# THE UNITY OF THE WHOLE AND FREEDOM OF PARTS: FACULTATIVENESS PRINCIPLE IN THE HEREDITARY SYSTEM

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Facultativeness in the genome structure and function reflects the general principle of life organization and evolution: *the unity of the whole and the freedom of parts*. The genome, or cell hereditary system code, maintains and transfers hereditary information both structurally and dynamically. The generalized genome concept presents a genome as an ensemble of both obligate and facultative elements. Template processes (Replication, Transcription and Translation) and Basic genetic processes (Repair, Recombination and Segregation) are capable of functional facultativeness and dynamic (epigenetic) modifications. It is reasonable to discriminate among three kinds of heritable changes: mutations, variations and epigenetic modifications. Structural genome facultativeness is expressed as a subdivision of cell DNA and RNA elements into two subsystems: Obligate genetic elements (OGEs) and Facultative genetic elements (FGEs). FGEs include various kinds of repeated sequences, mobile elements, amplicons, inserted viral and foreign DNA, B-chromosomes, plasmids and cytobionts. The abundance and intracellular topography of FGEs are different in different cells, tissues and individuals. Changes in the structure or order of OGEs correspond to classical mutations. For diverse changes in the number or cell/tissue topography of FGEs the term *variations* seems appropriate. Mutations and variations significantly differ in the pattern of their occurrence. Variations may occur simultaneously in many cells/individuals and are induced by nonmutagenic factors. Spontaneous hereditary changes in nature usually occur in the system ENVIRONMENT – FGEs – OGEs via a two-step pathway. FGEs are first to respond to both internal and external environmental challenges. Then their activation induces gene/chromosomal mutations. Both variations and epigenetic changes (epivariations and epimutations) may have non-Mendelian features, sometimes reminding the phenomenon of inheritance of acquired characteristics.

**Key words:** genome, facultative elements, mutation, variation, epigene, heritable changes.

## Introduction

The genome, which in the broad sense is the cell's hereditary system, codes, stores and transfers information in both structural and dynamic ways. Thus we need to discriminate among different forms of structural heritable changes of genome and dynamic (or epigenetic) ones. The amusing absence of a strict correlation of DNA content in the haploid nuclear DNA content with the taxonomic status of species and 2–10 fold differences in genome size in closely related species was called in 1970s the «C-value paradox» (Gregory, 2001; King *et al*., 2002). It appears that in most eukaryotes protein-coding sequences constitute only small part of nuclear DNA. For example, in humans they constitute less than 5 % of the haploid nuclear DNA. Other parts comprise regulatory DNA regions (about 15 % of genomic DNA) and diverse kinds of repetitive sequences including mobile elements (International Human Genome ..., 2001). A recent study of 270 human individuals from four populations in Europe, Africa and Asia revealed a total of 1,447 copy number variable regions covering 360 megabases, or about 12 % of the genome. These variable regions contained hundreds of genes, functional elements, segmental duplications and repeats (Redon *et al*., 2006).

To describe such unusual eukaryote genome organization and its variability we suggested that two genome subsystems: OGEs, or Obligate Genetic Elements (genes and their families), and FGEs,

or <u>F</u>acultative <u>G</u>enetic <u>E</u>lements, be recognized. FGEs are the predominant fraction in the genome content of most eukaryotes. FGEs include various kinds of repeats, mobile elements, amplicons, viral and foreign DNA, B-chromosomes, plasmids, and nuclear/cytoplasmic cytobionts. The abundance and intracellular topography of FGEs are different in different cells, tissues and individuals. Mutations in their classical Morgan's sense (point and chromosomal) are mainly changes in the OFG subsystem. Various changes in the number or cell topography of facultative elements were named *variations* (Golubovsky, 1985, 2000; Golubovsky, Manton, 2005).

Mutations and variations differ dramatically in (i) the rate of their occurrence, (ii) the mode of genotype/environment dependence, and (iii) the stability of their positions in the genome topography. FGEs are first to respond to genetic background or environmental challenges. They constitute an operational genome memory. Activation of OFGs leads directly or indirectly to gene mutations and chromosome rearrangements. The process of heritable changes in the nature occurs in two steps, mediated mainly by mobile elements and other FGEs. Recurrent global and local mutation bursts in wild Drosophila populations were observed in long-term studies (Berg, 1982). They appeared to result from activation and insertion of diverse mobile elements (Golubovsky, 1980; Golubovsky, Belyaeva, 1985). In the case of P-M hybrid dysgenesis in *Drosophila melanogaster*, multipoint rearrangements occur mostly in the sites of insertions of *P* mobile elements (Berg *et al*., 1980; Lim, 1981). Similarly, in the *D. virilis* species, which normally has a very stable karyotype, activation and amplification of the *Penelope* mobile element lead to hybrid dysgenesis and are accompanied by multisite rearrangements. It is worth noting that about 50 % of these rearrangements discriminate various species of this Drosophila subgenus (Evgen'ev *et al*., 2000). These facts point to direct involvement of mobile elements in speciation.

The subdivision of the hereditary system into the Obligate and Facultative subsystems reflects the general principle in organization and evolution of life organisms: *the unity of the whole and the freedom of parts,* or similarity in design but differences in details. FG elements can be mobile regulators of gene expression in many chromosomal sites. Thus, the chromosome/cell topography of FGEs may predetermine the direction of genomic evolutionary changes. In this paper we discuss how diverse interactions in the OFG and FGE subsystems lead to noncanonical (non-Mendelian) heritable changes.

Facultativeness characterizes also the functioning of two triades of genetic processes universal for all living organisms: (1) Template processes – Replication, Transcription and Translation, and (2) Basic genetic processes – Recombination, Repair and Segregation. These two triades determine the coding, maintenance and transfer of genetic information during individual development and during intergeneration transmission.

The dynamic aspects of coding, storage and transfer of genetic information are called epigenetic. The spectrum of epigenetic changes is wide: from the transformation of serotypes in Paramecium to chromosomal and gene imprinting. The terminology in this field has not yet been established. We argue in favor of the heuristic value of the epigene concept, developed both in theoretical and experimental aspects (Tchuraev, 2000, 2009).

## Facultativeness of genome structure and function

**Genome and cell information systems.** The term «genome» was coined by cytologist Winkler in 1920 to designate the haploid set of chromosome for a species. The term was used for an analysis of allopolyploid species or for such mutations as chromosome number amplification. Then its meaning widened to include the entire hereditary constitution of the cell: both structural and dynamic aspects of the coding, storage and transfer of species-specific hereditary information.

The necessity to include stochastic dynamics in the genome concept comes from the discovery of regulatory genes and specific chromosome sequences (such as enhancers). 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. 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 classical paper «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 systems.

Recent 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 check-points. By means of signal transduction pathways a cell receives external signals and transmits, amplifies and directs them internally. Seventeen discovered pathways are highly conserved in nematodes, flies and vertebrates (Nebert, 2002). 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 (Caporate, 2000).

Mobile elements (MEs) found now in all eukaryotic genomes, can move from one chromosomal position to another and induce chromosome rearrangements (review: Evgen'ev et al., 2000; Kazazian, 2004). Mobile elements contain genetic punctuation characters (promoters, enhancers, transcription termination signals, etc.), which regulate gene expression and promote the appearance of new constructs. The term «Natural Genetic Engineering», coined by Shapiro (1999, 2002), emphasizes that biotechnology uses the same enzymes (nucleases, ligases, reverse transcriptases and polymerases) that living cells use to reshuffle the genome and its function. Though MEs are repetitive and dispersed on different chromosomes, they can

be activated simultaneously by a cell signal (e.g., HSP90, the genetic «capacitor») to cause outbreaks of nonrandom genetic variability.

**Genome structure: obligate and facultative genetic elements.** The eukaryotic genome can be naturally subdivided on two subsystems: Obligate and Faculative genetic elements. FGEs include the hierarchy of intra and extra chromosomal elements in nucleus and cytoplasm. Nuclear FGEs comprise a highly repeated and nucleated DNA sequences, pseudogenes and retrotranscripts, transposons, amplicons, and even an additional, or B-chromosome. In cytoplasm, FGEs include plasmids, amplified rod and circular segments, and endosymbionts/cytobionts (Fig. 1).

OGEs and FGEs exhibit different patterns of heritable changes. Mutations in their classical sense are changes in structure, position and number of genes. These events are connected with OGEs. Diverse changes concerning FGEs are referred to as *variations*. Let us consider the human genome (International Human Genome ..., 2001; Golubovsky, Manton, 2005). Coding sequences constitute less than 5 % of all DNA; 15–20 % is connected with gene/chromosome activity regulation. FGEs occupy about 50 % of the genome and include highly repetitive sequences, duplication of chromosome segments, and distinct MEs of four types: three kinds of retro-elements (*LINE*, *SINE* and *Alu*) and one class of transposons. Segmental duplications of 1–200 kb blocks are a remarkable feature of the human genome and
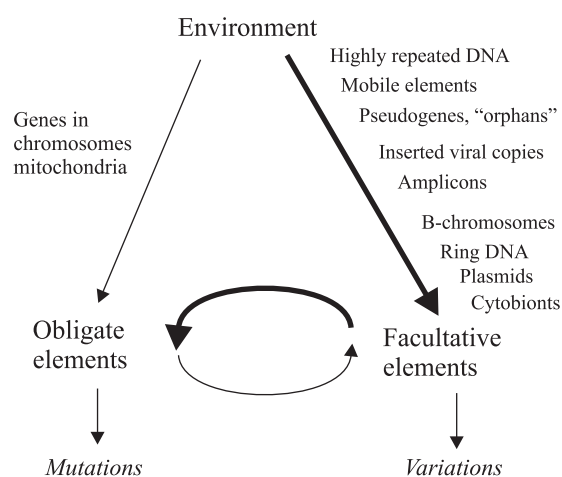


**Fig. 1**. Obligate and Facultative genetic elements in the genome and two types of hereditary changes: mutations and variations. Arrows indicate links, and their widths show the intensity of their forces.

comprise about 3,3 % of all DNA. Other repetitive elements are simple sequence repeats (SSRs): short repeated units, or mic-rosatellites (1–11 b.p), and longer SSRs, or minisatellites (14–500 b.p). 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 (Kazazian, 2004). The *LINE-1* retrotransposon, L1, is present in the human genome in 3000–5000 full-size and 500 000 truncated copies, ~ 15–17 % of the genome. About one million copies of *Alu* retrotransposons comprise 10–12 % of the genome. One of every 100–200 human births has a *de novo Alu* insertion. A similar rate is found for *L1*. More than thirty *L1*–mediated insertion mutations leading to diseases have been observed (hemophilia A and B, thalassemia, DMD).

Changes in the number and chromosome topography of the intracellular population of FGEs are drastically different from gene mutations. Wollman and Jacob (1961) were the first who studied similar hereditary changes in the phage–bacteria system and called them variations. It is clear now that variations in eukaryotes are frequent phenomena and they embrace diverse changes in intracellular populations of diverse FGEs. A typical example is the phenomenon of hybrid dysgenesis discovered in Drosophila. In an $F_1$ 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, being accompanied by multiple insertion mutations and rearrangements. Their incidence in the $F_1$ progeny of dysgenic crosses may reach about 10 %.

Chromosomal breaks in cases of P-M hybrid dysgenesis are ordered and site specific: they occur near the *P*-site location. Multi-site inversions occur in dysgenic hybrids as often as single ones (Berg *et al*., 1980; Lim, 1981). Activation of diverse MEs in nature result in mutation bursts of definite genes in distant natural populations (Golubovsky, Belyaeva, 1985).

Variations or hereditary changes in the FGE subsystem can be induced by nonmutagenic environmental factors such as line crosses or food/temperature fluctuations.

There is a two-step pathway of the spontaneous mutation process in nature (Fig. 1). First, activation of mobile elements (significant part of FGE) in response to diverse environment challenges. Second, insertional mutations and chromosome rearrangements.

Typical examples of variation are changes in the ratio between OGEs and FGEs. These changes accompany the 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.

Amplified segments, or amplicons, can exist as tandem duplications or be transformed into plasmids or even minichromosomes, capable of autonomous replication in cytoplasm. Both the number and topography of amplicons vary over cell lines. Amplification of chromosomal segments containing *myc* oncogene occurs in 25 % of human neuroblastomas. The exact number of amplified segments cannot be determined even in daughter cloned cells (Khesin, 1984).

**Records of FGE-mediated genetic variability in natural populations.** Since the middle of 1960s regular monito-ring of phenotypic and genetic variability of wild Drosophila population has been conducted at the Laboratory of Population Genetics of the Institute of Cytology and Genetics, Novosibirsk, Russia. The data obtained in the process of this long-term population genetics study resulted in the discovery of many unknown traits of spontaneous genetic variability. We mention only the discovery of insertion mutagenesis, the finding of the first case of natural genetic engineering, observations concer-ning the role of viruses and endosymbionts in vital host animal traits, detailed analysis of a highly mutable system in the case of intralocus insertion of two ME copies, and genetic analysis of mutational changes mediated by ME insertions (Table 1).

## Template and basic genetic processes and their facultativeness

The occurrence and fixation of new hereditary information are implemented via two triades of genetic events acting both in prokaryotes and eukaryotes: template and basic genetic processes. Template processes include Replication, Transcription and Translation. Basic genetic processes

Genetic variability events mediated by Facultative genetic elements
that were observed in wild Drosophila populations and examined in genetic experiments

| | |
|---|---|
| 1 | Global and local locus-specific mutability bursts are caused by ME insertions |
| 2 | Mutation fashion: synchronous activation of distinct MEs and waves of distinct ME insertions at the same target loci in geographically distant populations |
| 3 | First case of Natural genetic engineering: two genes from a wild population fall under the control of a *hobo* ME with resulting conjoint expression and mutations |
| 4 | Multiple unstable insertion alleles differing in transposition rate in the germ and somatic cells; direction and pattern of phenotypic expression |
| 5 | Picornavirus infection increases the general mutation rate; mutations in loci sensitive to viral DNA were found among those most frequent in wild populations |
| 6 | The cytobiont *Wolbachia* is ubiquitous in wild populations. It may have negative effect on host life span under optimal conditions but be adaptive under thermal stress depending on the host and *Wolbachia* genotypes |
| 7 | The transposition–homologous recombination association was discovered. ME-mediated mutations are accompanied by abnormal homological recombination events |
| 8 | ME-mediated mutations (transpositions) frequently occur during the first zygote divisions with resulting regular germline/somatic mosaicism |
| 9 | Discovery of a natural specific gene instability system induced by insertion of two identical MEs to different promoter sites and regular inversion–reinversion events between these two inserted MEs |
| 10 | Discovery of the fact that the rate of locus-specific ME-mediated mutability in germ and somatic cells depends on modifier genes and the constitution of the DNA repair system |

The data presented summarize the results obtained during long-term studies at the Laboratory of Population Genetics of the Institute of Cytology and Genetics, Novosibirsk (Golubovsky 2000; Ilinsky, Zakharov, 2007; Zakharov *et al*., 2008; Weisman *et al*., 2009).

include Recombination, Repair and Segregation (Golubovsky, 2000; Golubovsky, Manton, 2005). To be inherited, all DNA changes need to go through template and basic genetic processes. The *E. coli* bacterium has 4,228 genes. 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 post-translation protein modification; 21, in ribosomal r-RNA synthesis; and 86, tRNA (Blattner *et al*., 1997).

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

About 60 % of genes in humans are capable of alternative transcription and alternative splicing, depending on specific tissue or cell/tissue physiology. This ability is based on the existence of two or more promoters and the exon/intron structure of eukaryotic genes. In humans, due to alternative gene splicing, there are 2,6 transcripts per gene on the average.

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).

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 site-specific recombination and replicative transposition of LTR-containing mobile elements. The segrega-

tion process as the necessary end of both mitotic and meiotic divisions might be also facultative as in the case of such genetic factors as Segregation Distortion or some chromosomal rearrangements (Khesin, 1984).

## Dynamic epigenetic changes and the logics of an epigene

The dynamic aspects of the coding, storage and transfer of genetic formation are called epigenetic. Clear conceptual discrimination between genetic and epigenetic control systems was made more than 50 years ago by the protozoologist and geneticist David Nanney (1958). He underscored several diagnostic assumptions which point to the action of cellular epigenetic control systems: cells with 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».

The term *epigenotype* was introduced in 1960s. Holiday (1987, 1990) was the first who coined the term *epimutation* and associated DNA methylation with heritable variations in gene expression. The spectrum of epigenetic inheritance is very wide. It includes gene and chromosome imprinting, developmental genome reprogramming, and control of chromatin structure and dynamics (Epigenetics, 2004). There are at least four types of epigenetic inheritance systems (Jablonka, 2008): (i) self-sustaining metabolic loops (Monod, Jacob, 1961); (ii) chromatin marking mediated by histones and DNA-binding proteins; (iii) RNA-mediated variation in gene expression, and (iv) inheritance of some preexisting cellular structures (membrane) and some protein structures, prions.

Since the middle of 1970s, the concept of an *epigene* as a unit of epigenetic inheritance has been developed by R. Tchuraev. This fruitful idea was experimentally validated by an artificial epigene synthesis (Tchuraev, 2000, 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.

A one-component epigene scheme shown in Fig. 2 demonstrates the possibility of switching (*trans*-activation) from the inactive to active epigene state in cell epiheterozygotes. Such switching will correspond to an epimutation, displaying non-Mendelian inheritance («blending inheritance»). Noteworthy, if we imagine ten independent epigenes in the genome, the cell can have 1024
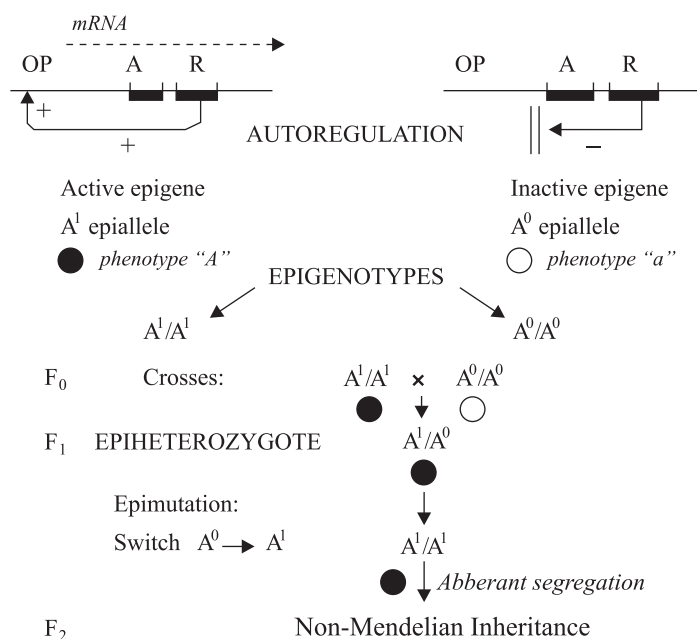


**Fig. 2.** Schematic presentation of an epigene.

Epigenes constitute autoregulatory feed back loops via DNA binding proteins. The figure shows the positive autoregulation at the transcription level. $A^1$ and $A^0$ designate active and inactive states of the epigene. Crosses may result in an epimutation in the progeny of $F_1$ epiheterozygotes.

potential states without any structural changes in DNA sequences. Their feedback can be positive, as in the bacterium–phage system with the auto-regulatory *c1* gene function. The state of the *c1* gene determines the genetic switch between the lysogenic or lythic lambda phage cycles (Ptashne, 2004). Similarly, transposons *P* in Drosophila and *Ac* and *Spm* in corn are organized as epigenes with positive autoregulation.

### Conclusions

The presented general approach to the genome organization and function posits the division of the genome into two subsystems, OGE and FGE, and assumes at least three types of heritable changes: mutations, variations, and epigenetic alterations. Heritable changes of diverse facultative genome elements or variations can occur simultaneously in many individuals. They can be site-specific and are induced by various weak nonmutagenic environmental factors as temperature, interstock crosses, or nutritional shifts («genotrophs» in plants). The same is true for epigenetic alterations.

Based on the comparative molecular anatomy of various MEs, Khesin (1984) postulated the general principles of their organization: terminal repeats, genetic punctuation marks (promoters and terminators), duplications flanking the site of insertion into target loci, and induction of gene instability. A hypothesis on two ways of their independent evolution, progressive and regressive, was put forward

and well justified. In the former case, progressive complication may occur in the following order: insertion elements – transposons – plasmids – viruses. In the latter case, retroviruses may lose their genes or have them damaged, losing the capacity of independent replication and transposition. They exist as immobile elements of the host genome. A remarkable confirmation of such evolution is presented by the discovery of molecular polymorphism in a series of Drosophila *copia*- and *gypsy*-like MEs having long terminal repeats. Some of these MEs carry only two of three typical retrovirus genes. The *gypsy* ME has all the three retroviral genes and may be infectious, like retroviruses. As a result, they were recently recognized as first endogenic insect retroviruses and were designated as errantiviruses (Nefedova, Kim, 2007).

The *P*-transposon, omnipresent in Drosophila, and HIV in humans appear remarkably similar in evolutionary behavior and fate (Table 2). Evidently, the evolutionary fate of both *P*-element and HIV virus involves regular horizontal transfer. Due to mobile elements, the gene pool of all organisms potentially constitutes an integrated biosphere gene pool (Khesin, 1984). Transfer of genes among taxa has been well documented. In mammals and birds almost identical proviral DNA sequences appeared after the evolutionary diversification of these taxa. Mice, rats, cats, pigs, and humans became «relatives»: they carry many common rudiments of endogenous viruses. The *Mariner* transposon, first found in Drosophila, was found in different

**Table 2**

Similar evolution fates of two facultative elements

| *P* element in Drosophila* | HIV retrovirus in humans** |
|---|---|
| Encodes transposase and is inserted in diverse chromosomes of the genome | Encodes integrase and is inserted in diverse sites of the human genome |
| ~ 40-50 yr BP: global activation and rapid spread in most wild populations | ~50 yr BP: global distribution in humans |
| Transpositions, mass germ line insertions, gonad sterility | Insertion in cells of immune systems and their damage |
| Horizontal transfer: both identical and divergent *P* variants in drosophilids | In diverse primates and nonhuman primate monkeys. Horizontal transfer |
| *D. melanogaster* transported from Africa to America on slavery ships | Slavery-associated transport from Africa |

* *P*-like transposons, omnipresent in Drosophila, were found also in vertebrates; they are still mobile in zebra fish but immobilized in human ancestors (Hummer *et al.*, 2005); ** HIV-1 virus: was transferred to humans from chimpanzees, which hosted and recombined two form of simian monkey SIV (Sharp, Hahn, 2010).

Diptera species, Crustacea, and humans. The human genome has about 14 000 copies of *Mariner*, comprising 2,6 Mb (Mandal *et al*., 2008).

Horizontal transfer of genes promoting adaptation constantly occurs in microorganisms. Gene migration by means of plasmids is necessary for bacteria to develop the resistance to antibiotics and capacity for environmental sanitation through elimination of anthropogenic pollutants. Were it not for insertion sequences and transposons/plasmids, not only numerous bacterial  species but also we humans would have disappeared because of poisoning with the products of our powerful chemical industry, which is neutralized by bacteria (Khesin, 1984).

On the other side, due to this regular interspecies and intergenera horizontal transfer human beings are eternally attacked by pathogenic microorganisms arising *de novo*. To mention but one example, the genome of the cholera agent *Vibrio cholerae* bacterium was completely deciphered in 2000. It consists of two circular chromosomes, the larger, 2,96 Mb, and the smaller, 1,07 Mb. Most genes responsible for vital functions are located on the larger chromosome, whereas the smaller chromosome is thought to be a megaplasmid taken up by one of the ancestral species of the genus *Vibrio* (Heidelberg *et al*., 2000 ). Thus, *V. cholerae* resembles the Earth-Moon system. The «Moon», or megaplasmid, contains gene complexes that ensure interspecies transposition and genes for virulence and resistance to antibiotics. Prior to being taken up by the cholera agent, the plasmid had accumulated genes from different bacteria. Under natural conditions, nonpathogenic bacteria of the genus *Vibrio* live in river estuaties and brackish waters as component of zooplankton. The pathogenicity of *V. cholerae* resulted from its «domestication» and its entering the new ecological niche after it acquired the plasmid, which was at first a facultative component of the genome and then became semiobligate.

The broad spectrum of events discovered in modern «mobile genetics», including the principle of the unity of the whole and the freedom of parts, was outlined in experimental studies by B. McClintock about 60 years ago and about 50 years ago by French geneticists (A. Lvov, E. Wollman, and F. Jacob), who analyzed the phenomena of sexuality in bacteria *E. coli* and the behavior of the

*E. coli*–lambda phage system. They came to the conclusion that there can be any forms intermediate between virus and normal cellular genetic determinants. Episomes (plasmids) may or may not be present in the cell; once in the cell, they may be located on chromosomes or in the cytoplasm and may be exogenous or pathogenic. These facultative elements erect bridges between heredity and infection, nuclear and cytoplasmic heredity, and cell pathology and physiology (Wollman, Jacob, 1961). These prophetic conclusions reflect the important principle of organization and function of all hereditary systems: the unity of the whole and the freedom of parts. The last principle was philosophically formulated as inherent in the whole organic nature by the philosopher Vladimir Solovyev in the end of the 19th century and was underlined by A.A. Lubischev (1890–1972) for the morphological evolution of living organisms.

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