RESEARCH ARTICLE

Ontogenes and the Genetics of Intraspecific Similarity

Authors

B. F. Chadov and N. B. Fedorova

Affiliation

Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, Novosibirsk, 630090 Russian Federation

Correspondence

B. F. Chadov

Email: boris_chadov@mail.ru

Abstract

The experiments by Gregor Mendel, which formed the background for genetics, were performed with the characters of intraspecific difference (alternative characters). Mendelian protein-coding genes are responsible for these characters. Until recently, these genes were regarded as the only and main hereditary factors responsible for ontogenesis and phylogenesis. The review outlines the information about another category of biological characters (the characters of intraspecific similarity) and, correspondingly, of a special category of genes responsible for these characters (ontogenes). The study into mutations of ontogenes in drosophila experiments suggests that (1) ontogenes control the construction of cell ensembles and trigger protein-coding genes in cells; (2) the program of individual development is encoded in ontogenes and "edited" in germline cells; (3) ontogenes fulfill a regulatory function without any contacts and chemical intermediaries, which suggests a kind of biophysical activity; and (4) two categories of cells—stem cells and terminally differentiated cells—correspond to these two categories of genes. Ontogenes are active in stem cells and protein-coding genes, in terminally differentiated cells.

Keywords: intraspecific similarity, ontogenes, cell ensemble, ontogenetic program, non-chemical gene interaction

Introduction

By definition character is the property according to which two objects either are similar or differ from one another (the categories of similarity and difference) [1]. The living organisms belonging to the same species have characters of both categories. All individuals of a particular species have the characters similar within the species. As for the intraspecific difference, some individuals of the species possess such characters and some do not [2]. The latter category of characters is also referred to as *alternative characters.* They are famous by that Gregor Mendel used these characters to create his genetic theory.

The characters of intraspecific similarity are the background of a living organism. They form the essence of a particular biological species. The position of a species in the hierarchy of the living is determined according to the similarity characters. Human is the best-studied biological object. The human biological sciences are in essence the descriptions of the characters of intraspecific similarity for the species *Homo sapiens.* Systemic anatomy details the structure of the human body and systemic physiology describes the details of its function. Anatomical pathology and pathophysiology describe the anatomical and physiological alterations in the case of diseases. The diseases themselves are described as nosological entities. All listed definitions are *species-level invariants* of the structure or function. They are characteristic of all representatives of the species *Homo sapiens.*

It is currently known that the characters of intraspecific difference at a genetic level are the variants of protein-coding genes. However, it is still unclear in terms of genetics what the similarity characters are. There are no doubts that they are also encoded in DNA and, most likely, as individual DNA regions but how they are organized and how they function are yet vague. Special disciplines—genetics of individual development and evolutionary genetics—deal with the establishment and genetic basis of the characters of intraspecific similarity. Although the set of research methods used for this purpose, both cytological and genetic, is very wide, the solutions are yet to be found.

The first and pivotal information about the characters of intraspecific difference was obtained in hybridological experiments, now classical. The research into the characters of intraspecific similarity may have followed the same way. However, invariance of the similarity characters suggested that their hybridization analysis was unfeasible. It has turned out with time that the invariance is not absolute and the capacities of the classical genetic analysis are particularly welcome there.

Method for genetic analysis of the characters of intraspecific similarity

In all uncertainty of our understanding of the genetic nature underlying the similarity characters, the very fact of genetic determination of this similarity is beyond any question. If so, the similarity in a character means homozygosity of the genes coding for this character and elimination of the mutant alleles in heterozygotes. A hypothetical portrait of a gene responsible for a similarity character is rather peculiar: *a mutation of the gene is viable in a homozygote but is lethal in a heterozygote*. The portrait of a Mendelian gene is completely opposite: mutants of Mendelian genes are viable in a heterozygote and rather frequently lethal in a homozygote [3].

In our search for the genes responsible for similarity, we decided to look for unusual mutations, i.e., those viable in a homozygote and lethal in a heterozygote. Drosophila is a convenient model for such study. After exposure to ionizing radiation, drosophila females were used to get sons, part of which presumably carried the target mutation in the X

chromosome. As expected, homozygosity of the mutation in the X chromosome (males carry one X chromosome) should guarantee that mutant males were viable. All generated males were individually mated with females and the males that had no daughters (heterozygotes for the mutation in the X chromosome) were regarded as mutant [4]. The found mutations met the expectation: they were viable in males (homozygous mutation) and lethal in females (heterozygous mutation). The proposed technique for selecting mutations formed the background for four different methods allowing for identification of mutations and permitted acquisition of a large collection, comprising over a hundred mutations in different drosophila chromosomes [5].

Properties of conditional mutations in drosophila

The first experiments with the obtained mutations amended the initial concept on the specificity of mutations. The death of heterozygotes for mutations planned in the test for mutation does not always reach 100%. The lethality rate depended on the genotype of the female used in mating. However, the anticipation of a high dominant lethality of the target mutations proved true. These mutations were named conditional mutations [5, 6]. Further study has demonstrated that here we deal with a new, previously unknown category of mutations.

Characteristic of conditional mutations is a lethality: dominant or recessive, or both. Their lethality manifests itself under some genetic conditions (restrictive) and does not appear under other conditions (permissive). In the latter case, conditional mutations display a set of properties unobservable in the case of common (Mendelian) mutations, namely, (1) emergence of monstrosities (morphoses); (2) parental inheritance; (3) genetic instability, including a high rate of secondary mutations; (4) meiotic abnormalities as a high rate of chromosome nondisjunction; and (5) disturbed basal metabolism [5, 6]. The genes responsible for emergence of conditional mutations were named ontogenes [7]. The underlying cause of this new term is the ability of mutations carried in these genes to interfere with the course of ontogenesis and induce monstrosities (morphoses).

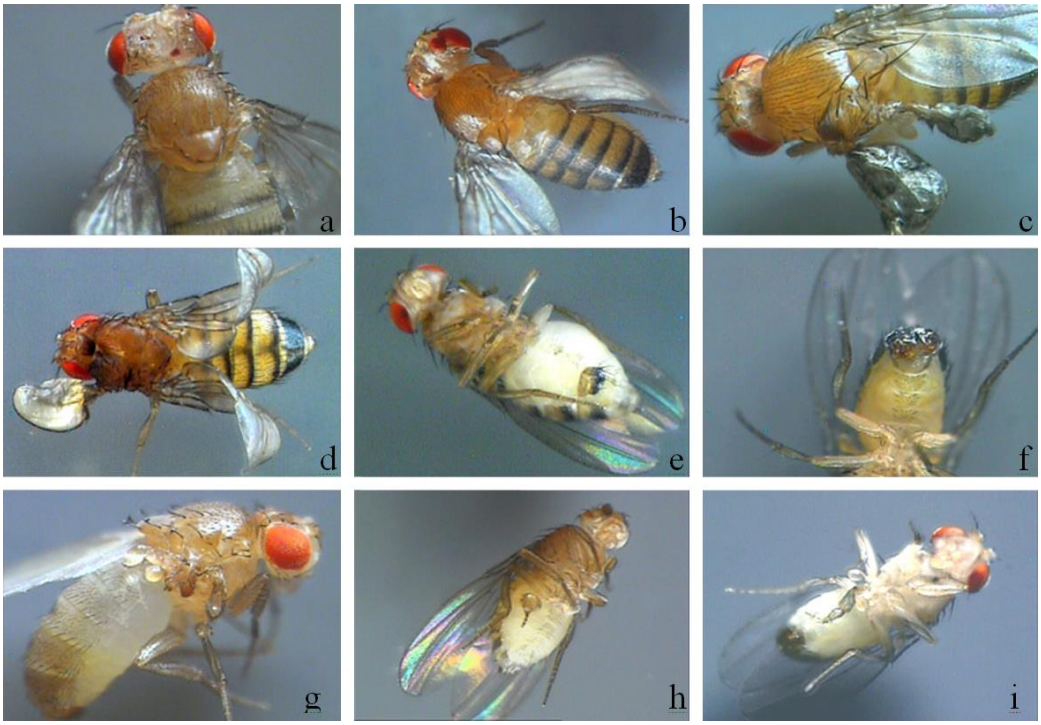

Fig. 1: The morphoses of the "plus tissue" type (surplus morphological structures): (a) groups of eye ommatidia (red spots) on the occiput; (b) an additional eye on the right side; (c) an additional thorax with an altered wing on the right side and a normal wing on the right side in a form of a structureless bubble; (d) an additional wing on the right side (directed forward) and an altered thorax on the right side; (e) a tergite fragment with bristles on the abdomen; (f) doubling of the external male genitalia; (g) four wing-like appendages with bristles instead of a normal wing on the right side; (h) tarsus on the abdomen; and (i) an additional altered seventh leg.

According to the methods used to induce, select, and stock mutations, the conditional mutation are DNA defects similar to the Mendelian mutations. However, the mode of manifestation of conditional mutations suggests that these defects belong to the genes of a different category and reside in some other DNA regions as compared with the Mendelian genes. Indeed, the genes belonging to one and the same category cannot be able to determine the characters inherited in a diametrically opposite manner: the Mendelian characters are inherited independently, whereas the manifestations caused by a mutation in an ontogene are inherited in a paternal manner. Most likely, the ontogenes occupy these 95% of the DNA molecule, which, as has been shown for human DNA [8], is free from the protein-coding genes.

A specific manifestation of the mutations in ontogenes, which is evidently distinct from the manifestation in Mendelian genes, suggests several important conclusions. Find below four of these inferences with the relevant lines of reasoning.

Ontogenes create cell ensembles and switch on Mendelian protein-coding genes in the cells

A characteristic manifestation of a mutation in an ontogene is emergence of morphoses in mutant individuals and their progenies (Fig. 1). Morphosis is a local structure with its size and shape resembling a certain structure of the adult fly but residing in an improper site and functionally useless. Commonly, morphoses are referred to as monstrosities. In some cases, a morphosis is a partial or complete absence of a normal structure. Morphosis looks as if the program of individual development is partially and erroneously implemented [9, 10]. However, the

assumption that this is a failure of the program during its implementation must be immediately rejected.

The obvious cause underlying emergence of a morphosis in a progeny is the presence of a conditional mutation in its parent; however, an interesting point is that the progeny develops morphosis independently of whether it got the mutation from parent or not [11, 12]. This cannot but mean that the mutant ontogene had been activated before it started to work or, more precisely, in the germline of the mutant before the beginning of meiosis. The changes induced by this activity must take place in the diploid genome (before meiotic reductional division). Only in this case, they can be also present in the progenies that have not received the parental mutation, as is seen in the experiment. It is clear that the defect in the form of morphosis has a genetic nature. The defect is bought to the embryo together with the gamete. Evidently, the prime cause of monstrosity in a progeny is a defect of an ontogene, one of the elements of the system that controls the establishment of a multicellular ensemble of the embryo.

Numerous morphoses observed in conditional mutants quite often display manifestations of known Mendelian mutations characteristic of the structure affected by a particular morphosis. For example, yellow coloration of the epithelium (*yellow* mutation), apricot ommatidia (*white–apricot* mutation), or specific bar-shaped eye (*Bar* mutation) accompanies head morphoses. Evidently, the development of a pathological cell structure in the form of morphosis is accompanied by switch-on of the Mendelian genes the activity of which fits the time and place of development of the corresponding structure. Thus, the ontogenes control the switch-on of Mendelian genes.

The asymmetry of morphoses makes it possible to assess the distribution of the functions between genes and ontogenes during morphogenesis. The phenomenon consists in that any morphosis emerges only on one body side, left or right (Fig. 1). As is known, the structures of adult flies are frequently distorted because of mutations in Mendelian genes; however, these abnormalities are always symmetric and bilateral. The difference in manifestation is explainable by that the formation of cell ensemble (the number of cells and their spatial arrangement, including symmetry and neighborhood) is determined by the function of ontogenes rather than by the function of a Mendelian gene. The function of a Mendelian gene is to produce the corresponding protein. If so, the mutations in ontogenes must disturb the symmetry of normally symmetric bilateral structures. The Mendelian genes, responsible for synthesizing proteins, work in the already formed cells and the mutations in these genes can lead to defects in structures but these defects will be bilaterally symmetric [13].

Symmetry is a cellular phenomenon and is determined by the work of ontogenes. Mendelian genes are unable to distort the symmetry as well as to restore it once the symmetry is disturbed by ontogenes. Thus, the program of individual development of an organism includes the formation of cell ensembles and initiation of the protein-coding genes in the cells of the formed ensembles. The responsibility for this function lies with the ontogenes. In this program, the organization of protein synthesis under the control of ontogenes is assigned to Mendelian protein-coding genes.

The program of individual development encoded in ontogenes is “edited” in germline cells

Conditional mutations have a set of manifestations inherited in a parental manner [5, 6, 11]. In this type of inheritance, a progeny gets the character independently of whether it receives the mutant gene responsible for the

character with gamete or not. Emergence of morphoses (mentioned above), recessive lethality, dominant lethality, interaction with chromosome rearrangement, etc., are inherited in a parental manner. The forms of parental inheritance of the types of ontogene manifestation are manifold and sometimes unique. For example, a conditional mutation can manifest itself in a progeny that has not received the mutant chromosome from the mutant parent; however, it does not matter whether mother or father is mutant [11, 12]. This phenomenon not only demonstrates that ontogenes are active in germline cells before they have passed through meiosis, but also that this activity is present in both female and male gametogenesis. Recall that the Mendelian genes are inactive in germline cells and are activated only after the zygote is formed. Their activity consists in DNA-dependent protein synthesis. It is not difficult to understand that the famous Mendelian inheritance of characters is determined not only by the behavior of chromosomes in meiosis, but also by the absence of their activity before meiosis.

The activity of ontogenes in the germline is definitely independent of protein synthesis. Any data on the intensive protein synthesis in germline cells are so far absent. Correspondingly, the activity of ontogenes can consist in an epigenetic transformation of some regions in ontogenes. It is postulated that this transformation may be implemented via a change in their conformation by nuclear RNAs [7]. It is appropriate to refer to this process as *the natural editing of the program of individual development.* It is quite logical to regard this program as invariant for all individuals of a particular species, coded for in ontogenes and inherited with the DNA molecule. However, each event of fertilization gives the zygote, which comprises similar but not identical sequences. Thus, the organism each and every time has to solve the problem of preparing a viable variant of the program for development of progenies on a new plane. This is what takes place during production of gametes in the germline [12, 14].

Our experimental data suggest that each event of editing of this program ends with creation of a variant unique in its details but with unchanged framework. Our experiment has shown that a conditional mutation of a male fly that manifests itself by the absence of daughters in the offspring yet allows them to appear in certain cases. The number of such exceptional cases can be changed in different directions by mating with females of different strains [3, 15]. In other words, the species-level program of development, with all its conservatism, has a certain degree of variation, i.e., *it has its norm of reaction.*

The aforesaid gives the insight into the problem of the so-called individual variation and rightly points to an epigenetic nature of such variation [16]. However, it is necessary to be aware that this refers to the operation style of the genes of a special type, ontogenes, in a special cell lineage, germline cells [9, 17]. Another process is rejection of some variants, which takes place when the parental genomes meet in the zygote and leads to the death of individual combinations [15, 18]. As has been shown, matching of the edited parental genomes to one another is important for the survival of a zygote [19, 21]. The rate of sterility in crosses reflects the intensity of zygotic selection [21].

Ontogenes fulfill their regulatory function without any contacts and chemical intermediaries, suggesting a biophysical nature of ontogene activity

Ontogenes with the above-defined function can be regarded as the Edström's master genes, dating back to the early 1960s (cited according to [22]). Note that that term "master gene" has a certain inexplicit meaning besides a supervisor and a super-regulator. The ability of master gene to exert control means

that it possesses some properties that are absent in the genes it controls. As it has emerged, ontogenes actually possess a unique property, namely, the cases when ontogenes are able to act at a distance without any contacts and chemical intermediaries [23].

Three such cases of their remote action have been discovered. The first case is the interaction between a conditional mutation of male and a chromosome rearrangement carried by female. The mutation of male leads to the absence of daughters in its offspring. The maternal chromosome rearrangement removes this effect [15]. The choice between the death of daughter and its cancel is made at the very moment the zygote forms, when the paternal and maternal chromosome sets come together. The chromosome rearrangement fails when it is carried by mutant father. This suggests that neither possible contacts between paternal and maternal chromosomes nor possible chemical intermediaries generated via gene activity has anything to do with the interaction between the parental chromosome sets. Thus, it can be considered that two parental chromosome sets meeting in the zygote actually interact at a distance.

The second case is the interaction of the mutant ontogenes responsible for formation of symmetric structures [13]. The ontogenes reside in different cells. Mutation in an ontogene interferes with their joint work on a coordinated development of the right and left structures. Correspondingly, this breaks the bilateral symmetry: one side retains a normal structure and the other side either loses it or develops a morphosis.

The third case is the simplest for understanding. As it has emerged, the mutants in ontogenes display high rates of meiotic X-chromosome nondisjunction [3, 6, 24]. This effect is unobservable for the mutations in Mendelian genes. Therefore, it is the sequences of ontogenes that in the norm bring homologs together in meiosis and the changes in these sequences caused by a mutation interfere with the pairing and co-orientation of homologs.

These three cases demonstrate a remote interaction of ontogenes, which is the phenomenon that cardinally distinguishes between ontogenes and Mendelian genes. We assume that the remote interaction between ontogenes involves the electromagnetic fields they induce and the interaction between these fields. The region of DNA double helix that houses an ontogene, forming a kind of solenoid, can well be the source of such field [23, 24]. A regulatory role of coiled DNA was postulated as early as by I.B. Panshin, a classic in the area of drosophila heterochromatin [25]. The electromagnetic field of an ontogene nucleotide sequence is another type of code, which is no less specific than the nucleotide sequence itself. It is assumed that the program of individual development utilizes this code during somatogenesis [23, 24]. As for the code itself, it relies on the nucleotide sequences of ontogenes and is edited during the maturation of gametes in the germline [7, 12, 14].

Two types of genes and two types of cells

The cells of a mature organism fall into two groups: stem cells and terminally differentiated cells [26]. Stem cells constantly refill the pool of failing terminally differentiated cells. This pattern of soma organization looks surprising and overcomplicated. It seems that it is easier to endow the cell with its function while it divides. The question arises on why the work of the soma is organized in this intricate manner. The discovered existence of ontogenes and a specific pattern of their function explain why the somatic cells are divided into two categories. Then, the ontogenes continue to function and implement the program of individual development in the stem cells of a mature organism. This work is regulatory and is associated with information retrieval and fine rearrangement of DNA regulatory regions.

As for the terminally differentiated cells, their work is associated with energy-consuming protein synthesis and energy-consuming operation of protein systems. This is an inert function, leading to rapid wear of working structures, and requires their periodical replacement. These two operation modes are hardly combinable; therefore, the work of ontogenes and the work of Mendelian genes are implemented in different cells.

The ontogenesis itself also requires a special operating order, which includes the changes in embryo morphology and function during continuous life-sustaining activities. The pool of terminally differentiated cells continues its work over a certain time interval (until a natural death of these cells) concurrently allowing the program of development to be changed and the new pool of terminally differentiated cells with a new program to be produced. There is no other way to switch from one program to another keeping up the life activities. Thus, the "stem" type of operation (preservation of continuous ancestral lineage with offshoots) is characteristic of all living processes: evolutionary hierarchy of species, division of the living into "immortal embryonic" and "mortal" somatic parts, and, finally, separation of the cells into stem and terminally differentiated types.

Conclusions

It was possible to technically discover these "other" genes using a hybridological technique, as we did it [4], as early as the 1940s. Most likely, this was not done because of ideology. The concept of a universal (Mendelian) gene was in its prime at that time and the capabilities of Mendelian gene seemed infinite. By the end of the 20th century, the explanation of ontogenesis [12, 14] and phylogenesis [20] in terms of the universal protein-coding gene encountered quite noticeable difficulties; however, the idea of "other" genes was still not in demand. Neither the discovered noncoding DNA (it was just named "junk" or "selfish" DNA [27]) nor the mutant phenes unrelated to altered primary DNA sequence suggested the existence of another gene category. The mutant phenes were referred to as epigenetic [16, 17, 28], that is, actually, nongenetic.

The problem consists in that proteins, being an obligatory component of each living structure, are frequently regarded not only as a necessary but also as a sufficient condition for emergence of a structure. Correspondingly, the protein-coding genes are quite sufficient to construct a living organism. In fact, not all "biological" characters are the function of protein(s). To be formed, many (and, actually, most) characters require not only proteins, but also cells and, correspondingly, new DNA molecules and new cell envelopes. These are *elementary structures*, which are not formed de novo similar to protein molecules but rather multiplied. The number of cells, their spatial arrangement, and their neighboring cells must be also unambiguously defined. Otherwise, it is impossible to get an organism of a particular species. The listed tasks cannot be managed by Mendelian genes, involved in protein synthesis. This requires both some other genes able to organize the construction of the cellular framework of a future organism and the other genetic mechanisms besides the DNA-dependent protein synthesis.

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References

1. Kondakov NI. Logicheskii slovar'–spravochnik (Logical Dictionary–Handbook). Moscow, IN: Nauka; 1975:477.
2. Chadov BF, Chadova EV, Kopyl SA, Artemova EV, Khotskina EA, Fedorova NB. From genetics of intraspecific differences to genetics of intraspecific similarity. Russ. J. Genet. 2004;40(9):945–958.
3. Chadov BF. Mutations capable of inducing speciation. In: Stegnij VN, ed. Evolution Biology. Tomsk: Tomsk State University Press; 2001:138–162. http://www.evolbiol.ru.
4. Chadov BF, Chadova EV, Kopyl SA, Fedorova NB. A new class of mutations in Drosophila melanogaster. Dokl. Biol. Sci. 2000; 373:423–426.
5. Chadov BF, Fedorova NB, Chadova EV, Khotskina EA. Conditional mutations in Drosophila. J Life Sci. 2011;5: 224-240.
6. Chadov BF, Fedorova NB, Chadova EV. Conditional mutations in Drosophila melanogaster: On the Occasion of the 150th Anniversary of G. Mendel's Report in Brünn. Mutat. Res. Rev. Mutat. Res. 2015; 765:40–55. doi.org/10.1016/j.mrrev.2015.06.001.
7. Fedorova NB, Chadova EV, Chadov BF. Genes and Ontogenes in Drosophila: The Role of RNA Forms. Transcriptomics. 2016; 4:137. doi: 10.4172/2329-8936.1000137.
8. Venter J., Adams MD, Myers EW et al. The sequence of the human genome. Science. 2001; 291:1304-1351.
9. Chadov BF, Chadova EV, Fedorova NB. Epigenetic phenomenology in conditional mutants of Drosophila melanogaster: morphoses and modifications, IN: Zakijan SM, Vlasov SM, Dement'eva EV, eds. Epigenetics. Novosibirsk: SD RAN; 2012:499–533 (in Russian).
10. Chadov BF, Chadova EV, Fedorova NB. Images of morphoses and modifications in Drosophila melanogaster conditional mutants. 2015. http://www.researchgate. doi: 10.13140/RG.2.1.2721.9042.
11. Chadov BF, Fedorova NB, Chadova EV. Parental effects of conditional mutations and their explanations. Russian Journal of Genetics. 2013; 49:141-50. doi:10.1134/S1022795413020038.
12. Chadov BF, Chadova EV, Fedorova NB. The Genetics of Conditional Mutations and Individual developmental Programs in D. Melanogaster. SCIOL Genet Sci. 2017; 1:3-21.
13. Chadov BF, Fedorova NB. The Mutations Disturbing the Bilateral Symmetry in Drosophila. SCIOL Genet Sci. 2019; 2:139-152.
14. Chadov BF, Chadova EV, Fedorova NB. Conditional Mutations in Drosophila: Concept of Genes That Control Individual Development. Advances in Bioscience and Biotechnology. 2018; 9:243-272.
15. Chadov BF, Chadova EV, Fedorova NB. A Novel Type of Gene Interaction in D. melanogaster. Mutation Research. Fundamental and Molecular Mechanisms of Mutagenesis. 2017; 795:27-30. http://dx.doi.org/10.1016/j.mrfmmm.2017.01.002.
16. Russo VEA, Martienssen RA, Riggs AD, Briggs AD, eds. Epigenetic Mechanisms of Gene Regulation. New York: Cold Spring Harbor Laboratory Press; 1996: 693 pp.
17. Chadov B.F. A New Stage in the Development of Genetics and Term Epigenetics. Russian Journal of Genetics, 2006, Vol. 42, N9, 1053-65.
18. Chadov BF, Chadova EV, Khotskina EA, Artemova EV, Fedorova NB. The main effect of chromosomal rearrangement is

changing the action of regulatory genes. Russ. J. Genet. 2004;40 (7):723–731.
19. Chadov BF, Fedorova NB. Zygotic selection in Drosophila melanogaster and a new edition of Darwin's concept of speciation. In: Podobina VM, ed. Evolution of Life on the Earth: Proceedings of the V International Symposium; November 12-16. Tomsk: Publishing House of TSU. 2018: 49-51.
20. Chadov BF, Chadova EV, Fedorova NB. Ontogenes and the Problem of Speciation. Journal of Evolutionary Science. 2019;1(1):3-47.
21. Chadov BF. The Ontogenes in Drosophila and the Problem of Fertility. Ann. Infert. Rep. Endocrin. 2018;1(1):1004.
22. Korochkin LI. Biology of Individual Development (Genetical Aspect). Moscow: MGU Press; 2002:121 (in Russian).
23. Fedorova NB, Chadov BF. Gene interactions in Drosophila without contacts and chemical intermediaries. Abstracts Book of: International Conference on Cell and Experimental Biology (Virtual Conference); December 9-11, 2020:6. https://cellexpbiol.unitedscientificgroup.org/proceedings/CEB-2020_Abstracts.pdf>.
24. Chadov BF, Fedorova NB. Ontogenes and the Paradox of Homologous Pairing. Advances in Bioscience and Biotechnology. 2021; 12:1-9. https://doi.org/10.4236/abb.2021.121001.
25. Panshin IB. The second system of hereditary variation as a consequence of quantitative regularities of heterochromatic gene position effect, IN: Khvostova VV, ed. The Gene Position Effect in the Studies. Novosibirsk: ICG SO RAN; 1992:23–98 (in Russian).
26. Korochkin LI. Stem Cells: What are they? Priroda (Nature). 2005; 6:3-11 (in Russian).
27. Orgel LE & Crick FHC. Selfish DNA: the ultimate parasite. Nature. 1980; 284:604–607.
28. Zakijan SM, Vlasov SM, Dement'eva EV, eds. Epigenetics. Novosibirsk: SD RAN. 2012: pp 5 (in Russian).

