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Beyond Mendel and Morgan to the dynamic genome[1]

The conceptional shifts on genome organization and hereditary variability occurred during transition from classical mendelian to current mobile or dynamic genetics. The main changed premises of this transition are firstly presented in detail. Mendelian genetics mainly conceived genome as the set of chromosomes with of all genes. Now genome semantics is changed. It comprises entire hereditary constitution of the cell, including both structural and dynamic aspects of coding, storage and transfer of species-specific information. There are three kinds of heritable changes: mutations, variations and epigenetic alterations. It is reasonable to discriminate in the genome two subsystems: Obligate genetic elements (OGE) and Facultative genetic elements (FGE). FGEs comprise various kinds of repeated DNA, mobile elements, amplicons, inserted viral and foreign DNA, B-chromosomes and cytobionts. FGEs are predominant genome content of many plants. The number and cell topography of FGEs are different in different cells/tissues and most eukaryote individuals. Changes in the structure or order of OGEs correspond to classical mutations. Various changes in FGEs it is reasonable to call variations. Facultative elements and their variations are the first genomic reaction on biotic and environmental challenges. Together with epigenetic alterations they implement the operational genomic memory. Three template genome processes Replication, Transcription, Translation and three basic genetic processes – Repair, Recombination and Segregation are capable to facultative expression according to principle: the unity of the whole and freedom of the parts. This is the essence of the presented generalized concept of the genome organization and hereditary variations.

Key words: *genome organization, conceptual shifts, mobile genetics, non-Mendelian inheritance*

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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От Менделя и Моргана к динамическому геному[2]

При переходе от классической менделевской генетики к современной мобильной, или динамической, генетике произошли концептуальные сдвиги во взглядах на организацию генома и наследственную изменчивость. В данной статье эти сдвиги детально проанализированы. Менделевская генетика в основном рассматривала геном как набор хромосом со всеми генами. Теперь семантика генома изменилась. Она охватывает всю наследственную конституцию клетки, включая структурные и динамические аспекты кодирования, хранения и передачи видоспецифичной информации. Существуют три основных типа наследственных изменений: мутации, вариации и эпигенетические альтерации. В структуре генома следует выделять две подсистемы: Облигатные генетические элементы (ОГЭ) и Факультативные элементы (ФГЭ). Изменения в структуре, числе или в порядке расположения ОГЭ соответствуют классическим мутациям. ФГЭ включают разные виды повторенной ДНК, мобильные элементы, амплифицированные сегменты, встроенную вирусную и чужеродную ДНК, В-хромосомы и цитобионты. ФГЭ преобладают в геноме многих видов растений. Различные изменения в ФГЭ разумно называть вариации. Факультативные элементы и их вариации являются первой геномной реакцией на биотические и средовые вызовы. Вместе с эпигенетическими изменениями они образуют операционную память генома. Три матричных геномных процесса – репликация, транскрипция, трансляция, и три основных генетических процесса – репарация, рекомбинация и сегрегация способны к факультативному выражению, что соответствует эволюционному принципу: единство целого при свободе частей. В этом один из главных аспектов представленной обобщенной концепции организации генома и наследственной изменчивости.

Ключевые слова: *организация генома, концептуальные сдвиги, мобильная генетика, неменделевское наследование*

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Appreciation of the various degrees of reassortment of components of a genome that appear during and following various type of genome shock, allows of degrees of freedom. In the future attention undoubtedly will be centered on the genome as a highly sensitive organ of the cell, monitoring genomic activities and correcting common errors, sensing the unusual and unexpected events, and responding to them, often by restructuring the genome.

Barbara McClintock. Nobel lecture, 1983

Introduction

Let me give a brief outline of the situation in genetics when transition to dynamic genome concept has occurred. The epigraph of outstanding geneticist Barbara McClintock reflects an essence of the dynamic genome concept (Fedoroff, Botstein, 1992).

Three types of discovery may be distinguished in the development of scientific knowledge: experimental, conceptual, and methodological. For instance, the existence of chloroplast DNA was confirmed in 1962 by electron microscopy method together with experiments. A methodological revolution in molecular genetics took place since mid-1970s. I mention here some examples.

The method of individual DNA fragments developed by E.M. Southern in 1975. He transferred DNA fragments that hybridized to radioactive RNA and the hybrids detected by autoradiography. The first entire genome of the phage phiX174 was deciphered in 1977. W. Gilbert used genetic engineering methods to make a bacteria synthesize proteins (insulin and interferon) via recombinant DNA. In 1985, K.B. Mullis developed method of the polymerase chain reaction (PCR) for quickly amplifying desirable DNA segment. The possibility to analyze the structure of genes and chromosomal fragments at the DNA level led to many unexpected discoveries (King et al., 2006).

At the same time, there are essential conceptual innovations and discoveries, including a new semantic, linguistic, or symbolical presentation of knowledge. They present clear statement of the problems calling for experimental proof, as well as suitable systematization of a set of facts and new empirical generalizations (Polanyi, 1962). The brilliant double helix model of DNA that was suggested in 1953 by J. Watson and H. Crick is a very well-known example.

Even a term coined for pure linguistic convenience often becomes a potent scientific importance. In 1909, the Danish botanist and geneticist Wilhelm Johannsen invented a short term “gene” and created two basic derivative terms – genotype and phenotype. He wrote in 1911: “It is desirable to create a new terminology in all cases where new or revised conceptions are being developed (Johannsen, 1911. P. 132). In 1926, he was surprised that his “catchword” gene was materialized in Thomas Morgan’s chromosomal theory (Golubovsky, 2000; Beurton et al., 2000).

Conceptual discoveries may coincide with experimental data obtained. This was the case with Gregor Mendel. Indeed, the formulation and experimental demonstration of the laws of inheritance in hybrids was not all that Mendel did in genetics. Mendel also developed clear principles of genetic analysis of hybrid offspring and introduced the literal denotation that is used in this analysis. In a sense, Mendel’s

system of denotation proved to be even more invariant and universal, because it is still used in prokaryotes when the classical mendelian analysis is inapplicable. Crucial Mendel's conceptual discovery consists of suggestion of pairs of hereditary factors, which don't mix in hybrids and segregate in equal number in both parents. Hereditary factors pairing suggested by Mendel – chromosome pairing in meiosis – replication and transcription of DNA double helix manifests the mainstream of genetics development from the middle of XIX up to middle of XX century (Golubovsky, 2000).

Conceptual discoveries are sometimes the result of a nontrivial approach to the facts long since established. The importance of conceptual discoveries for development of genetics is considered much less frequently. Interesting example is the concept of gene dosage compensation developed by Herman Muller in the 1950s. Before Muller, nobody discerned the fundamental genetic significance of the simple fact that X-linked color eye mutations in Drosophila are equally expressed in males (one dose of the gene) and females (two doses of the gene). Dosage compensation mechanisms in plants evolution were recently reviewed (Muyle et al., 2022). Another example. A. Olovnikov (Olovnikov, 1973) was the first recognizing the problem of telomere shortening and predicted the existence of a chromosomal telomere repeats and telomerase, its special role in cell divisions and in ontogeny.

There is astonishing delay period in about 25–30 years in recognition of many essential conceptual discoveries. This delay seems invariant in the history of science. There was a delay in recognition of classical Mendel's discovery. Similar delay occurred many decades later in recognition of mobile controlling elements postulated by Barbara McClintock. Two paradoxical ideas, were put forward by McClintock in 1950s, contradicting with classical genetics. First, a mutant event of definite gene may be connected not with change of the gene itself, but due to inserted mobile element that regulate this gene expression. Second, assumption of diverse transposable elements capable to induce mutations and chromosome rearrangements. First detailed experimental data confirming her conception were presented in 1951 and then in a series of relevant reports (McClintock, 1951, 1978). Most geneticists had no doubts to McClintock's experimental data but perceived her conception as a curiosity occurring only in some maize lines (Fedoroff, Botstein, 1992).

Famous geneticist Melvin Green described similar skeptical situation. After studying of unstable mutations in the *white* locus of Drosophila, he published in the 1969, a report demonstrating that the regulatory region of this gene is transposed to other chromosome. Green was discouraged by the absence of requests for copies and any interest in his discovery. When he visited McClintock in her laboratory and complained at this circumstance, she replied that Green should not worry too much, because there was nothing unusual about his article on transposition. Scientists were merely not read it (Green, 1969, 1992).

McClintock said that she herself ceased publishing her results in genetic journals in 1964, because nobody read what she wrote. However, by the late 1970s, the conceptual background was changed. In 1977, collaborative article presented by M. Green in Proceedings Natural Academy Sciences USA (Golubovsky et al., 1977), in which multiple unstable mutations from natural Drosophila populations were attributed to insertions of MEs was even noted by the science columnist of The Times (London) newspaper.

In 1972 a molecular discovery of inserted mutations in *Escherichia coli* was made simultaneously in Germany (H. Saedler and P. Starlinger) and J. Shapiro (USA). Peter Starlinger remembered that his first review on insertion

mutagenesis in bacteria published in 1972 did not attract much attention. However, in 1977, when he presented a lecture in Cold Spring Harbor, there was hardly enough room for all comers. Then in 1984, maize mobile elements Ac and Ds, firstly found by McClintock, were cloned in the laboratory of Starlinger (Saedler, Starlinger, 1992).

In respect of the importance of conceptual innovation, there is remarkable example of Walter Gilbert's short article "Why gene in pieces". It was published in the section News and Views of *Nature* in 1978 (Gilbert, 1978). It remained one of the most frequently cited publications on molecular genetics for about a decade. The article did not contain any new data but was crucial from the conceptual viewpoint. Gilbert coined two important terms, exon and intron, and explained their meaning. The eukaryotic exon-intron gene concept made it possible to understand the essence of several unexpected experimental discoveries made in different laboratories in 1976–1977. Gilbert touched on the key points of transition from the classical to modern views on eukaryotic genes. It explained the observed paradox of the absence of a linear correspondence between genes size at the DNA level and the proteins size controlled by them. Gilbert briefly demonstrated theretofore unknown pathways of gene expression, variability of transcription units and the mechanism whereby new constructions arise through combination of intragenic blocks faster than by gradual changes of DNA bases.

We can see how amazing these facts and concepts were from the confession that Francis Crick, a coauthor of The Double Helix, made soon thereafter. Crick wrote that, when he came to California in September 1976, he could not even imagine that a common gene could be split into several pieces, and he doubted that anyone suspected it could (Crick, 1979).

The discovery of the split structure of eukaryotic genes was one of the most unexpected events in genetics. The terms exon, intron, and splicing rushed into genetics after Gilbert's article, signifying the transformation of the generally accepted views. For example, it became possible to answer the enigma as to why, in higher organisms (e. g., the fruit fly and maize), many functionally integrated genes have the molecular sizes that are an order of magnitude greater than those expected (necessary) for encoding an average protein.

In addition to the exon/intron structure, I indicate important discovery made in 1977–1978, an artificially induced amplification of DNA segments. These segments proved to be able to amplify in chromosomal loci and also to "detach themselves from the bosom" of their chromosome, assume different cytoplasmic embodiments, and autonomously replicate. This was demonstrated in the studies by R. Schimke and coworkers on the selection of cells for resistance to cytostatics and toxins. Interestingly, some attentive cancer cytogeneticists observed amplicons as minichromosomes in the cytoplasm long before 1978 but considered them artifacts. The researchers were forced to think so because replication of loci outside chromosomes was implicitly forbidden (Schimke, 1989).

"Technological and conceptual breakthrough" occurred in our understanding of plant genome structure and evolution in recent years. It was shown that flowering plants manifest extraordinary variation in size and their set of genomic elements. Most plant species exhibit cyclical evolutionary episodes of genome doubling following by fractionation and genomic restructuring. These phenomena are mostly result of proliferation and loss of transposable elements mediated by small RNAs (Wendel et al., 2016).

I would like to summarize here the basic premises (paradigms) which occurred from Mendelian to Mobile genetics transition. It comprises eukaryotic genome structure and function and the pattern of hereditary variations. I will present the current generalized genomes

concept on genome organization and function. It contemplates a genome as an ensemble of both obligate and facultative genetic elements. Facultative traits in the genome structure and function reflects the general principle of evolution: the unity of the whole and the freedom of parts (Golubovsky, 2011).

Genome semantics and cell informative system

The term "genome" was coined by German botanist Hans Winkler in 1920 to designate the haploid set of chromosomes together with cytoplasm for a species. The term was used for an analysis of allopolyploid species or for such mutations as chromosome number variation (polyploidy and diploidy). Then its meaning widened to include the entire hereditary constitution of the cell, including both structural and dynamic aspects of the coding, storage and transfer of species-specific hereditary information.

Since classical studies of Monod and Jacob in the earlier 1960s, it has been evident that the genome contains not only blueprints, but a coordinate program of protein synthesis and cell function (Jacob, Monod, 1961). The holistic aspects of species-specific hereditary systems might be viewed metaphorically as the structural design of a temple that cannot be understood by studying separate breaks, genes, at one point. The discoverers of the operon and principles of gene regulation entitled their generalization: "Teleonomic mechanisms in cellular metabolism, growth, and differentiation" (Monod, Jacob, 1961). To preserve intracellular homeostasis and the adaptive response of the genome to environmental challenges, they emphasized the biological purposefulness or the teleonomy of cell regulatory system.

Molecular discoveries of signal transduction pathways and chromosome organization have shifted focus from genes as units of heredity and function to the genome as a complex dynamic system. The ability of a cell to analyze external and internal conditions (and to control growth, movement and differentiation) can be compared with an information computing network and checkpoints. By means of signal transduction pathways a cell receives external signals and transmits, amplifies and directs them internally. Each pathway includes a signal receiving receptor, membrane or cytosolic proteins including kinases and phosphatases to convey the signal, and key transcription factors capable of switching their states, activating or suppressing transcription of particular genes.

DNA repair systems remove damages. Multiple proofreading mechanisms recognize and remove errors that occur during DNA replication or due to mutagens. Repair systems allow the cells not to be passive victims of random physical and chemical forces. They control the level of mutability by modulating the repair system activity.

Mobile elements (MEs) found now in all eukaryote genomes code the transposition enzymes and contain genetic punctuation signs (promoters, enhancers, transcription termination signals, etc.), which regulate gene expression and promote the appearance of new constructs. The term "Natural Genetic Engineering", coined by J. Shapiro (Shapiro, 1992, 2002), emphasizes that living cells use the same enzymes (nucleases, ligases, reverse transcriptases and polymerases) to reshuffle the genome and its function as biotechnologists. Though MEs are repetitive and dispersed on different chromosomes, they can be activated simultaneously by one relevant cell signal.

Genome structure: obligate and facultative genetic elements and their interactions

Data on molecular genome analysis of various eukaryotes obtained up 1980s (including my and coworkers long term studies of insertion

mutations in natural *Drosophila* populations) led me to conclusion that eukaryotic genome can be inartificially subdivided on two subsystems: Obligate and Faculative genetic elements (OGE and FGE). OGE (gene/genetic loci) have normally definite chromosome position and definite number in most individuals of one species (except cases of inversions/translocations population polymorphism). FGEs include the hierarchy of intra and extra chromosomal elements in nucleus and cytoplasm (Golubovsky, 1985, 2000; Golubovsky, Manton, 2005).

In contrast, FGE may have diverse number and chromosome/cell topography in different eukaryotic individuals, different tissues and even in daughter cells. And their number and cell topography may drastically change depending on environmental and genetic background, especially in stress conditions.

Nuclear FGEs comprise a highly repeated DNA sequences, pseudogenes and retrotranscripts, transposons, amplicons, an additional, or B-chromosomes devoid of structural genes and widespread among flowering plants. In cytoplasm, FGEs include plasmids, amplified rod and circular DNA/RNA segments, endosymbionts or cytobionts like sigma virus in Drosophila and like bacteria Wolbachia in many invertebrates (Golubovsky, 2000; Golubovsky, Manton, 2005).

OGEs and FGEs exhibit different patterns of heritable changes. Mutations in their classical sense are changes in structure, position and number of chromosomal genes, chromosome rearrangement and genome mutations like polyploidy. These events constitute OGEs. Diverse changes concerning FGEs are referred to as *variations* (see Figure 1).

From this concept let us consider the molecular structure of the best studied human genome. Coding sequences (protein genes together with rRNA and tRNA) constitute about 5% of all DNA. 15–20% is connected with gene/chromosome expression regulation. At the same time the FGEs occupy about 50% of the genome and include highly repetitive sequences, duplication of chromosome segments, and distinct MEs of various types: three kinds of retroelements (LINE, SINE including Alu) and one class of transposons. Segmental duplications of 1–200 kb blocks are the remarkable feature of the human genome and comprise about 3.3% of all DNA. Other repetitive elements are simple sequence repeats (SSRs): short repeated units, or microsatellites (1–11 bp), and longer SSRs, or minisatellites (14–500 bp). SSRs, comprising ~3% of the genome, are important in human genetic studies because they show a higher degree of length polymorphism in populations and are helpful for molecular localization. The human genome includes also several families of human endogenous retroviruses dispersed on chromosomes (Lander et al., 2001).

In plants, retrotransposons in many cases comprise over 50% of nuclear DNA. Plant ME are similar in principle to the elements in other eukaryotes (Lisch, 2012; Wendel et al., 2016).

Changes in the number and chromosome/cell topography of the FGEs are drastically different from gene mutations. Wollman and Jacob were the first who studied similar hereditary changes in the phage-bacteria system and called them variations. They concluded that any forms intermediate between virus and normal cellular genetic determinants may appear. Episomes (plasmids) may or not be present in the cell. Once in the cell, they may be located in the chromosome or cytoplasm and may be exogenous or pathogenic. They draw bridges between nuclear and cytoplasmic heredity, and cell physiology and pathology (Jacob, Wollman, 1961).

The numerous variants of genome interaction in lambda phage – *E. coli* bacteria system proved to be essentially similar to the behavior of MEs in yeast, fruit fly, and maize, as well as the behavior of retroviruses in the genomes of mammals, including humans. Hereditary variations in

eukaryotes mediated by FGE are frequent evolutionary phenomenon (Golubovsky, 2000).

All these facts justify subdivision of eukaryotic genomes on two subsystems OGE and FGE. They lead to conclusion that the diversity and assemblage of self-reproducing hereditary elements of the nucleus and cytoplasm should be analyzed in terms of intracellular population genetics (Khesin, 1984). Similar conceptual approach lead recently to the term *pangenome*. It is defined as the set of all genes, present in a given species. It can be subdivided into *core* genome present in all individuals and *accessory* genome present only in some individuals (Brockhurst et al., 2019).

These facts also lead to recognition of various non-canonical, non-Mendelian forms of genetic variability. Hereditary changes may be caused by changes in the distribution of (i) different forms of molecular plasmids, (ii) different forms of amplified DNA segments, and (iii) different distribution of facultative elements among daughter cells. Finally, genotypic differences may be caused by changes in the ratio between the cytoplasmic regulatory molecules that either control the self-reproduction of the facultative elements or switch the system into another hereditary mode of operation (McClintock, 1984).

A typical example is the phenomenon of hybrid dysgenesis discovered in Drosophila in the F1 hybrid from crosses of paternal P-stock containing active P-transposons with females of M stocks devoid of P-active copies of cytoplasmic repressor. Numerous P-transpositions occur in the germ line, accompanied by multiple insertion mutations and rearrangements. Their incidence in the F1 progeny of dysgenic crosses may reach about 10% (!). Chromosomal breaks in cases of PM hybrid dysgenesis are ordered and site specific: they occur near various P-site locations. Thus, multisite inversions occur in dysgenic hybrids as often as single ones according to the first such cytogenetic observation (Berg et al., 1980). It was absolutely unexpected and unbelievable event in the tenets of classical cytogenetics. Recent studies have revealed that small RNA piwi can control splicing of the P element pre-mRNA (Ghanim et al., 2020).

These facts are very important for understanding the amazing phenomenon of secondary diploidisation in plant polyploidy species. The return to diploidisation is usually accompanied by multiple chromosomal rearrangements (deletions, inversions, translocations) that can be mediated by omnipresent transposable elements (Wendel et al., 2016; Rodionov, 2022).

In many cases there is a two-step mechanism of the spontaneous mutation occurrence in nature. First, there is activation of mobile elements (significant part of FGE) in response to diverse environment challenges. Second, FGE-mediated insertion mutations and chromosome rearrangements occur.

Variations or hereditary changes in the FGE subsystem can be induced by nonmutagenic environmental and biotic factors such as food/ temperature fluctuations or interline and interspecies hybridization. The nuclear DNA of certain flax lines can drastically vary within a single generation under specific nutrient development. The varieties occur across the whole spectrum of the DNA sequencies - highly repeated, middle and low repeats, including ME elements. At the same time, these DNA changes are site specific and accompanied by definite phenotypic hereditary variations, so called plant genotrophs (Cullis, 2005). Relevant modern data on environmental stress and transposition in plants are reviewed by Ito (Ito, 2002).

Typical examples of variation are changes in the ratio between OGEs and FGEs. These changes accompany the above mentioned phenomenon of amplification of definite chromosomal segments during the development or in the course of adaptation of somatic cells to drugs that block cell division (Schimke, 1989). Amplified segments,

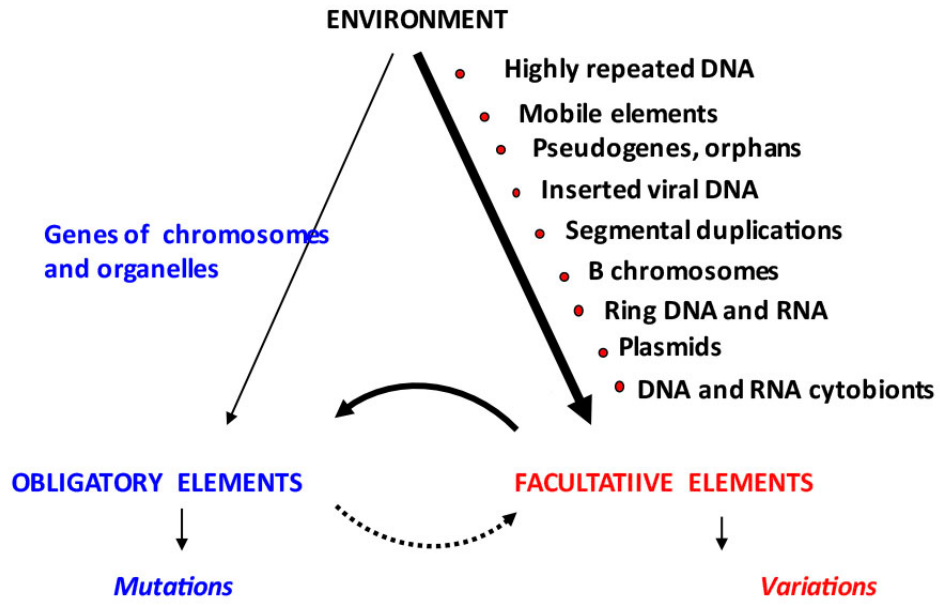

Figure 1. Obligatory and Facultative genetic elements in the eukaryotic genome and two types of hereditary changes: mutations and variations.
Arrows indicate the direction of the links, while their width corresponds to the intensity of their force. Most facultative genetic elements are more sensitive to the environment, and their activation leads to the gene/chromosome insertions and mutations. FGE-mediated hereditary changes may occur simultaneously in many individuals (Golubovsky, 2000, 2011)

Рис. 1. Облигатные и факультативные генетические элементы в геноме эукариот и два типа наследственных изменений: мутации и вариации.
Стрелки указывают направление и характер связей, а толщина стрелок отражает интенсивность их действия. Факультативные генетические элементы более чувствительны к вызовам среды, и их активация может вести к ген/хромосомным инсерциям и мутациям. Наследственные изменения, опосредованные факультативными элементами, способны происходить одновременно у многих особей (Golubovsky, 2000, 2011)

or amplicons, can exist as tandem duplications or be transformed into plasmids or even mini-chromosomes, capable of autonomous replication in cytoplasm. Both the number and topography of amplicons may vary over cell lines. The exact number of amplified facultative DNA segments cannot be determined even in daughter cloned cells.

Template and basic genetic processes and their facultative character

The occurrence and fixation of new hereditary information are implemented via two triades of genetic events existing both in prokaryotes and eukaryotes: template and basic genetic processes. Template processes include Replication, Transcription and Translation. Basic genetic processes include Recombination, Repair and Segregation. To be inherited, all DNA changes need to go through both template and basic genetic processes (!). The number of genes *E. coli* established in 1990s was 4.228. Of them, 115 (2.7%) are involved in replication, recombination and DNA repair; 55 (1.3%), in transcription, synthesis and RNA modification; 182 (4.2%), in translation and posttranslation protein modification; 21, in ribosomal r-RNA synthesis; and

tRNA (Blattner et al., 1997).

After next 25 years of genetic studies more exact data were established. Thus we may compare in the first approximation the gene number involved into template and basic genetic processes both in bacteria and plant.

It is interesting that number of genes involved in such evolutionary conservative process as DNA replication is equal both in prokaryote and eukaryotes. But in eukaryotes there is sharp increase of genes involved in transcription, RNA modification and translation processes (Table 1).

Seems it manifests the more sophisticated regulation levels of these basic cell genetic functions.

There are a lot of examples of facultative pattern in the cellular implementation of template and basic genetic processes. First, facultative overreplication or under replication of chromosomal segments enriched in DNA repeats (heterochromatin areas). Amplification of definite segments under cytostatic stress is an example of local DNA overreplication during development or in the cases of environmental challenges

Table 1. Gene number

(The relevant modern data for this table were kindly presented by geneticist P.M. Zhurbenko through professor A.V. Rodionov (personal communication). I express my sincere gratitude)

Таблица 1. Число генов

(Современные данные для этой таблицы любезно предоставлены генетиком П.М. Журбенко через профессора А.В. Родионова (личное сообщение). Выражаю им искреннюю благодарность).

	Gene number			
	Bacteria *Escherichia coli*		Potato *Solanum tuberosum*	
DNA replication	55	0.85%	51	0.09%
DNA transcription	68	1.05%	99	0.18%
RNA modification	7	0.11%	279	0.50%
Translation	135	2.09%	528	0.94%
DNA recombination	94	1.45%	28	0.05%
DNA repair	69	1.07%	125	0.22%
	Total genes	6463	56112	

About 60% of genes in humans are capable of alternative transcription and alternative splicing, depending on specific tissue or cell/ tissue physiology. In Arabidopsis plant about 20% of genes manifest alternative splicing (Kim et al., 2007). This ability is based on the existence of two or more promoters and the exon/intron structure of eukaryotic genes.

Facultative translation is reliably proven in yeast. With the presence of protein Sup35, which controls a subunit of the translation termination complex and exhibits prion features, ribosomes begin to read through stop codons in an appreciable proportion of cases. This releases a hidden genetic variation and creates a variety of new phenotypes, particularly, under stress conditions (Tyedmers et al., 2008). The discovery of prion proteins capable of transferring their structure in a series of cell generations adds the matrix principle of genetics (Inge-Vechtomov, 2015).

DNA repair is the main guardian against diverse errors and injuries of the DNA structure. In addition to normal mechanisms of the repair process, there are facultative ones: photoreactivation, excision and postreplicative repair. Facultative recombination includes such variants as sitespecific recombination and replicative transposition of LTR containing ME. The segregation process as the necessary final

of mitotic and meiotic divisions might be also facultative. It occurs in the case of definite genetic factors as Segregation Distortion or in the cases of chromosomal rearrangements as in the *Oenothera* species, studied by classic of genetics Hugo de Vries.

Epigenetic alterations and the logic of the epigene

The dynamic aspects of the coding, storage and transfer of genetic information are called epigenetic. Clear conceptual discrimination between genetic and epigenetic control systems was made by the protozoologist and geneticist David Nanney as early as 1958 (Nanney, 1958). He underscored several diagnostic assumptions which point to the action of cellular epigenetic control systems: cells with the same genetic material can manifest different phenotypes; the genetic potentialities of a cell are expressed in integrated patterns when the expression of one specific trait prevents the expression of others; particular patterns of expression can be specifically induced; epigenetic alterations, although specifically induced, may be perpetuated in the absence of the inducing conditions (ciliate serotypes and mating type); some epigenetic devices are located in the nucleus. Nanney emphasized that epigenetic states and their repertoire were limited "by the information available in the genetic library".

Robert Holliday was the first who in 1985 proposed for epigenetic alteration the term *epimutation*. He associated DNA methylation with heritable alteration in gene expression (Holliday, 1987). The spectrum of epigenetic inheritance is very wide. It includes gene and chromosome imprinting, developmental genome reprogramming, and control of chromatin structure and dynamics. There are at least four main types of epigenetic inheritance systems: (i) self-sustaining metabolic loops; (ii) chromatin marking mediated by histones and DNA-binding proteins; (iii) microRNA and small interfering RNA-mediated variation in gene expression and (iv) inheritance of some preexisting cellular structures (membrane) and some protein structures, prions (Stillman, 2005; Jablonka, Lamb, 2008).

Since the middle of 1970s, the concept of an epigene as a unit of epigenetic inheritance and epialleles has been developed by Rustem Tchuraev. This fruitful idea was experimentally validated by an artificial epigene synthesis (Tchuraev et al., 2000; Tchuraev, Galimzyamov, 2009). The epigene is an autoregulatory hereditary unit, a genetic system with cyclic links, or feedback, having two or more functional states and able to maintain each other over cell generations. Figure 2 presents a simple one component epigene scheme. It demonstrates the possibility of switching (transactivation) from the inactive to active epigene state in cell epiheterozygotes. Such hereditary switching will correspond to epimutation, displaying non-Mendelian inheritance.

Noteworthy, if we imagine five independent epigenes in the genome, the cell will manifest 32 potential states without any structural changes in DNA sequences (!). The feedback can be positive, as in the *E. coli* – lambda phage system with the positive or negative. The state of the one gene determines the genetic switch between the lysogenic or lytic lambda phage cycles. Diverse mechanisms that can underline the stable epialleles in plants were recently summarized (Tikhodeyev, 2018).

Similarly, transposons *P* in Drosophila and maize *Ac* and *Spm* mobile elements described by McClintock are organized as the epigenes with positive/negative regulation (Golubovsky, Tchuraev, 1997).

The Figure 2 epigene scheme is the simple and single component system where the structural gene and its regulator are combined in one transcription unit. But regulator factor may be

located distantly and lead to trans-silencing in epiheterozygotes. Namely this situation appeared typical for an enigmatic phenomenon of paramutation.

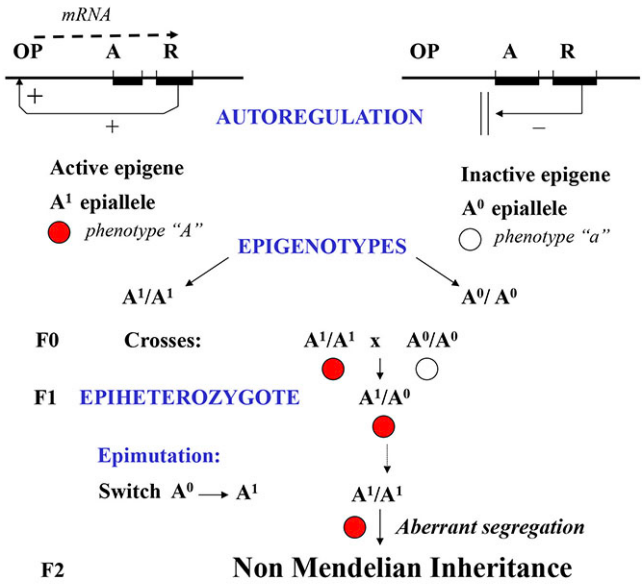

Fig. 2. The scheme of the epigene with positive autoregulation and main its definitions.
The structural gene A, controlling trait "A" (red circle) and its positive R-regulator are in one transcription unit. The epigene has two states or *epialleles*: active and inactive when R- regulator product is blocked, resulting in "a" trait. In *epiheterozygote* transactivation is possible and switch of inactive epiallele state to active (*epimitation*). This leads to non-Mendelian inheritance with absent or abnormal segregation in the F2 progeny.

Рис. 2. Схема эпигена с позитивной авторегуляцией, основные обозначения и определения.
Предполагается, что структурный ген А, который контролирует доминантный признак «А» (красный кружок) и его позитивный ген регулятор R находятся в одной единице транскрипции и образуют эпиген. Он имеет два состояния или эпиаллеля: активное А1 и неактивное А0 и два эпигенотипа А1 / А1 и А0 / А0. Когда продукт регулятора R блокирован (справа), это приводит к рецессивному фенотипу «а» (белый кружок). У эпигетерозигот А1 / А0 возможна трансактивация эпиаллеля А0. Это явление называют эпимутация. Превращение у эпигетерозигот неактивного состояния эпиаллеля в активное – неменделевское событие. В этом случае в следующем поколении возможно неменделевское расщепление ввиду перехода неактивного эпиаллеля А0 в активный А1

It was firstly described by remarkable maize geneticists Drs. A. Brink and Ed. Coe in 1950s for two genes that encode transcription factors that activate biosynthesis of red pigment expressed in different plant tissues. For example, *B-1 allele* is converted to non-pigmented allele designated *B-1'* in heterozygotes *B-1* (red colour)/*b1* (light color*)*. This epigenetic silencing is stable in many generations. Key sequences mediated this epimutation are seven tandem repeats located about 100 kb upstream of the *b1* transcription start. These repeats produce siRNA which is critical for trans-silencing (Chandler, 2007, 2010; Arteaga-Vazquez, Chandler, 2010).

Genome organization and hereditary changes in classical and mobile genetics

Table 2 and Table 3 present main conceptual shifts on genome organization and hereditary

variability from Mendelian to contemporary mobile or dynamic genetics. Most contrasting premises indicated in two tables are well known.

Let's discuss in detail the problem of natural mutation process. In 1901 Hugo de Vries, a famous Dutch botanist and rediscoverer of Mendel's laws, coined term mutation. He described main principles of mutation occurrence and conceived the idea of mutational speciation. He introduced also the idea of mutation periods or mutation bursts that was neglected by most of geneticists for many decades.

But situation was changed after McClintock's discovery of mobile elements and insertional mutagenesis. My and colleagues long-termed studies on population genetics of *Drosophila* led to discovery that mutational bursts are result of activation of diverse MEs inducing super-unstable insertional mutations. We found also remarkable example of natural genetic engineering during one mutational burst which happened in 1973. Two genes (one determines bristle and another wing form) appeared to be under the control of one transposon and simultaneously expressed and mutated as a new genetic construction (Golubovsky, 2000). This finding shows as new evolutionary novations mediated by mobile elements may occur.

The features of genome structure and variability, indicated in Table 2 and Table 3 are clearly exhibited in evolutionary analysis of plant genome architecture (Wendel et al., 2016). Authors called "revelation" an extraordinary variation in plant genome size having in mind constancy of their genic content. For instance, the barley genome is 11.5 times larger than genome of another cereal, rice. Even species and subspecies of the one genera may have drastical differences in genome size.

Table 2. Genome structure: conceptual shifts from Mendelian to Mobile genetics

Таблица 2. Структура генома: концептуальные сдвиги от менделевско-морrановской генетики к мобильной генетике

Mendelian classical genetics	Mobile genetics
Chromosomal DNA is the sole carrier of hereditary information. All DNA changes are vital	There are non-informative repeated DNA fractions and a lot of diverse facultative genetic elements in the genome
More DNA in the genome – more genes	Close species may differ both in content and DNA size. having the same gene number
Colinearity: physical size of a definite gene corresponds to coding protein size	Mosaic gene structure of eukaryotes: introns and exons. RNA splicing and editing
Every gene occupies definite locus and has one or duplicated copies in all species individuals	Gene loci are capable to amplification within and out of chromosomes
Apart of sexual propagation a genome of every species is predominantly closed genetic system	Mobile elements are omnipresent; there is horizontal gene transfer
Genome changes occur due to rare spontaneous gene / chromosome mutations and due to hybrid recombination	Genome is a highly sensitive organ of the cell monitoring genomic activities, corrects errors, senses stress events and may responds to them by restructuring genome
Only DNA/RNA are capable to template ability by convariant reduplication	There are specific proteins, prions, that transfer their conformation to the homologous proteins

The mechanism of this paradox is rapid saltational proliferation of mobile elements widespread in plants. Here are impressive data on mobile elements percentage in genomes of some cultural species: *Brassica oleracea* (cabbage) – 39%, *Beta vulgaris* (sugar beet) – 63%, *Hordeum vulgare* (barley) – 84%, *Oryza sativa* (Asian rice) – 35%, Zea mays – 82%, *Solanum lycopersicum* (tomato) – 63%, *Solanum tuberosum* (potato) – 62%, *Vitis vinifera* (grape)– 41%.

Table 3. Hereditary changes: postulates of Mendelian and current Mobile genetics

Таблица 3. Наследственные изменения: постулаты менделевской и современной мобильной генетики

Classical Mendelian Genetics	Mobile Genetics
All hereditary changes are mutations: changes of definite gene loci structure, chromosome rearrangements or chromosome number	Apart of mutations there are two hereditary changes: (i) variations, or changes of number, chromosome topography of FGE and (ii) epigenetic alterations
Mutations occur in the progeny of some individuals, spontaneously, with small rate	Hereditary changes induced by ME and epimutations may occur orderly in many individuals
Most newly occurring mutations in nature are rather stable. The rate of mutation process is stable	There are regular bursts of mutability due to activation of ME. Insertion mutations mediated by ME are unstable
Nuclear genes predominantly determine functions of all cytoplasmic elements	Nucleo-cytoplasmic relations are complicated, there are various autonomic and semi-autonomic genetic elements
Epigenetic alterations in eukaryotes occur only in somatic cells	Epigenetic alterations may transfer germinally, as in the case of paramutation
Specific gene structure and activity does not change in hybrids, the essence of Mendelian laws	In the tenets of epigenetic determination of a trait, allelic transfection and paramutation events are possible
Both sexes are equal in transfer of a gene/ chromosome specific structure and state	Parental imprinting exists: a gene expression may depend upon the parent transmitting it
Inheritance of traits occurring during individual development is impossible Gene transfer and recombination occurs only by sexual propagation.	Such events may occur if a trait is determined by epigenetically or mediated by FGE There is horizontal gene flow even between distant organisms. Potential unity of evolutional gene pool

Conclusion

I would like to underline that most problems presented here are discussed in the comprehensive book “Genome Inconstansy” by Roman Khesin (Khesin, 1984). The author had great experience both in classical and molecular genetics. He analyzed in detail how sequence of unpredictable discoveries and the avalanche of new data obtained after the methodological revolution of the 1970s had changed the visage of genetics. The traditional views on the structure and function of the genetic apparatus were dramatically transformed (Golubovsky, 2002). The study of genome inconstancy proved to be closely connected with various genetic phenomena, including sex of bacteria, unstable mutations in the fruit fly and maize, adaptation to antibiotics, cytoplasmic heredity, immunoglobulins, carcinogenesis, nitrogen fixation, evolutionary genetics.

He states his main conceptual approach or even credo: “Molecular biology itself does not set general biological problems. It only answers the requirements of other branches of science”. Hence the characteristic feature of his book: detailed analysis of factual data on the “molecular anatomy” of various MEs and viruses is always accompanied by revealing their behavior in the system of the genotype, as well as their biological and evolutionary significance. This is extremely important, because many researchers, enchanted by the advances in DNA engineering, are susceptible to what E. Chargaff, a patriarch of this of science, called “molecular slavery”.

In the early 1980s, it became obvious that MEs are an integral part of the genome and a potent factor of its natural variation, rather than an exotic phenomenon. Whatever is the mechanism of ME transposition, it must involve a stage of recombination at the DNA level. Khesin developed the idea that the potential for genetic recombination is congenital for all reproducing cells. In addition to the obligatory variant of homologous recombination, two optional variants are possible: recombination at signal repeats

scattered over the genome and site-specific ones.

Yu.A. Filipchenko, the author of the terms microevolution and macroevolution, in his book "Evolutionary Idea in Biology" (Filipchenko, 1977) postulated that "inner forces" inherent in the structure of living organisms were the main factor of organic evolution. One source of these inner forces is the DNA linear structure and the characteristics of template processes (replication, transcription, and translation) and genetic processes per se (repair, recombination, and segregation). Repeats are inevitably formed during these processes. Khesin suggested that any DNA segment flanked with repeats may become transposable. It may acquire the capacity for burst replication and spread over the genome, and lead to an increase in the proportion of noninformative DNA.

Unquestioning belief of molecular biologists in selectogenesis (all traits are result of natural selection) led to an impasse in the 1970s: geneticists searched for the adaptive significance of all variations in the composition and amount of DNA, but they encountered the C-value paradox, the surprising diversity of repetitious-DNA families and MEs.

Plant genome size variations is a dynamic process of and bloating and purging DNA. The emerging trend is that plant genomes bloat due to the copy-and-paste proliferation of a few facultative elements: long terminal repeats retrotransposons, LTR and aggressive purge these amplifying LTR through several mechanisms. They include facultative and incomplete recombination, and double strand break repair non-homologous end joining (Todd, 2014).

The largest published genome, *Picea abies* (Norway Spruce) is 19 800 Mb. It has bloated with divers and divergent LTRs that have evaded DNA purging mechanisms or they are absent in gymnosperm.

What is Khesin's approach to this imbroglio? He holds to the theory of relative adaptedness and warns against "the false notion that all there is in the cell is adaptive and useful for it." Based on comparative molecular anatomy of various MEs he postulates the general principles of their organization: end repeats, genetic punctuation marks (promoters and terminators), duplications flanking the insertions into target loci, and induced instability at the sites of insertion.

In my seminal presentation (1985) and following book and papers (Golubovsky 2000; Golubovsky, Manton, 2005) for the first time an attempt was made to compare the main provisions of classical and modern genetics. Many of the above postulates were not called that anywhere, although they were implicitly implied. What follows from these comparisons?

First of all, the prospect opens up in an accessible and concise form to follow the course of development of genetics. The possibility of conceptual comparison of postulates or paradigms testifies not to the weakness, but to the strength of this field of science. By no means should one think that now it is necessary to abandon classical mendelian genetics. No! The research methodology created within its framework, the system of concepts and the discoveries made are *a golden fund*, a reliable foundation, without which all innovations are impossible.

However, the entire conceptual canvas is changing. There is a transformation, a revision of many basic concepts, as well as the introduction of new ones. The possibility of conceptual choice makes it possible to give a new interpretation or a re-examination of many non-canonical facts buried in the storehouses of science. Freedom of choice predetermines the readiness to deviate from the usual canons when explaining the non-trivial behavior of a particular biological object; in other words, it is the willingness to experiment differently in order to discover conceptually new phenomena.

In the tenet of generalized approach to the genome structure and function it is rational to

subdivide cell genetic system into two subsystems: obligate genetic elements (OGE) and facultative ones (FGE). Current genome semantics includes also various dynamic ways of coding, storage and transfer of genetic information (epigenetics). The foregoing account suggests existence at least three types of heritable changes: classical mutations (in T. Morgan's sense), variations and epigenetic alterations. Heritable changes in number or chromosome/cell topography of diverse facultative elements can occur simultaneously in many individuals (variations). Such heritable change might be induced by action of nonmutagenic environmental factors as temperature, interline crosses, nutritional stress ("genotrophs"), genomic stress like polyploidy, hybridization or viral infection. The same is true for epigenetic alterations.

FGEs are ubiquitous among plants often comprising more than 50% of plants genomes. Maize has nearly 80% of its genome composed of transposons. Diverse non-Mendelian phenomena are well documented in allopolyploid genome evolution. Genomic stress may trigger MEs activation due to interspecies hybrid genomes conflict. This results in non-Mendelian events. They comprise rapid loss/gain DNA fragments, reciprocal intergenomic repeats invasion, DNA methylation changes, gene silencing, and functional reproduction novelties such as flowering time (Liu, Wendel, 2002; Wendel et al., 2016).

Transfer of genes has been well documented among evolutionary distant species. In mammals and birds, almost identical proviral DNA sequences appeared after the evolutionary diversification. Mice, rats, cats, pigs, and humans became "relatives": they carry many common rudiments of endogenous viruses. The Mariner transposon which was found in Drosophila then was discovered in different Diptera species, Crustacea, and humans. Due to mobile elements, the gene pool of all organisms potentially constitutes an integrated biosphere gene pool as firstly suggested molecular geneticist Roman Khesin (Khesin, 1984). This postulate has a great importance for biology (Golubovsky, 2000, 2002). IV

References / Литература

Arteaga-Vazquez M.A., Chandler V.L. Paramutation in maize: trans-generation gene silencing. *Current Opinion in Genetics and Development*. 2010;20(2):156-163. DOI: 10.1016/j.gde.2010.01.008

Berg R.L., Engels W.R., Kreber R.A. Site-specific X-chromosome rearrangements from hybrid dysgenesis in *Drosophila melanogaster*. *Science*. 1980;210(4468):427-429. DOI: 10.1126/science.6776625

Beurton P.J., Falk R., Rheinberger H.-J. (eds.). The Concept of the Gene in Development and Evolution. Cambridge: Cambridge University Press; 2000. DOI: 10.1017/CBO9780511527296

Blattner F.R.; Plunkett G., Bloch C.A., Perna N.T., Burland V., Riley M., Collado-Vides J., Glasner J.D. The complete genome sequence of *Escherichia coli K-12*. *Science*. 1997;277(5331):1453-1462. DOI: 10.1126/science.277.5331.1453

Brockhurst M.A, Harrison E., Hall J.P.J., Richards T., McNally A., MacLean C. The ecology and evolution of pangenomes. *Current Biology*. 2019;29(20):1094-1103. DOI: 10.1016/j.cub.2019.08.012

Chandler V.L. Paramutation: from maize to mice. *Cell*. 2007;128(4):641-645. DOI: 10.1016/j.cell.2007.02.007

Chandler V.L. Paramutation's properties and puzzles. *Science*. 2010;330(6004):628-629. DOI: 10.1126/science.1191044

Crick F. Split genes and RNA splicing. *Science*. 1979;204(4390):264-271. DOI: 10.1126/science.373120

Cullis C.A. Mechanisms and control of rapid genome changes in flax. *Annals of botany*. 2005;95(1):201-206. DOI: 10.1093/aob/mci013

Fedoroff N., Botstein D. (eds.). The Dynamic Genome: Barbara McClintock's ideas in the century of genetics. New York: Cold Spring Harbor Laboratory Press; 1992.

Filipchenko Yu. A. The evolutionary idea in biology (Evolyutsionnaya ideya v biologii). 3nd ed. Moscow: Nauka; 1977. [in Russian] (Филипченко Ю.А. Эволюционная идея в биологии. 3-е изд. Москва: Наука; 1977).

Ghanim G.E., Rio D.C., Teixeira F.K. Mechanism and regulation of P element transposition. *Open biology*. 2020;10(12):200-244. DOI: 10.1098/rsob.200244

Gilbert W. Why genes in pieces? *Nature*. 1978;271:501-504. DOI: 10.1038/271501a0

Golubovsky M.D. Genome Inconstancy by Roman B. Khesin in terms of conceptual history of genetics. *Molecular Biology*. 2002;36(2):259-266. DOI: 10.1023/A:1015382209018

Golubovsky M.D. Genotype organization and forms of hereditary variations in eukaryotes. *Advances in Current Biology*. 1985;100(6):323-339. [in Russian] (Голубовский М.Д. Организация генотипа и формы наследственной изменчивости эукариот. *Успехи современной биологии*. 1985;100(6):323-339).

Golubovsky M.D. The Century of Genetics: Evolution of ideas and concepts (Vek genetiki: evolyutsiya idey i ponyatiy). St. Petersburg; 2000. [in Russian] (Голубовский М.Д. Век генетики: эволюция идей и понятий. Санкт-Петербург; 2000).

Golubovsky M.D. The unity of the whole and freedom of parts: Facultativeness principle in the hereditary system. *Russian Journal of Genetics: Applied Research*. 2011;1(6):587-594.

DOI: 10.1134/S2079059711060050
Golubovsky M.D., Churaev R.N. Dynamic heredity and epigenes. *Priroda.* 1997;4:16-25. [in Russian] (Голубовский М.Д., Чураев Р.Н. Динамическая наследственность и эпигены. *Природа.* 1997;4:16-25).
Golubovsky M.D., Ivanov Yu., Green M.M. Genetic instability in *Drosophila melanogaster*: Putative multiple insertional mutants of the singed bristle locus. *Proceedings of the National Academy of Sciences of the United States of America*. 1977;74(7):2973-2975. DOI: 10.1073/pnas.74.7.297
Golubovsky M.D., Manton K.G. Genome organization and three kinds of heritable changes: general description and stochastic factors (a review). *Frontiers in Bioscience*. 2005;10(1):335-344. DOI: 10.2741/1531
Green M.M. Annals of mobile DNA elements in Drosophila. In: *The Dynamic Genome. Barbara McClintock's ideas in the century of genetics*. N. Fedoroff, D. Botstein (eds.). New York: Cold Spring Harbor Laboratory Press; 1992. p.117-122.
Green M.M. Controlling element mediated transposition of the white gene in *Drosophila melanogaster*. *Genetics*. 1969;61(2):429-441. DOI: 10.1093/genetics/61.2.429
Holliday R. The inheritance of epigenetic defects. *Science*. 1987;238(4824):163-170. DOI: 10.1126/science.3310230
Inge-Vechtomov S.G. Genetics in Retrospect. A Course of lectures. St. Petersburg: Publishing house N.-L.; 2015. [in Russian] (Инге-Вечтомов С.Г. Ретроспектива генетики: (курс лекций). Санкт-Петербург: Издательство Н.-Л.; 2015).
Ito H. Environmental stress and transpositions in plants. *Genes & Genetic Systems.* 2022;97(4):169-175. DOI: 10.1266/ggs.22-00045
Jablonka E., Lamb M. The epigenome in evolution: Beyond the modern synthesis. *Vavilov Journal of Genetics and Breeding*. 2008;12(1/2):242-254.
Jacob F., Monod J. Genetic regulatory mechanisms in the synthesis of proteins. *Journal of Molecular Biology.* 1961;3:318-356. DOI: 10.1016/s0022-2836(61)80072-7
Jacob F., Wollman E.L. Sexuality and genetics of bacteria. New York; London: Academic Press; 1961.
Johannsen W. The genotype conception of heredity. *The American Naturalist*. 1911;45(531):129-159. DOI: 10.1086/279202
Khesin R.B. *Genome Inconstancy*. Moscow: Nauka; 1984. [in Russian] (Хесин Р.Б. Непостоянство генома. Москва: Наука; 1984).
Kim E., Magen A., Ast G. Different levels of alternative splicing among eukaryotes. *Nucleic Acids Research*. 2007;35(1):125-131. DOI: 10.1093/nar/gkl924
King R.C., Stansfield W.D., Mulligan P.K. A dictionary of genetics. 7nd ed. Oxford University Press; 2006.
Lander E.S., Linton L.M., Birren B., Nusbaum C., Zody M.C., Baldwin J., Devon K. et al. International Human Genome Sequencing Consortium: Initial sequencing and analysis of the human genome. *Nature*. 2001;409(6822):860-921. DOI: 10.1038/35057062. Erratum in: *Nature*. 2001;412(6846):565. Erratum in: *Nature*. 2001;411(6838):720.
Lisch D. Regulaton of transposable elements in maize. *Current Opinion in Plant Biology*. 2012;15(5):511-516. DOI: 10.1016/j.pbi.2012.07.001
Liu B., Wendel J.F. Non-Mendelian Phenomena in Allopolyploid Genome Evolution. *Current Genomics*. 2002;3(6):489-505. DOI: 10.2174/1389202023350255
McClintock B. Chromosome organization and genic expression. *Cold Spring Harbor Symposia on Quantitative Biology.* 1951;16:13-47. DOI: 10.1101/sqb.1951.016.01.004
McClintock B. Mechanisms that rapidly reorganize genome. *Stadler Symposium*. 1978;10:25-48.
McClintock. The significance of responses of the genome to challenge. *Science*. 1984;226(4676):792-801. DOI: 10.1126/science.15739260
Monod J.; Jacob F. General conclusion: Teleonomic mechanisms in cellular metabolism, growth and differentiation. *Cold Spring Harbor Symposium Quantitative Biology*. 1961;26:389-401. DOI: 10.1101/sqb.1961.026.01.048
Muyle A., Marais G., Bačovský V., Hobza R., Lenormand Th. Dosage compensation evolution in plants: theories, controversies and mechanisms. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences.* 2022;377(1850):20210222. DOI: 10.1098/rstb.2021.0222
Nanney D.J. Epigenetic control systems. *Proceedings of the National Academy of Sciences of the United States of America*. 1958;44(7):712-717. DOI: 10.1073/pnas.44.7.712
Olovnikov A.M. A theory of marginotomy. The incomplete copying of template margin in enzymatic synthesis of polynucleotides and biological significance of the phenomenon. *Journal of theoretical biology*. 1973;41(1):181-190. DOI: 10.1016/0022-5193(73)90198-7
Polanyi M. Personal knowledge. Chicago: The University of Chicago Press; 1962.
Rodionov A.V. Tandem duplications, euploidy and secondarary diploidization-genetic mechanisms of plant speciation and progressive evolution. *Turczaninowia*. 2022;25(4):87-121. [in Russian] (Родионов А.В. Тандемные дупликации генов, эуплоидия и вторичная диплоидизация – генетические механизмы видообразования и прогрессивной эволюции в мире растений. *Turczaninowia*. 2022;25(4):87-121). DOI: 10.14258/turczaninowia.25.4.12
Saedler H., Starlinger P. Twenty-five years of transposable elements research in Koln. In: *The Dynamic Genome. Barbara McClintock's ideas in the century of genetics*. N. Fedoroff, D. Botstein (eds.). New York: Cold Spring Harbor Laboratory Press; 1992. p.243-263.
Schimke R.T. The discovery of gene amplification in mammalian cells: To be in the right place at the right term. *Bioessays*. 1989;11(2-3):69-73. DOI: 10.1002/bies.950110208
Shapiro J. Genome organization and reorganization in evolution: formatting for computation and function. *Annal New York Academy of Science*. 2002;981:11-134. DOI: 10.1111/j.1749-6632.2002.tb04915.x
Shapiro J.A. Natural genetic engineering in evolution. *Genetica*. 1992;86(1-3):99-111. DOI: 10.1007/BF00133714
Stillman B. (ed.). Epigenetics: Cold Spring Harbor Symposia on Quantitative Biology. Vol. LXIX. 1nd ed. Cold Spring Harbor Laboratory Press; 2005.
Tchuraev R.N., Galimzyamov A.V. Gene and epigene network: two level of organizing of hereditary system. *Journal Theoretical Biology*. 2009;259(4):659-669. DOI: 10.1016/j.jtbi.2009.03.034
Tchuraev R.N., Stupak I.V., Tropinina, T.S., Stupak E.E. Epigene: design and construction of new hereditary units. *FEBS Letters*. 2000;486(3):200-202. DOI: 10.1016/s0014-5793(00)02300-0
Tikhodeyev O. The mechanisms of epigenetic inheritance: how diverse are they? *Biological Review of the Cambridge Philosophical Society*. 2018;93(4):1987-2005. DOI: 10.1111/brv.12429
Todd P.M. Plant genome size variation: bloating and purging DNA. *Briefings in Functional Genomics.* 2014;13(4):308-317. DOI: 10.1093/bfgp/elu005
Tyedmers J.; Madariaga M.L., Lindquist S. Prion switching in response to environmental stress. *PLOS Biology*. 2008;6(11):2605-2613. DOI: 10.1371/journal.pbio.0060294
Wendel J.F., Jackson S.A., Meyer B.C, Wing R.A. Evolution of Plant Genome Architecture. *Genome Biology*. 2016;17:37. DOI: 10.1186/s13059-016-0908-1

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