Japan Journal of Research

Review Article

New Class of Genes in D. melanogaster (Conditional Mutations, Ontogenes, and Biological Role of Ontogenes)

B. F. Chadov, N. B. Fedorova

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

Correspondence

B. F. Chadov
Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, Novosibirsk, 630090 Russian Federation

- Received Date: 7 July 2023
- Accepted Date: 14 July 2023
- Publication Date: 18 July 2023

Keywords

conditional mutations, ontogenes, Mendelian genes, biophysical interaction of genes, D. melanogaster

Abstract

The review briefs the history of the search for non-Mendelian genes, including the rationale for their existence and the methods for their discovery in D. melanogaster. The genes are named ontogenes and their mutations, conditional mutations. Characteristic features of conditional mutations in hybridological experiments have been described. Three separate sections dwell on the experimental facts that distinctly outline the difference of this novel group of genes from the classical protein-coding (Mendelian) genes. According to these facts, the specificity in the function of ontogenes consists in (1) the warrant that an organism belongs to a particular species; (2) the control of cellular construction; and, most likely, (3) the presence of nonchemical (biophysical) way of interaction between ontogenes.

Introduction

The first batch of mutations of this new class was generated in *D. melanogaster* in 2000 [1,2]. As of today, after almost 20 years of the research into these mutations, it is in general clear what their differences from Mendelian mutations are and what are the differences of the genes determining these mutations from classical Mendelian genes. The goal of this review is to brief the main experimental facts on the so-called *conditional mutations* and *ontogenes,* which are responsible for the formation of conditional mutations, as well as the theoretical generalizations in this recently appeared area of genetics.

The definition of a gene(s) as "new" is often met in genetic literature but in terms of characterization of functional diversity of the corresponding proteins coded for by the genes rather than the genes per se. Here, this is not the case. We speak about genuinely new genes that are fundamentally different from the Mendelian protein-coding genes. At the first glance, the study of this kind should have been performed much earlier, during the classical period in genetics, when the concept of gene was shaped. The theoretical circumstance that interfered with the discovery of the genes other than the Mendelian ones will become clear in the course of the narrative. Along with the information about new genes, the review may be of interest to the researchers interested in the history of genetics and establishment of the fundamental concept of gene.

Conception of the work

Historically, the study of the reproduction of living organisms in terms of biology from the very beginning followed the way of studying inheritance, that is, the transmission of individual characters of parents to their descendants in the series of generations. Gregor Mendel proposed to study inheritance in the crosses of parents with alternative characters [3]. The species-level traits existing as mutually exclusive variants are referred to as alternative. The alternative characters form the *intraspecific diversity* of organisms [4,5]. These characters are convenient when studying the inheritance since they do not prevent crosses of individuals and make it possible to track the inheritance in any number of generations [3]. The proposal by Mendel to study heredity according to the inheritance of this class of characters has emerged to be most efficient, allowing genetics to reach first the level of chromosomes and then, the molecular level.

The onrush of genetics in the direction determined by Mendel and "materialization" of gene as a DNA region containing the code for construction of the corresponding protein led to the idea that the protein-coding gene is a universal unit of heredity, the particular universal factor of heredity the existence of which came to Mendel's mind. The idea of universal gene received strong support from the evolutionary concept of Charles Darwin. According to this concept, the species are the result of selection of the variants of a trait that

Citation: Chadov BF, Fedorova NB. New Class of Genes in D. melanogaster. Japan J Res. 2023;4(6):1-8.

provide the highest fitness of an organism. Thus, the presence of variants of a trait in this concept is the pivot with the evolution of the living "coiling" around it. The traits having variants are a kind of the "source" of living.

However, the species-level traits are not confined to the characters that have variants, namely, there are *the traits determining the intraspecific similarity* [4,5]. Any representative of a species possesses such traits. They are conserved, determine the species-specific appearance, and indicate the position of species in the hierarchy of the living. These traits are inapplicable to hybridological analysis but most important for the genetic theory. The fact that *the traits determining the intraspecific similarity* are conserved suggests that they may be attended by *specific genes. Their specificity consists in that they are prohibited to have variants.* The presence of such genes makes it possible to explain (1) the existence of a unified program of individual development for all members of a species and (2) the inability to produce progeny in interspecific crosses; and to create with their help (3) a new model of speciation instead of the current one, which does not stand up to scrutiny.

We decided to experimentally verify the hypothesis on the existence of "other" genes by searching for mutations in these genes. How should these mutations look like? Theoretically, either the prohibition of mutation of a gene responsible for a trait or elimination of the appearing gene mutation is necessary in order to provide the constant presence of similarity according to the trait in population. The former assumption looks unreal and the latter demands that the mutant allele is eliminated immediately after its emergence, that is, in heterozygote. As for the elimination in heterozygote, the only chance for new genes to "come into being" is to appear at once in a double dose, that is, in homozygote. This chance should be taken into account because otherwise any biological evolution will become unfeasible. Thus, a virtual portrait of the gene responsible for a similarity trait is rather peculiar: *the mutations in the gene must be viable in a homozygous state but lethal in a heterozygote.* The Mendelian gene, with which genetics deals for already over a century, is totally antithetical to the new gene: the mutations in Mendelian genes are viable in a heterozygote but lethal (in all cases or often) in a homozygote. To test the hypothesis on existence of "other genes", we decided to search for the mutations paradoxical from the standpoint of modern genetics, that is, the mutations *viable in a homozygote and lethal in a heterozygote.* Once mutations were found, this would prove the existence of the postulated "other genes".

Generation of mutations

Drosophila is a convenient object when searching for the mutations of interest. Males carry only one X chromosome (and one Y chromosome) and females, two X chromosomes. Thus, males are appropriate to test the manifestation of an X-chromosome mutation in a homozygous state and females, in a heterozygous state (in the daughters of a mutant male). *D. melanogaster* females were exposed to γ-irradiation and the progeny of sons and daughters was produced. Part of the sons should putatively contain the target mutation in the X chromosome. The viability of mutations should be provided by a homozygous state of mutations. Sons were individually crossed with tester females (in the first experiment, these were *yellow* females). The fathers with the absence of daughters (heterozygotes for mutation in the X chromosome) in the progeny were regarded as mutants [1,2]. The mutations selected in this way fit the planned requirements, i.e., they were viable in males (homozygous for mutation) and lethal in females (heterozygous for mutation). The selection pattern, which demonstrated its efficacy, formed the background for other similar methods of mutation identification [6,7].

The key specific feature of the used technique is generation of the mutations lethal in heterozygote (dominant lethals). However, the very first crosses of the generated mutations demonstrated that the dominant lethality was of a conditional nature. This lethality emerged to be dependent not only of the mutated gene, but also of the overall genome wherein it was present. The mutations were named *conditional* [6-8], which significantly refined their definition. Thus, these mutations not only differ in the lethality in homo- and heterozygote but also the mutations lethal in a single dose (dominant lethality) with their manifestation depending on genotype (*conditional dominant lethals*). Both features—*dominant lethality* and *conditional manifestation*—determine a fundamental difference of the generated mutations from the Mendelian mutations, lacking these features. Moreover, the features of Mendelian mutations are directly opposite.

The most frequent condition for manifestation/absence of manifestation of a conditional mutation is the sex of mutant. The condition next in its frequency is the presence of a chromosome rearrangement in the genome. The chromosome rearrangement may be localized (1) in the chromosome opposite to that carrying mutation; (2) in the chromosomes of another pair; and (3) even in the genome of the partner in cross. Taking into account the properties of chromosome rearrangements, we designed the technique to generate conditional mutations in drosophila chromosome 2. The mutants (both males and females) carrying mutant chromosome 2 together with the opposite chromosome 2 carrying an inversion survived, whereas the mutants with normal opposite chromosome 2 died [6,8,9].

Independently of the phenomenon of dominant lethality, the conditional mutations also possess recessive lethality. This is demonstrated by the lethality of homozygotes for mutation in permissive genotypes. Based on the property of recessive lethality, we designed the technique for selection of conditional mutations from the collection of recessive lethals in the X chromosome generated according to *Muller-5* test. The selected mutations in the X chromosome manifest themselves in males as lethals if the initial female is crossed with a *Muller-5* male (as in common stocks) but do not manifest as lethals if the initial female is crossed with the male without a *Muller-5* inversion [9].

As was found out, conditional mutations induced the development of monstrosities (morphoses) in the progeny [10,11]. This property was also used to search for conditional mutations. Individuals with monstrosities were observed in the irradiated flies in the first generation. They were further tested for the presence of recessive lethality. The selected mutants with confirmed recessive lethality were cultivated for further observation and addition to the list of conditional mutations [7]. The collection of conditional mutations in drosophila maintained in our laboratory comprised at different times over a hundred of mutations in chromosomes X, 2, and 3.

Properties of mutations in ontogenes

As is mentioned above, the first experiments with mutants showed that the *paradoxical lethality,* used to select the mutants, was a special case of a more basic property of these mutations. The lethality in a heterozygous state appears and disappears depending on genetic conditions, for example, the genotype of

the partner in cross. The genuine basic property of these new mutations is *conditional pattern of their manifestation.* The conditional pattern of manifestation is what fundamentally distinguishes them from the Mendelian mutations, which demonstrate their unconditional and independent nature being inherited according to Mendel. The conditions for manifestation/absence of manifestation of new mutations are the genotype of the partner in cross, direction of cross, sex of individual, and the presence of a chromosome rearrangement in the opposite chromosome or the chromosomes of another pair [6,8].

Genetics is aware of similar mutations, for example, the mutations manifestation of which depends on environmental factors, such as temperature and food chemical components [12]. Another example is the mutations with incomplete penetrance [13,14]. Conditional mutations differ from both variants: from the former type, by changing their manifestation depending on genetic rather than environmental conditions and from the latter, by that the manifestation or absence of manifestation is strictly associated with particular genotypes. A strict association with particular genotypes is untypical of the mutations with incomplete penetrance.

Although conditional mutations may also have a visual manifestation, the so-called dimorphic mutations [6,8], the major manifestation is conditional dominant lethality, which is accompanied by obligate recessive lethality. The latter appears in the mutants with permissive genotypes, in which dominant lethality is absent. Recessive lethality makes it possible to test mutations for allelism and, which is important, demonstrates a discrete character of the genes responsible for mutations. Using a standard procedure of deletion mapping, we localized the mutations manifesting recessive lethality on the map of polythene chromosomes. This mapping revealed an unusual phenomenon of multilocality: of the ten tested mutations in chromosome 2, five mutations were localized to two and more chromosome 2 regions [15].

Characteristic of the mutants is an unusually wide time interval when mutations manifest themselves in the drosophila life cycle. Their manifestation in the soma in the form of the so-called *morphoses,* complex somatic monstrosities, is impressive [6,8,10,16,17]. This type of manifestation suggested us to refer to the genes responsible for these mutations as *ontogenes* [11]. Mutations also manifest themselves in the germline tissue. They induce meiotic abnormalities by drastically increasing the rates chromosome nondisjunction and loss [18].

Ontogenes differ from Mendelian genes by their activity during premeiosis. Without any exclusions, all manifestations of ontogenes, be it lethality and its modifications or development of morphoses, follow a *parental type* of inheritance [19]. The parental type appears in different forms (maternal, paternal, mixed, or nonreciprocal). Parental inheritance suggests that a product is formed in premeiotic cell that will be distributed with the progress of meiosis independently of the gene that gave rise to it [20]. The most amazing and earlier unknown property of the mutants is that they display an increased level of basic metabolism and locomotor activity [21].

This summary of the properties of conditional mutations demonstrate that they represent the genes principally different from Mendelian genes. See [6,8,20,22,23] for the properties of conditional mutations in more detail. Currently, the content of the term "*ontogene*" has much in common with the term "*long noncoding RNA genes*", which appeared in molecular genetics [20]. In the sections below, we continue to consider the properties of ontogenes by grouping complexes of the properties as the arguments in favor of particular biological missions of ontogenes.

Ontogenes determine species attribution

The manifestation of mutations in ontogenes gives a hint at the features characteristic of distant hybridization, i.e., crossing of individuals that belong to different taxa (species, genera, families, and so on) [24]. Hybridization is accompanied by the common picture of abnormalities independent of a particular cross and the kingdom, plant or animal, of the parents. The pattern of abnormalities (as in the pattern of interspecific incompatibility) includes (1) high sterility of crosses; (2) parental effect when producing the hybrid; (3) mosaicism and development of monstrosities in the hybrid; and (4) the meiotic abnormalities in the hybrid leading to sterility [24,25].

The generated ontomutations (mutations in ontogenes) in drosophila also display:

(1) ***Sterility of crosses.*** Ontomutations are conditional dominant lethals. The progeny in the crosses with ontomutations can be absent at all or in part [6,8].

(2) ***Parental type of inheritance,*** which is a typical form of inheritance of the manifestations of ontomutations. Ontomutations display different types of parental effect both rarely met or absent at all when dealing with Mendelian mutations, including paternal and mixed paternal–maternal types of inheritance. For comprehensive description of the forms of parental effect, see [19,26,27,28].

(3) ***Mosaicism and development of monstrosities (morphoses)***. Mutants for ontogenes often develop mosaic sites [10,11,16,29]. Monstrosities (morphoses) in mutants are among the most striking manifestations in mutants [10,16,17]. The development of morphoses is described by Sokolov for the hybrids between *D. virilis* and *D. littoralis* in reciprocal crosses [30].

(4) ***Meiotic abnormalities.*** Extremely high rates of the X-chromosome nondisjunction in meiosis are recorded for 30 ontomutations [18,22]. The share of matroclinous daughters for the X-chromosome reaches 24.7% of the overall progeny. In addition to nondisjunction, the X chromosome is lost and part of nondisjoined X chromosomes is exchange chromosomes. A high rate of X-chromosome nondisjunction in drosophila females shows a trend of inheritance in daughters. These data suggest a profound disorder of the meiotic division in the mutants for ontogenes [18].

As is evident, the pattern of abnormalities in ontomutants is similar to the pattern of interspecific incompatibility. We cannot help but wonder what reason is underlying incompatibility. Heterozygosity for Mendelian genes cannot be the cause of incompatibility-because it does not lead to lethality; moreover, it frequently leads to hybrid vigor, heterosis. In addition, mutations in Mendelian genes do not interfere with meiosis, and they are viable even in the compound with a deletion. It is clear that *the heterozygosity for Mendelian genes cannot be responsible for interspecific incompatibility. Correspondingly, we can suppose that the cause underlying incompatibility is the heterozygosity for the genes that determine species attribution.* In their native genome, these genes are in a homozygous state, which allows them to properly perform their mission.

The discovered similarity between the manifestation of ontomutations and the pattern of interspecific incompatibility in distant hybridization allows us to infer that (1) ontogenes

belong to the group of genes responsible for intraspecific similarity and (2) the unusual phenomenology of ontomutations is caused by their heterozygosity for ontogenes. The latter is akin to the heterozygosity in distant hybridization but is attained in a different way. Ontomutations are obtained by mutagenesis, whereas the heterozygotes for an ontogene emerge in the hybrids between normal individuals and mutants. Indeed, we should keep in mind that all genes responsible for species attribution are in a heterozygous state in an interspecific hybrid and in the experiments with ontomutations, only one gene (ontogene).

The discovered similarity to the pattern of interspecific incompatibility significantly simplified the understanding of the role of ontogenes in the organism. "Incompatibility" does not exist for Mendelian genes. Interspecific incompatibility is the conflict of the genes that form the species-level specificity of the organisms and ontogenes, in particular, are these genes. Just bring back to mind the pattern of incompatibility in distant hybridization and the role of ontogenes is clear.

Ontogenes control the process of cellular construction

Among all manifestations of the mutations in ontogenes, a group of five manifestations suggests that *ontogenes control cellular construction.* When speaking about the control of cellular construction, we mean (1) an event in ontogenesis that (2) consists in initiation of cell division and (3) fixes the position of cell division plane, which determines the growth direction of cell mass [29]. This group of five manifestations comprises the phenomena of (1) development of morphoses; (2) parental type of manifestation of a morphosis in progeny; (3) asymmetry of morphoses; (4) disturbance of cell meiotic division: and (5) disturbance of cell mitotic division [29].

In genetic literature, morphosis (monstrosity) is defined as a "nonadaptive and usually unstable variation in individual morphogenesis associated with a change in environment" [31-34]. In our case, morphosis is an inheritable morphological abnormality caused by a mutation in an ontogene [10,16,17]. The genetic nature of morphoses is evident from a parental type of their development in the progeny of a mutant. Both the progenies that received the mutant ontogene from the parent and the progenies that did not receive the mutant ontogene can also develop morphoses [26,27,29,35]. Thus, it is clear that the emergence of a morphosis is not a certain "physiological aberration" of the ongoing ontogenesis but rather the result of a change in the genetic program of development that occurred much time ago in the parent's germline.

The phenomenon of parental "inheritance" of a morphosis is also important in another respect. As is mentioned above, parental inheritance is an indicator of the gene activity in premeiosis. The Mendelian genes are inactive in premeiosis (in germline cells) and the protein synthesis is absent. This suggests that neither protein molecules nor protein-coding genes have anything to do with the formation of monstrous structures. The question arises on how do ontogenes implement this. The phenomenon of asymmetry of morphoses gives the answer.

Morphoses manifest themselves in two ways: as a "+ tissue" (outgrowths) and as a "– tissue" (the absence of normal structures). The phenomenon of asymmetry of morphoses consists in the fact that the morphoses of both types appear on only one side (right or left) of the fly body, whereas their normal analogs are bilaterally symmetric structures (wings, legs, and so on) [35]. The presence of an abnormal structure, for example, on the left side and its absence on the right side means that a mutant ontogene induced a series of successive cell divisions on the left body side, which did not take place on the right side. *The target for the action of ontogene is cell.* This agrees with the above conclusion that protein is not implicated in the emergence of morphoses.

In current genetics, protein, be it structural or regulatory, is regarded as the only biological product of gene. Unlike the Mendelian genes, the product of activity of ontogene is cell. Mendelian gene creates protein de novo from precursors, whereas ontogene creates a new cell by initiating division of a precursor cell. In the case of morphoses, it appears that ontogene not only initiates cell division, but also determines the side of the body where it must be done [29].

As is known, the mutations of Mendelian genes are also able to induce morphological defects. However, note that these defects, unlike the morphoses, are always symmetric and are inherited according to the rules of Mendel rather than according to a parental type. Thus, it is clear that the Mendelian protein-coding genes cannot pretend to control cellular construction.

Other phenomena, listed at the beginning of this section, also confirm the implication of ontogenes in cellular construction, in particular, the abnormalities of meiotic and mitotic divisions. Extremely high rates of chromosome nondisjunction and chromosome loss directly indicate disturbances of meiosis [18]. Note that a single dose of mutation causes an increase in chromosome nondisjunction. Mitotic cell division is also disturbed in the mutants for ontogenes, as is suggested by the formation of mosaics and gynandromorphs in these mutants [10,11,16,29]. As is known, point mutations in Mendelian genes do not interfere with either meiotic or mitotic cell division [36].

The totality of the discovered phenomena makes it possible not only to infer that ontogenes are engaged in cellular construction, but also to get the insight into the details of their involvement in this process. The phenomenon of asymmetry demonstrates that ontogenes are able to orient the forming cell in three-dimensional space (1) leftward or rightward, (2) upward or downward, or (3) forward or backward. This job can be done if the event of cell division initiation is accompanied by determination of the division plane. Three positions in this plane are sufficient to determine the growth of cell mass in (1) anterior–posterior, (2) lower–upper, or (3) lateral directions [29]. Assuming that ontogenes are able to "count cell divisions" from the moment of zygote formation, the program of individual development is almost ready. The activity of ontogenes in premeiosis may be regarded as evidence of fine-tuning (editing) of this program in germline cells.

The experimental work with mutations of ontogenes frequently requires using fly stocks containing Mendelian mutations. The manifestation pattern of Mendelian mutations on the background of morphoses is very interesting: the Mendelian mutations continue to typically manifest themselves even in the structures that are altered by morphoses and lost their symmetry and typical location on the body. This suggests that the *body plan* of a particular species is determined by ontogenes and ontogenes fine-tune Mendelian genes to this body plan. We believe that the program of individual development consists of sequentially switched-on ontogenes. Triggering cell divisions, ontogenes construct the cell framework for the future organism. In strict accordance with the program of individual development, ontogenes switch on Mendelian genes in the newly formed cells [29,35]. For simplicity, the details associated with the cell segregation into stem and differentiated ones are omitted from this scheme.

Biophysical nature of ontogene activity

The ability to control cellular construction functionally distinguishes ontogenes from Mendelian genes, involved in protein synthesis. It is logical to expect that this distinction will be extended to the genetic style of gene operation as well. The experimental data confirm this expectation: ontogenes (1) interact with their own kind in a remote manner; (2) are active in a compact state; and (3) manifest the so-called paradox of homologous pairing. Such manifestations are unobservable for the Mendelian genes.

Remote interaction of ontogenes

Meiosis starts from pairing of homologous chromosomes. The approaching of homologs is provided by the interaction of homologous genes. Earlier, it was believed that the interacting genes were Mendelian genes; however, it has emerged that these genes are ontogenes. This is demonstrated by high rates of nondisjunction of homologous chromosomes in the mutants for ontogenes [18,22]. Noteworthy that here we speak about *a remote interaction, that is, the interaction in the absence of a physical contact between them.* Another example of remote interaction is the interaction between parental pronuclei after fertilization. This interaction is blocked in part of zygotes; pronuclei fail to approach one another; and zygotes die before starting to develop [26,27,28,37].

Activity of ontogenes within heterochromatin

The chromosome material in a dividing meiocyte is in a compact state. Correspondingly, *the ontogenes that initiate pairing of homologs accomplish their activity being in a compact state.* The activity of ontogenes in a compact state is also confirmed by the pathology in the interaction of pronuclei in the zygote, as is mentioned above. As is known, the chromosomes within gametes are also highly compacted. Thus, we may state that the chromosome material display its activity not only in an uncoiled state (Mendelian protein-coding genes during protein synthesis), but also in a compact state (ontogenes) [29].

Paradox of homologous pairing

Analysis of an event of meiotic pairing involving the homologs one of which carries an inversion distinctly demonstrates that the approaching of homologous ontogenes is independent of the mutual positions of their sequences in space [38]. This means that the nucleotide sequences of ontogenes are able to interact (1) at a distance and (2) independently of their mutual positions in space [38].

All three specific features are logically interconnected and all three suggest that ontogenes function in a way different from Mendelian genes despite their chemical kinship. The remote interaction independent of mutual positions of nucleotide sequences in space directly leads to the conclusion that the interaction is of a physical nature (via formation of a physical, say, electromagnetic, field) rather than of a chemical one. The putative compaction of active ontogenes perfectly fits an electromagnetic nature of the interaction. In addition, note that the formation of a three-dimensional structure, which a multicellular organism is, requires a spatial orientation of the formed new cells and this is unfeasible without a certain spatially oriented external field and the genetic elements capable of linking them to the three-dimensional spatial position.

Blyumenfel'd postulated the existence of DNA magnetic properties in his experimental works as early as 1959 [39]. The stacks of DNA bases were shown to be good conductors in the experiments on assessing DNA electrical conductance. The stacks exhibit semiconductor properties and can transfer holes and electrons [40]. The formation of chemical bonds of a certain type referred to as resonance bonds (an example is benzene molecule) creates a specific situation when some electrons become delocalized and thus able to freely travel across the entire molecule. The delocalized pi-electrons or delocalized protons of the hydrogen bonds in DNA can migrate so that a stack of nucleotide bases acquires the properties of an isolated conductor [41], while the DNA strand on nucleosomes becomes an inductance coil that generates a magnetic field. According to Myakishev-Rempel et al. [42-44], a number of nucleosomes with a DNA region form an oscillatory circuit that creates an oscillating magnetic field. The DNA regions that form the oscillating magnetic field are able to induce the oscillation of the DNA regions similar or close in their molecular structure [42-44].

However, this new biophysical activity type, as far as we know, is not the only one for ontogenes. The dominant lethality of ontogenes suggests that their activity changes depending on the presence in the genome of chromosome inversions in a heterozygous state [9]. The effect of inversions follows a parental type; this fact demonstrates that ontogenes are active in premeiosis. This type of activity excludes their involvement in protein synthesis, as is mentioned above, but does not comply with the activity associated with a physical field as well. The activity related to the field cannot depend on the rearrangement of spatial positions of the interacting objects. Correspondingly, we have to assume that the activity of ontogenes in germline cells consists in the production of small nuclear RNAs [45]. Thus, ontogenes are putatively able to accomplish two types of activity, namely, a biochemical one utilizing small nuclear RNAs and a biophysical one, utilizing wave activity. The first variant is implemented in germline cells while editing the program of individual development and the second, during implementation of this program in the developing soma.

Ontogenes and other biological problems

Ontogenes and only ontogenes have allowed the three biological problems considered above - (1) intraspecific similarity, (2) cellular construction, and (3) biophysical interaction—to appear in the area of genetics. However, ontogenes are also pertinent to the problems raised as early as the Mendelian genetics. A novel view on some problems traditional for genetics, namely, in terms of a two-component genome comprising the Mendelian protein-coding genes and ontogenes, gives the chance to resolve these challenges. Below, we will dwell on some problems.

Biological trait

Genetics started from the assertion that any biological trait was determined by hereditary factors (genes). Many genes can be involved in this process (multigenic traits), as well as two genes (digenic trait, digenic cross), or only one gene (monogenic trait, monogenic cross). Our data on the control of cellular construction by ontogenes define a biological trait either as a morphological structure composed of cells or as a function of a cellular structure. As such, the trait appears as part of the organism of its particular species and can be compared to the corresponding traits of organisms belonging to other species. *In this standpoint, any biological trait is multigenic.* Even in the limiting case, it is controlled by at least two genes: an ontogene responsible for emergence of a cell and a Mendelian gene responsible for production of a protein. All the remaining definitions and classification of traits (qualitative, quantitative, monogenic, and polygenic) are artificial and provisional and

may be useful only for certain specified situations. The old terms "monogenic", and "polygenic" are also admissible but only with a distinct understanding that *they refer not to biological traits but rather to variants of these traits* that are determined by the defects of one, two, or more genes (ontogenes or Mendelian genes) [29].

Ontogenesis

The process of individual development of a living organism follows a unique program characteristic of only this species and no other one. The role of protein-coding genes is known and is not discussed; however, the protein-coding genes can vary and this excludes the possibility to consider Mendelian genes as a warrantor of uniqueness and conservation of the individual development program for a species. The uniqueness and conservation are determined by ontogenes. Thanks to their ability to provide a lethal effect in heterozygote, ontogenes demonstrate both the very fact of uniqueness of the program of individual development and the mechanism that underlies the maintenance of conservation of this program within a species [11,26,27,46]

Phylogenesis

The current evolutionary genetics in the form of the modern evolutionary synthesis assigns the primary importance to the selection of alleles of protein-coding genes. Darwinian selection provides for the best fitness of an organism. This interpretation of the evolutionary process is wide open to criticism since the living organisms of the overall "ladder of life" starting from the most primitive ones until now display an excellent fitness. This fact discredits the very idea. Once the brunt of the problem is shifted to ontogenes [47], this withdraws the main objection against the theory of selection. Darwinian selection for fitness at the level of adult organisms does take place but this is not the chief factor in the evolutionary process. *The chief is the selection of ontogenes and their ensembles in the zygote when the chromosome sets of the parents met.* It is the zygotic selection that leads to a change in the genetic program of individual development. The very same selection forms the mechanism underlying the isolation of a nascent species [22,29,48,49].

The paramount role of ontogenes in the evolutionary process for the first time solves the mystery of a special evolutionary pattern characteristic of unicellular organisms. Similar to multicellular organisms, cell is their component and they possess DNA and genes, that is, all ingredients allowing them to evolve according to the Darwinian scheme of selection for better fitness. However, unicellular organisms do not show any evolution at least in the variant that is regarded as evolution by biologists. They divide but do not form complex cellular constructions. It is reasonable here to assert that they even have no tools for this purpose, first and foremost, the specific genes (ontogenes) capable of cellular construction in a three-dimensional space.

Mutagenesis

The evolution of the living demands that gene material is mutated. For mutations to occur, this material must be in an active state [50]. If we consider protein-coding genes alone, active only during somatic development, all or the overwhelming majority of formed mutations die together with their owners without being passed to the offspring. Thus, it is reasonable to ask where and when mutations (without which any evolution in impossible) are formed.

The experiments with mutations of ontogenes directly indicate the source and time moment when mutations are formed, namely, in the DNA in the germline. The DNA activity is suggested by inheritance of the manifestation of conditional mutations according to a parental type. The parental type of inheritance (in a broad sense) emerges if a gene is active before meiosis and produces the gene product that loses the link with the gene that gave birth to it [26,27]. The gene material in the germline acquires the status of "active" thanks to ontogenes. The Mendelian protein-coding genes in germline cells are inactive. Thus, genetic instability [51,52], transposition of mobile elements [53-55], hybrid dysgenesis [56], epigenetic transformation [16,57], and "genome editing" [58], taking place during gametogenesis in the germline, can be rightly regarded as the events involving ontogenes [29].

Inbreeding depression and heterosis

Inbreeding in animals and plants leads to formation of weak progeny with a low fertility (inbreeding depression) [59]. An opposite phenomenon is the formation of strong and highly fertile progenies exceeding their parents (heterosis) [60]. The latter phenomenon is observable in the crosses of the remote relatives of the same species. The hypotheses on the mechanisms underlying inbreeding depression and heterosis are similar in that the cause is of a genetic nature. The difference is in the degree of homozygosity of the genome, which is maximal in the case of inbreeding depression and minimal in heterosis [61]. However, the mechanism that would explain how the level of homozygosity influences the habitus of progeny is so far vague. The phenomena of heterosis and inbreeding depression are already referred to as "a challenge to genetics" [62].

The very fact that ontogenes exist makes it possible to explain these phenomena. Thanks to ontogenes, genome emerges to be two-component, comprising the classical Mendelian genes and ontogenes. In the genome of a species, ontogenes are in a homozygous state. The procedure of maximal heterozygotization of the genome (production of hybrids of highly inbred parents) should lead to the situation when homozygous ontogenes are on the background of heterozygous Mendelian genes. *The resulting contrast* may enhance the recognition and switching on of homozygous ontogenes (the phenomenon of heterosis). On the contrary, the procedure of homozygotization of the genome should conceal the locations of homozygous ontogenes among similarly homozygous Mendelian genes. This may complicate the recognition and switching on of ontogenes (the phenomenon of inbreeding depression) [63,64]. The earlier hypotheses focused on different modes of function of a one-component genome as the cause of these phenomena and, alas, failed. As for our postulated hypothesis, the underlying cause consists in a two-component composition of the genome and the influence of the genes of one type on the function of the genes of the other type as early as the recognition of sequences.

Conclusions

Our research continues the classical genetic studies started by Mendel and actively performed now. Our work could not succeed without regard to the role of DNA in heredity and the knowledge about chromosomes and protein-coding genes. This information inspired the idea of the work and assisted in the interpretation of results. However, our research made a sharp turn from the beaten path in genetics, which focused on studying the genetics of alternative characters. In this way, we discovered the genes other than Mendelian ones, namely, ontogenes. In turn, ontogenes have made it possible to reveal the incompleteness of biological knowledge, based exclusively on Mendelian protein-

coding genes. It has become clear that the genetic research until recently has dealt only with the traits specifying intraspecific differences, omitting the traits that determine intraspecific similarity, which include the fundamental characteristics of the living. Until recently, only a protein side of the biological traits has been available for genetic research, whereas a cellular side, or in other words, the cellular architecture of organism, remained on the sidelines. The new genes, ontogenes, will assist in filling in these gaps in genetic knowledge and the advance in the ontogenetic and phylogenetic issues, waiting long for their resolution.

The results of our work give rise to reasonable doubt in the universality of the chemical modus operandi of genetic machinery. Some new facts favor a biophysical interaction between genes (kind of electromagnetic field–based interaction). The field-associated interaction in inanimate nature is a routine event and the fact that it is absent in the current genetic knowledge about animate nature does not look rationale. Our results and the changes in the energetics of the mutants for ontogenes [65,66] also suggest the existence of field-associated interaction.

Acknowledgements

This research was founded by the Ministry of Science and Higher Education of the Russian Federation via the Institute of Cytology and Genetics SB RAS (No. FWNR-2022-0015) for the microdissection and FISH analysis. The microscopy was performed at the Core Facility for Microscopy of Biological Objects, the Institute of Cytology and Genetics SB RAS (reg. No.3054), Russia.

References

1. Chadov BF, Chadova EV, Kopyl SA, Fedorova NB. A new class of mutations in Drosophila melanogaster. Dokl Biol Sci. 2000;373:423-426.
2. Chadov BF. Mutations in the regulatory genes in Drosophila melanogaster, in: Proc. Intern. Conf. Biodiversity and Dynamics of Ecosystems in North Eurasia, IC@G, Novosibirsk, August 21–26 (2000) 16–18.
3. Gaisinovich AE. The birth and development of genetics. Moscow: Nauka, 1988 (In Russian).
4. Chadov BF. Features of intraspecific similarity and peculiarities of Mendel's approach to study of heredity. Philos Sci. 2005;3(26):94-114. (In Russian).
5. Chadov BF, Chadova EV, Kopyl SA, Artemova EV, Khotskina EA, Fedorova NB. From genetics of intraspecific differences to genetics of intraspecific similarity. Genetika. 2004;40(9):1157-1172.
6. Chadov BF, Fedorova NB, Chadova EV, Khotskina EA. Conditional mutations in Drosophila. J Life Sci. 2011;5:224-240.
7. Fedorova NB, Chadova EV, Khotskina EA, Chadov BF. Conditional mutations: obtainment by the method of morphoses, in: V.A. Kunakh (Ed.), Topics in Experimental Evolution of Organisms. Kiev: Logos; 2010. Pp: 78-83 (In Russian).
8. 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.
9. 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.
10. Chadov BF, Chadova EV, Kopyl SA, Khotskina EA, Fedorova NB. Genes controlling development: morphoses, phenocopies, dimorphs and other visible expressions of mutant genes. Russ J Genet. 2004;40(3):271-281.
11. Chadov BF. Ontogenes in Drosophila melanogaster: genetic features and role in onto – and phylogeny, in: V.L. Korogodina, A. Chini and M. Durante (Eds), Modern Problems of Genetics, Radiobiology, Radioecology and Evolution, JINR, Dubna (2007) 80-91 (In Russian).
12. Ashburner M. Drosophila. A Laboratory Handbook, Cold Spring Harbor Laboratory Press, N.Y; 1989. Pp: 427-432.
13. Timoféeff-Ressovsky NW. Studies on the Phenotypic Manifestation of Hereditary Factors. I. on the Phenotypic Manifestation of the Genovariation Radius Incompletus in DROSOPHILA FUNEBRIS. Genetics. 1927;12(2):128-198.
14. Timofeeff-Ressovsky NV. Relation between gene and phenotypic character, in: O.G. Gazenko and V.I. Ivanov N.V. (Eds). Timofeeff-Ressovsky, Selected Works, Moscow: Meditsina; 1996. Pp: 59–84 (In Russian).
15. Chadov BF, Chadova EV, Fedorova NB. Conditional mutations in D. melanogaster: Specific features in localization and secondary mutation. In: Proceedings of the International Conference Chromosoma 2012; 2–7 September 2012. Russia: Novosibirsk; [In Russian]
16. Chadov BF, Chadova EV, Fedorova NB. Epigenetic phenomenology in conditional mutants of Drosophila melanogaster: morphoses and modifications, in: S.M. Zakijan, S.M. Vlasov, E.V. Dement'eva (Eds.), Epigenetics, SD RAN, Novosibirsk; 2012. Pp: 499–533 (In Russian).
17. Chadov BF, Chadova EV, Fedorova NB. Images of morphoses and modifications in Drosophila melanogaster conditional mutants. Mutation Research/Reviews in Mutation Research. 2015;765:40-55.
18. Chadov BF, Fedorova NB. Ontogenes and Chromosome Nondisjunction in the D. melanogaster Meiosis. Advances in Bioscience and Biotechnology. 2022; 13:317-335.
19. Chadov BF, Fedorova NB, Chadova EV. Parental effects of conditional mutations and their explanations. Russ J Genet. 2013; 49 (2):141-150.
20. Chadov BF, Fedorova NB. Conditional Mutations and New Genes in Drosophila, in: M. Fasullo and A. Catala (Eds) Mutagenesis and Mitochondrial-Associated Pathologies; 2020.
21. Chadov BF, Fedorova NB, Chadova EV, Khotskina EA, Moshkin MP, Petrovski DV. Genetic Mutation Affects Energy Status of Drosophila. Russian J Genet. 2010;46(9):1062-1066,.
22. Chadov BF. Mutations capable of inducing speciation, in: V.N. Stegnij (Ed.), Evolution Biology, Tomsk State University Press, Tomsk; 2001. Pp: 138–162 (in Russian).
23. Chadov BF, Fedorova NB. Ontogenes and the Genetics of Intraspecific Similarity. Medical Research Archives. 2021;9(4):2-10.
24. Serebrovsky AS. Animal Hybridization. Moscow–Leningrad: Biomedgiz; 1935. p. 290.
25. Lobashev ME. Distant hybridization. In: Genetics. Leningrad: Leningrad Gosudarstvennogo University; 1967. Pp: 491-518 (In Russian).
26. Chadov BF, Chadova EV, Fedorova NB. The Genetics of Conditional Mutations and Individual Developmental Program in D. melanogaster. SCIOL Genet Sci. 2017;1:3-21.
27. 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.
28. 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.
29. Chadov BF, Fedorova NB. Ontogenes and Their Role in Cellular

Construction. Advances in Bioscience and Biotechnology. 2023; 14:49-73.

30. Sokolov NN. Interaction of the Nucleus and Cytoplasm in Remote hybridization of Animals. Moscow: Nauka (1959) (In Russain).
31. Frizen G. Roentgenmorphoses in Drosophila. Biol Zh. 1935;4:687-704 (In Russian).
32. Rapoport IA. Specific morphoses induced in Drosophila melanogaster by chemical compounds, Biull Eksp Biol Med. 1939;7:415-17. (In Russian).
33. Rieger R, Michaelis A, Green MM. Glossary of Genetics. Classical and Molecular. Berlin: Springer-Verlag; 1991. Pp: 553.
34. Ashburner M. Drosophila. A Laboratory Handbook, N. Y.: Cold Spring Harbor Laboratory Press; 1989. PP:1065—1074.
35. Chadov BF, Fedorova NB. The Mutations Disturbing the Bilateral Symmetry in Drosophila. SCIOL Genet Sci. 2019;2:139-152.
36. Chadov BF. Nonhomologous Chromosome Pairing in Oogenesis of Drosophila melanogaster, Abstract of Dissertation for the Degree of Ph.D in Institute of Developmental Biology, Moscow, 1971 (In Russian).
37. Fedorova NB, Chadov BF. Gene interactions in Drosophila without contacts and chemical intermediaries, in: Abstracts Book of the International Conference on Cell and Experimental Biology (Virtual Conference), December 9-11, 2020, p. 6.
38. Chadov BF, Fedorova NB. Ontogenes and the paradox of homologous pairing. Advances in Bioscience and Biotechnology. 2021;12:1-9.
39. Blyumenfel'd LA. Abnormal magnetic properties of nucleic acids. Biofizika. 1959;4(5):515–519. (In Russian).
40. Arnold AR, Grodick MA, Barton JK. DNA Charge Transport: from Chemical Principles to the Cell. Cell Chem Biol. 2016;23(1):183-197.
41. Holmlin RE, Dandliker PJ, Barton JK. Charge Transfer through the DNA Base Stack. Angew Chem Int Ed Engl. 1997;36(24):2714-2730.
42. Polesskaya O, Guschin V, Kondratev N, et al., On possible role of DNA electrodynamics in chromatin regulation. Prog Biophys Mol Biol. 2018;134:50–54.
43. Savelyev IV, Zyryanova NV, Polesskaya OO, Myakishev-Rempel M. On The Existence of The DNA Resonance Code and Its Possible Mechanistic Connection to The Neural Code. NeuroQuantology. 2019;17(2):56-71.
44. Savelyev IV, Myakishev-Rempel MV. Possible traces of resonance signaling in the genome. Prog Biophys Mol Biol. 2020;151:23–31.
45. Fedorova NB, Chadova EV, Chadov BF. Genes and Ontogenes in Drosophila: The Role of RNA Forms. Transcriptomics. 2016;4:137.
46. Chadov BF, Fedorova NB. The Elementary Event of Development. Doklady Biological Sciences. 2003;389:183–187.
47. Chadov BF, Chadova EV, Fedorova NB. Ontogenes and the Problem of Speciation. Journal of Evolutionary Science. 2019;1:33-47.
48. Chadov BF, Chadova EV, Fedorova NB. Orthogenesis and Darwinism: Perspective of their synthesis in light of the conditional mutations data. Modern Problems of Evolution and Ecology. Proceedings of the XXX Lubishev's Reading. March 30--31, 2017. Ulyanovsk (Russia): UlGPU. P. 133-142 (in Russian).
49. Chadov BF, Fedorova NB. Zygotic selection in Drosophila melanogaster and a new edition of Darwin's concept of specification. In: Evolution of Life on the Earth: Proceedings of the V International Symposium, November 12-16, 2018, Tomsk. 49-51. (In Russian).
50. Auerbach Ch. Mutation Research: Problems, Results, and Perspectives.Springer, New York; 1976.
51. Chadov BF, Chadova EV, Khotskina EA, Fedorova NB. Mutation in the ontogene – genome instability – appearance of new forms. In: "Evolution Biology" (ed. V.N. Stegniy). Tomsk: Tomsk State University; 2005. Pp: 92-106. (In Russian).
52. Chadov BF, Chadova EV, Khotskina EA, Fedorova NB. Conditional lethal mutations shift the genome from stability to instability. Russ J Genet. 2009;45:276–286.
53. Fedorova NB, Chadova EV. Mutation in ontogene causes transposition of retrotransposon 412, In: V.A. Kunakh (Ed.), Factors of Experimental Evolution of Organisms, Logos, Kiev; 2008. Pp: 210–215 (In Russian).
54. Finnegan DJ. Eucaryotic Transposable Elements and Genome Evolution. Trends in Genetics. 1989;5:103-107.
55. Ratner VA, Vasil'eva LA. Induction of Transpositions of Mobile Genetic Elements by Stress Impacts. Sorosovskii Obrazovatel'nyi Zhurnal. 2000;6:14-20. (In Russian)
56. Ashburner M. Hybrid Dysgenesis and Related Phenomena. In: Drosophila. A Laboratory Handbook. Cold Spring Harbor Laboratory Press, Cold Spring Harbor. NY; 1989. Pp: 969-1015.
57. Russo VEA, Martienssen RA, Riggs AD, Briggs AD, Eds. Epigenetic Mechanisms of Gene Regulation. Cold Spring Harbor Laboratory Press, New York; 1996.
58. Baranov VS, Kuznetsova TV, Pendina FF, et al. Epigenetic Mechanisms in Human Normal and Pathological Development. In: Zakijan, S.M., Vlasov, S.M. and Dement'eva, E.V., Eds., Epigenetics, (2012) SD RAN, Novosibirsk, 225-266 (In Russian).
59. Mather K. Variation and selection of polygenetic characters. Journal of Genetics. 1941;41:159-93.
60. Shull GH. Experiments with maize. Botanical Gazette. 1911;52:480-5.
61. Strunnikov VA. The Nature and problems of heterosis. Priroda (Moscow). 1987;5:64-76.
62. Strunnikov VA, Strunnikova LV. Heterosis Can Be Fixed in the Progeny. Priroda (Moscow). 2003;1:3-7.
63. Chadov BF, Fedorova NB. Inbreeding Depression and Heterosis as the Phenomena of Two-Component Genome. Advances in Genetics Research. 2020;19(5):161-190.
64. Chadov BF. Inbreeding Depression and Heterosis: Explanation by Two-Component Genome Composition. SCIOL Genet Sci. 2018;1:41-44.
65. Chadov BF, Fedorova NB, Chadova EV, Khotskina EA, Moshkin MP, Petrovski DV. Genetic Mutation Affects Energy Status of Drosophila. Russian Journal of Genetics. 2010;46:1062-1066.
66. Fedorova NB, Chadov BF. Genetics: the energy aspect, Regional Interdisciplinary Conference - Humboldt Kolleg «Energy conversion: from nature to technology», 28 August – 2 September. 2016, Novosibirsk, Russia.