УДК 575.17

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BIOLOGICAL MUTAGENES AND THEIR ROLE IN THE NATURAL MUTATION PROCESS

Two sets of lethal mutations in chromosome 2 of Drosophila melanogaster have been tested for allelism: lethals induced by viruses and exogenous DNA and those found in different natural populations or arising de novo in the progeny of wild-type flies. It was concluded that the mutagenic effect of different viruses and other sources of DNA, exogenous for the host cells, is to induce single-locus and multiple mutations, which can spread throughout natural populations. Certain population-genetical consequences of the data obtained are discussed, and in particular, the position that during virus-induced mutagenesis, similar multiple chromosome lesions can occur repeatedly and independently in isolated populations of flies a result of a single mutation event.

A long-term analysis of the appearance of mutations and their distribution in geographically isolated populations of *Drosophila* indicated that biocenotic interactions of viruses (and their genomic components) with the host genome could serve not only as a powerful selective factor, but could also lead to an intensification of the rate of the mutation process and to the activation of mobile elements of the genome [1, 2]. A many-sided investigation of the mutagenic effect of exogenous DNA and different viruses, noninfectious for *Drosophila,* led to the same conclusion [3—5].

From the viewpoint of population and evolutionary genetics, it is not only the principle of virus and exogenous DNA mutagenicity, firmly established by many works which is interesting, but also the direct determination of which kind of hereditary changes, associated with the effect of these factors, are distributed in natural populations. The possibility of answering this question appeared after comparing two sets of second chromosome lethals obtained and analyzed during many years in two laboratories: (a) induced by DNA and RNA viruses and foreign DNA [4, 5] and (b) isolated from natural populations in the USSR [1]. The suitability of an investigation of lethals in the case of *Drosophila* for these purposes is obvious, since lethals represent an objectively registerable class of mutations, which occur in not less than 80 % of loci in the genome. Moreover, reasonable simple methods are available, which make it possible to isolate and localize lethals in a particular chromosome, and to study their allelic relationships. So both sets of lethals were studied for allelism and some of them were localized.

The mutagenic effect both of various viruses noninfectious for *Drosophila* and foreign DNA is characterized by strong site-specificity. Analysis of even small samples consisting of 15—20 lethal chromosomes shows complex allelic reactions and high allelism frequency. The mutations occur in definite groups of loci specific for each agent tested [5]. The chromosomes with lethal defects in many sites (*multilethal*) appear regularly (see Fig. 1). The mutant loci are either clustered or dispersed among the chromosome.

On the contrary, allelic relations of large groups of lethals isolated from nature are rather simple. The mutations usually appear in a great number of loci. Some lethals, however, have been found repeatedly both within one population and among adjacent ones. The *multilethal* chro-

mosomes were also isolated (see Fig. 2). Among these groups of natural lethals wee found allelism with the lethals induced by viruses and foreign DNA (see Table).

The main conclusion are: (1) mutagenic action of different viral agents and foreign DNA sources causes the multisite mutations which may be distributed in natural populations; and (2) this form of mutagenesis is similar to the action of movable genetic elements [7—9]. In both cases the site-specific chromosomal lesions (including rearrangements) may occur due to single mutation events. Similar multisite mutations may appear repeatedly and independently in isolated populations.

Thus viruses and various types of DNA-carriers when entering the eukaryotic genome, can sharply intensity the rate of mutagenesis, can lead to site-specific multiple chromosome lesions,

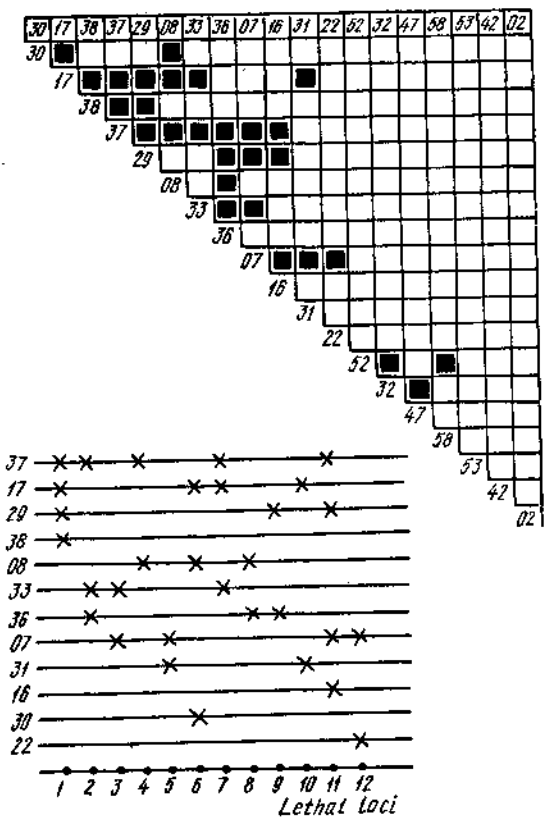

Fig. 1. Diallelic crosses between 19 second chromocomes in which lethals were induced by addition of influenza virus in food. Allelism is shown by black squares. Allelic relationships are complex; their interpretation is given at left. Mutations occur in 12 loci; 8 chromosomes are multilethal and have 2—5 lethals in different loci. The order of loci is given here arbitrarily. Chromosomes 52 and 32 are dilethal. So among 19 lethal chromosomes 10 are multilethal; they occur due to single mutational events

Results of a test for allelism between two groups of lethal mutations (induced by viruses and exogenous DNA and those frequently met in natural populations of Drosophila) *

Mutagen **	Number of chromosomes with induced lethals taken in the experiment	Number of cases of allelism	Information about natural lethal chromosomes which displayed allelism	
			Index, population, year	Included in the group of multilethals
Algophage (DNA)	8	1	237, 264, Dilizhan, 1964	Yes
Influenza virus (RNA)	10	2	247, 255, Dilizhan, 1964	»
Herring DNA	10	2	137, Uman, 1963	»
			305, Uman, 1965	No
Calf thymus DNA	29	5	97, Uman, 1963	Yes
			121, Uman, 1963	No
			181, Uman, 1963	Yes
			587, 654, Uman, 1967	»
Picornavirus C***	5	1	108, Uman, 1963	»
Drosophila DNA	10	0	— —	—
Total	72	11	— —	—

* In the test for allelism we compared 64 chromosomes with lethals, frequently met in natural populations, with the indicated samples of induced lethals in 72·64 = 4608 crosses; ** In brackets we indicate the nucleic acid of the particular virus; *** The lethal mutations were isolates in the progeny of flies infected with picornavirus subtype C, pathogenic for *Drosophila* [6].

and can induce instability of the genes. It becomes increasingly obvious that the interaction of various DNA- and RNA-carriers plays a substantial role in the natural mutation process [10]. Having presented this viewpoint, we are able to explain a series of baffling phenomena in population genetics and cytogenetics: the mode of mutation in particular genes,

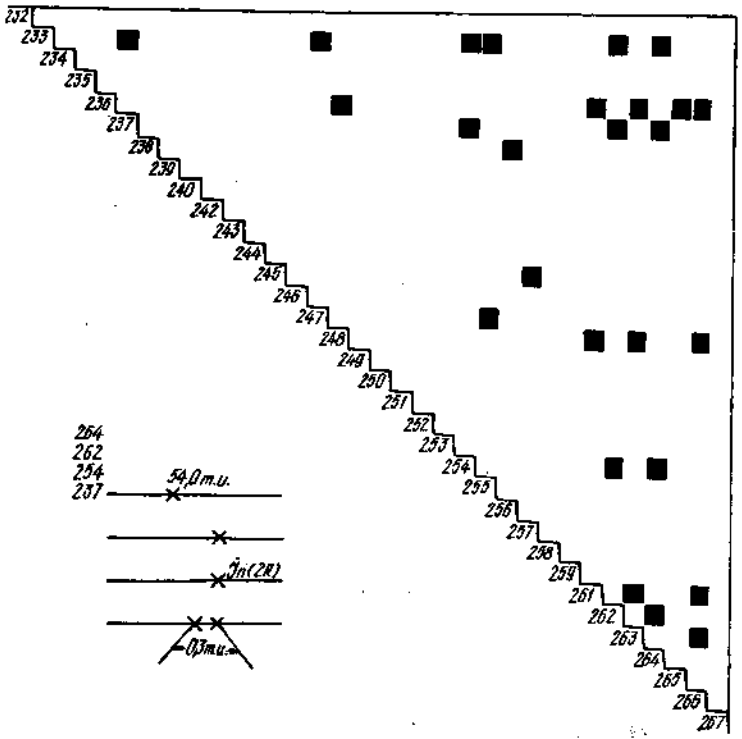

Fig. 2. Diallelic crosses between 34 chromosomes with lethals isolated from a natural population in Dilizhan (Armenia) in 1964. Allelic relationships as a rule are simple. One exclusion is shown at left. Chromosome 233 contains two closely linked lethals; both of them were allelic to the virus induced mutations (see Table). Chromosome 255 carries a short inversion on the right arm, In (2R); 51A; 57B

which arises synchronously in remote regions; outburst of mutability accompanied by the appearance of multiple unstable alleles; the presence of similar multiple crossovers in different parts of an area occupied by the species, etc. We arrive at biocenotic and at the hypothesis that the main factor in the natural mutational process is the interaction of components of the biocenosis.

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БІОЛОГІЧНІ МУТАГЕНИ ТА ІХ РОЛЬ
У ПРИРОДНОМУ МУТАЦІЙНОМУ ПРОЦЕСІ

Р е з ю м е

Здійснено тест на алелізм між двома наборами летальних мутацій 2-ї хромосоми *Drosophila melanogaster,* індукованих вірусами і екзогенною ДНК і виявлених в різних природних популяціях у потомстві мух дикого типу. Зроблено висновок про те, що мутагенна дія різних вірусів і інших джерел екзогенної для клітин-хазяїв ДНК викликає появу однолокусних і множинних мутацій, здатних розповсюджуватися у природних популяціях. Обговорюються деякі популяційно-генетичні наслідки, які випливають із отриманих даних, зокрема, положення про те, що при вірусному мутагенезі схожі множинні хромосоми можуть виникати багаторазово і незалежним чином у віддалених популяціях мух за рахунок одного мутаційного акту.

REFERENCES

1. *Golubovsky M. D., Ivanov Yu. N., Zakharov I. K., Berg R. L.* An investigation of synchronous and parallel changes in the gene pool in natural populations of fruit flies *Drosophila melanogaster* // Genetika.— 1974.— **72**, N 4.— P. 72—83. (USSR).
2. *Golubovsky M. D.* The mutation process and microevolution // Genetics.— 1980.— **52/53**.— P. 139—149.
3. *Gershenson S. M.* The character of mutations inducible in *Drosophila* by the sodium salt of thymonucleic acid // Dokl. Acad. Nauk USSR.— 1940.— **26**.— P. 609—611.
4. *Alexandrov Yu. N., Gershenson S. M., Malyuta S. S.* The mutagenic properties of DNA- and RNA-containing viruses, nonvirulent for *Drosophila* // Genetika.— 1971.— **7**, N 9.— P. 102—112. (USSR).
5. *Gershenson S. M., Alexandrov Yu. N., Malyuta S. S.* The mutagenic effect of DNA and viruses in *Drosophila*.— Kiev : Nauk. Dumka, 1975.— 160 p.
6. *Golubovsky M. D., Plus N.* Mutability studies in two *Drosophila melanogaster* isogenic stocks endemic for C picornavirus and virus free // Mutat. Res.— 1982.— N 1.— P. 29—32.
7. *Lim J. K.* Site specific instability in *Drosophila melanogaster*. The origin of mutations and cytogenetic evidence in the site specificity // Genetics.— 1979.— **93**.— P. 681—701.
8. *Berg R. L., Engels W. K., Kreber R. A.* Site-specific X-chromosome rearrangements from hybrid dysgenesis in *Drosophila melanogaster* // Science.— 1980.— **210**, N 4468.— P. 427—429.
9. *Green M. M.* Mobile DNA element and spontaneous gene mutations // Eukaryotic transposable elements as mutagenic agents.— New York : Cold Spring Harbor Lab., 1988.— P. 41—50.
10. *Khesin R. B.* The instability of the genome.— Moskow : Nauka, 1984.— 472 p.

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24.03.95