proportion to a polygenic structure in each environmental condition. The Mantel test can also tell whether there are any relationships between polygenic structures and environmental conditions.

The MXCOMP program of NTSYS-pc (Numerical Taxonomy and Multivariate Analysis System) developed by Rohlf (1990) performs the Mantel test. Similarity matrices of average distances between genomes in each chromosome, interaction and overall effect were calculated by the SIMINT program. The formula used for the average distance between lines *i* and *j* is:

$$d_{ij}=\sqrt{\frac{1}{n}\sum_{k}^{n}(X_{ki}-X_{kj})^2}$$

where X_{ki} and X_{kj} are the effects of lines *i* and *j*, which

Table 1. Whole chromosome effects on sternopleural bristle number at 25℃ and cycling temperature

	25℃			cycling		
line	chromosome 2	chromosome 3	interaction	chromosome 2	chromosome 3	interaction
1	-0.050	0.100	-0.350	-1.067***	0.083*	0.683
2	-0.050***	0.550***	0.183	-0.150	0.433	-0.217
3	0.500***	-0.567**	0.217	2.117***	-0.650***	-0.167
4	0.733***	-0.083	-0.017	0.733**	-0.433**	-0.283
5	0.033	1.033***	0.267	0.150	0.733*	-0.400
6	0.217	2.100***	-0.517	-0.567	-0.367	0.650
7	0.417*	1.117***	-0.050			
12	1.467***	3.367***	0.983**	0.917***	3.717***	0.317
14	-0.267***	0.550	-0.567			
15	-0.117	0.933***	-0.317	0.033	-0.133	0.267
16	0.483***	1.117***	-0.017			
20	1.500***	0.333	-0.933**	0.767****	-0.617*	0.200
23	0.983***	0.017	-0.517	0.600	0.683	-0.850
27	0.783***	-0.917***	-0.050	0.917***	-0.500*	-0.167
29	1.017***	2.467***	-0.117	0.900**	2.267***	-0.450
30	-0.717*	0.767***	0.717*			
33	0.633***	0.450***	0.267			
34	0.500	0.567	-0.450	-0.717***	2.833***	-0.617
35	0.483***	-0.383	0.250			
36	0.600***	-0.700***	-0.283	-0.417	-1.483***	0.217
39	0.517	0.867*	-0.867*	0.133	0.150	0.050
40	0.917***	0.600***	0.167			
44	0.583**	-0.033	-0.350	1.717***	0.100	0.300
45	0.983*	1.867***	-1.133**	1.417***	1.017***	0.783
46	0.617***	0.100**	0.717*			
56	0.717***	0.417**	0.033			
59	0.967***	1.117***	0.583			
60	-0.133	2.383***	0.067	-0.433	1.567***	0.183
62	0.600***	-0.017	0.283	0.333*	-0.517	0.433
65	-0.183	0.467**	0.100			
71	0.450*	0.250	-0.200			
72	0.133***	-0.533	1.233***	1.367***	-0.267	-0.083
77	0.750**	1.317***	-0.583			
78	-0.267**	1.017***	-0.467	-0.367	0.550*	-0.150
79	0.783***	0.167	0.083			
81	0.467**	-0.450***	-0.117			
82	-0.150	1.083***	0.383			
84	0.667***	-0.317	0.167			
87	0.400***	0.567***	0.650*	0.333*	-0.167	0.400
89	-0.567***	0.767***	-0.133	-0.867**	0.517**	0.317
93	1.150***	1.050***	-0.267	0.317***	-0.100	1.017*
101	0.367**	0.567***	0.283	1.083**	2.233***	-0.883
102	0.217	-1.150***	-0.183	0.233	1.067***	-0.100
104	01.450***	0.367***	0.850*			
105	0.050	-0.700***	-0.200	0.467	0.000	-0.467
106	0.583**	1.100***	-0.267			
109	0.517*	-0.300*	-0.233			
111	0.600**	-0.417**	0.000			
112	0.900***	1.417***	0.283			
116	0.850***	1.067***	0.017	-0.367*	0.650**	-0.167

Significance levels are determined from ANOVAs, see text for detail.
* 0.01<p<0.05. 0.001<p<0.05. *** p<0.001

are to be compared to each other, in characteristic k (e.g. chromosome 2 and 3).

Cluster analysis

If only a small number of polygenic loci can explain the majority of the quantitative variation, all the chromosomes should be classifiable into a few groups or clusters. To test the hypothesis that a few loci account for most the variation, all the chromosomes were clustered by the SAHN program of NTSYS-pc (Rohlf, 1990). We employed the Unweighted Pair Group Method Using Arithmetic Averages (UPGMA) with similarity matrices of average distances between chromosomes (Sneath and Sokal, 1973).

Results

Polygenic structure at 25℃

Table 1 shows the effects of chromosome 2, 3 and the 2 x 3 interaction. As expected, both chromosomes 2 and 3 had significant effects on the quantitative variation in sternopleural bristle number, but interchromosome interaction as a rule did not show significant effects. In most cases, both chromosomes 2 and 3 had significant effects on sternopleural bristle number as compared to the internal standard *bw; st* flies. Only nine out of 50 chromosome pairs showed significant interactions.

However, chromosome effects were not equal. The third chromosome provided a larger contribution to polygenic variation than did the second chromosome. Chromosome 3 showed a higher average effect (0.549

Table 2. Matrix correlation between distributions of individual chromosome effects and overall effects on sternopleural bristle number at 25℃

	correlation[a]	t[b]	p[c]
chromosome 2 vs. overall	0.43256	5.143	1.000
chromosome 3 vs. overall	0.85130	10.140	1.000
interaction vs. overall	0.38948	4.635	1.000

Sample size is 50.
[a] Correlation (r) is normalized Mantel statistic Z. 0.8 ≤ r < 0.9: good fit. 0.7 ≤ r < 0.8: poor fit. r < 0.7: very poor fit.
[b] Approximate t-test.
[c] Probability of random Z < observed Z.

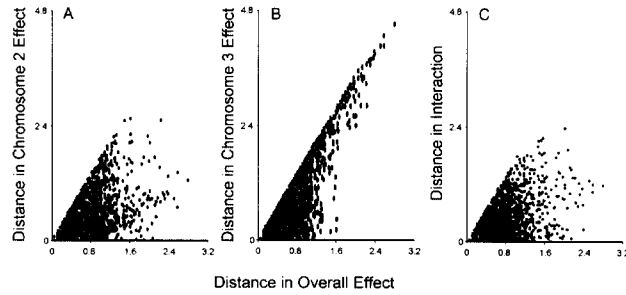

Fig. 2. Comparison of distributions of second (A), third chromosome effects (B) and interactions between second and third chromosomes (C) to distribution of overall effects. Identical distributions produce a diagonal line. In particular, compare the right side to a distance of 1.6 in overall effect.

bristle per fly) and a larger standard deviation (0.907) than did chromosome 2 (0.462±0.534). The difference between chromosome 2 and 3 effects in variance was significant by F test (F[49,49]=2.888, p<0.001). Interactions between chromosome 2 and 3 had small average effects and most of the interactions were not significant, but the variation of the interaction was comparable to that of chromosomes 2 and 3 effects.

Even though polygenic structure can be explained by individual gene or chromosome effects and their statistics, the polygenic structure of quantitative traits should also be analyzed as a whole unit. To analyze the genetic structure as a unit, the Mantel test was employed. The distribution of the third chromosome effects showed good correlation to the distribution of overall effects, which is a three dimensional distribution of chromosome pairs having each chromosome effect and interaction as three axes. The distributions of second chromosome effects and interactions showed very poor correlation to the distribution of overall effects (Table 2). The comparisons are graphically presented by the NTSYS-pc program (Fig. 2). Chromosome 3 shows especially well the clear correlation to the overall effects when average distances in overall effect are larger than 1.6. The results imply that the third chromosome plays a more important role than the second chromosome in the polygenic structure of sternopleural bristle number.

Polygenic structure and environment

To see whether there is any relationship between constant temperature and cycling temperature in chromosomal effects on this trait, we selected 28 pairs of wild-type autosomes out of the 50 pairs that had been screened at 25℃. They were selected to show relatively even distribution of each chromosome effect at 25℃. Whole chromosome effects of the subset were measured under the cycling temperature (10 to 30℃ in 24 hours). The effects of each autosome and interaction under the constant and cycling temperatures are shown in Table 1. Many second and third chromosomes showed significant effects on bristle number under the cycling temperature, too. However, the number of chromosomes that showed significant effects was lower in the cycling temperature environment as compared with the constant environment. Only one case showed significant interaction in the cycling environment.

Although the third chromosomes showed a higher average effect and larger variation than the second chromosomes, the differences between the second and third chromosome were smaller in cycling temperatures (Table 3). The difference between chromosome 2 and 3 effects in variance was significant by F test in constant temperature (F[27,27]=3.342, 0.001<p<0.01) but not in the cycling temperature (F[27,27]=2.118, p=0.056). While average effects of both chromosomes 2 and 3 were smaller in the cycling environment than in the constant environment, variation of the second chromosome effects increased more in the cycling environment. The ratio of standard deviations of chromosome 2 to chromosome 3 in the cycling environment

Table 3. Averages of whole chromosome effects on sternopleural bristle number at 25℃ and cycling temperature

		mean	SD	minimum	maximum	q1	q3
25℃	II	0.429	0.583	-1.050	1.500	0.037	0.833
	III	0.654	1.067	-1.150	3.367	-0.029	1.046
	interaction	-0.106	0.523	-1.133	1.233	-0.425	0.209
cycling	II	0.342	0.798	-1.067	2.117	0.367	0.913
	III	0.477	1.161	-1.483	3.717	-0.342	0.946
	interaction	-0.029	0.474	-1.883	1.017	-0.267	0.317

Number of samples is 28.
q1 and q3 stand for the first and third quartiles, respectively.

Table 4. Matrix correlation of distributions of whole chromosome effects on sternopleural bristle number between 25℃ and cycling temperature

	Correlation[a]	t[b]	p[c]
overall	0.36857	3.189	0.999
II	0.05479	0.575	0.717
III	0.43137	3.822	1.000
interaction	-0.04051	-0.383	0.351

Sample size is 28.
[a] Correlation (r) is normalized Mantel statistic Z. r < 0.7: very poor fit.
[b] Approximate t-test.
[c] Probability of random Z < observed Z.

(0.69) was larger than the ratio in the constant environment (0.53). In particular, the quartile range of chromosome 2 effects was nearly equal to the range of chromosome 3 effects in the cycling environment. These results implied that the second chromosome QTLs are more sensitive to environmental conditions than are those on the third chromosome. The lower correlation (0.464, $0.01<p<0.05$) between the constant and the cycling temperature in chromosomes 2 effects, compared to the correlation (0.606, $p<0.01$) in chromosome 3 effects, also implied that the polygenes on the second chromosome would more strongly interact with environmental variables.

The Mantel test was used to compare the polygenic systems as units in constant and cycling environments. The lack of correlation between the distributions of chromosome 2 effects (Table 4) suggested that each second chromosome interacts with environmental conditions in its own way, rather than in parallel, whereas the third chromosomes are influenced by environmental conditions in a common way.

Polygenic architecture

Quantitative traits can be determined by many polygenes having small effects (Mather, 1943) or only a small number of polygenic loci having comparatively large effects that are responsible for the majority of quantitative variation (Thompson and Thoday, 1974). In either case, if linkages are balanced, a small number of phenotypic sets is expected to be found in nature. The second chromosomes and the third chromosomes were clustered by the UPGMA. There were a small number of phenotypic clusters (Figs. 3, 4, 5 and 6). Because many studies have shown that segregation at a small number of loci could explain most of phenotypic variance (Gibson and Thoday, 1962; Wolstenholme and Thoday, 1963; Thoday et al., 1964; Spickett and Thoday, 1966; Schnee and Thompson, 1984a; Shrimpton and Robertson, 1988a, b; Long et al., 1995), identical clustering would be expected in constant and cycling temperatures under the assumption that all the alleles should be affected in parallel by temperature changes. The clustering of chromosome 2 and 3 in cycling conditions was, however, not identical to the clustering in constant conditions (Figs. 5 and 6). Two cluster patterns can be compared indirectly by the cophenetic correlation (Sneath and Sokal, 1973). From each phenogram, a similarity matrix of cophenetic values or distances was obtained. For example, chromosome 2 of strain 1 has a cophenetic value of 0.75 from all the members of the neighbor cluster, to which strain 3 belongs, in constant temperature (Fig. 5A). Cophenetic

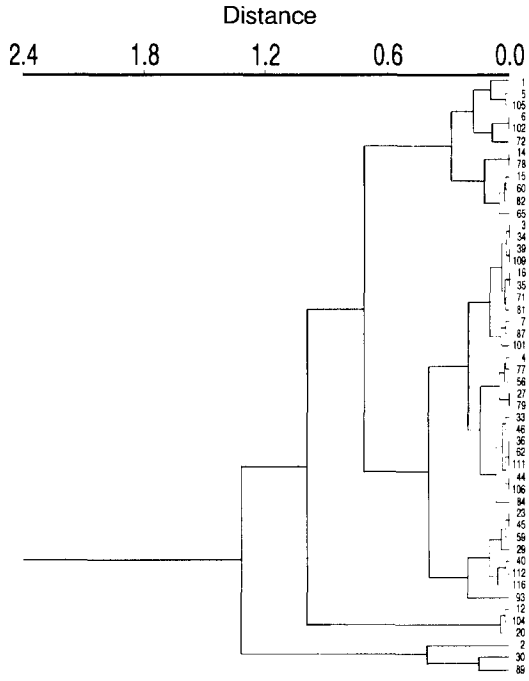

Fig. 3. Phenograms showing similarities among lines in second chromosome effects at 25℃. All 50 lines are clustered. Individual effects are shown in Table 1. Numbers on the right side denote strains.

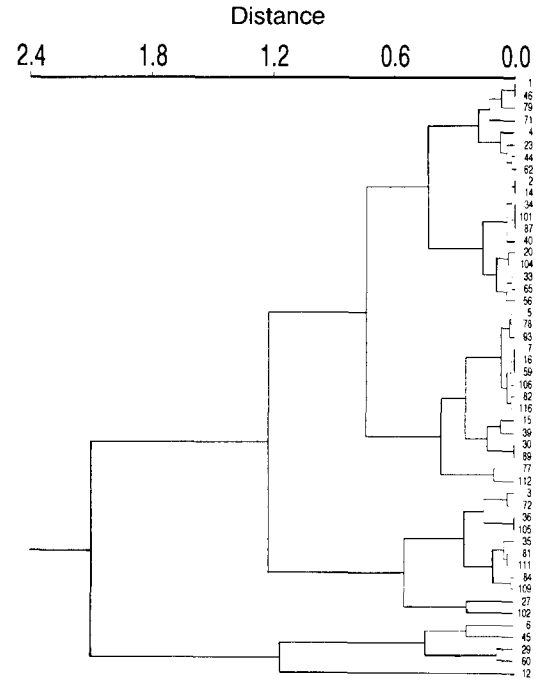

Fig. 4. Phenograms showing similarities among lines in third chromosome effects at 25℃. All 50 lines are clustered. Individual effects are shown in Table 1. Numbers on the right side denote strains.

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