EVOLUTION WITHOUT GENES

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Abstract-Nowadays genes are claimed to explain almost everything that is somehow or another connected with manifestations of the biological life on the Earth, including evolution. It is now clear, however, that major incongruities exist and that there is only a weak relationship between biological complexity and the number of protein coding genes. The genome can be divided into two main sections, the coding (genes) and non coding portions. Non coding DNAs have been considered as non-functional DNA by many authors. And to determine which of them is the most important in evolution based on the input of genes and non coding DNAs into the origin of the basic forms of life and its diversity. Information about non coding DNAs as the main evolving component of the genome is presented. It is supposed that evolution has not stopped on DNA, which is transcribed into RNA which in turn is translated into proteins.
Key words: non coding DNAs, eukaryote evolution, human evolution, constitutive heterochromatin.

Introduction

The statement that sensible judgment on evolution is impossible until laws of heredity are not elucidated contradicts to the facts. It is generally admitted that Darwin's theory of evolution was mostly true; however his genetic theory was extremely erroneous. On the contrary, early Mendelists who, properly speaking, were first biologists (except Mendel himself) and were on the right positions in genetics explained almost all evolutionary phenomena in the wrong way [1].

According to Modern Synthesis the speciation is the central problem of the evolution issue in general and the gene is its sole source. However such gene-centric approach could not give an answer for, as they thought, central question of evolution – speciation. Thus for example Lewontin [2] writes: 'It is an irony of evolutionary genetics that, although it is a fusion of Mendelism and Darwinism, it has made no direct contribution to what Darwin obviously saw as the fundamental problem: the origin of species'. Moreover, geneticists not only failed to produce new species, they even could not find at least one case when any new species appeared only due to gene mutation.

Protests against the gene as the sole basis of heredity and evolution have paralleled the development of genetics from its inception. They have continued into the twenty-first century against the centrality on the gene. It had been recognized since the early 1970s that eukaryote contained huge regions of nucleotide sequences that do not code proteins or RNA – so called junk DNA. Today, it is estimated that more than 98 percent of human DNA is made up of such non coding sequences – although the adaptive value of junk DNA is still debated. Decoding the human genome has turned out to be more complicated than had been expected. The human genome was 200 times larger (in the sense of the number of nucleotide sequences) than baker's yeast, but 200 times smaller than amoebae (see [3]).

One of creators of modern synthesis Mayr [1] admitted that there were questions on which they could not reach an agreement: ways of adaptation, evolution mechanisms of higher and lower organisms, origin of sex. To our opinion it is not full list of questions which are still waiting for due consideration by neo-Darwinians. To this list should be added the origin of eukaryotic cells, nucleosomes, chromatin, mitotic chromosomes, chromosome bands, chromosomal heterochromatic regions, sex, multicellularity, differentiation of somatic cells, temperature regulation, homoeothermic organisms, human being and his adaptation to climate distinct from East Africa and many other issues. There are numerous other phenomena that have not received satisfactory explanation in the framework of modern synthesis.

If not genes then what? There are some reasons to believe that out of known to science DNA types only non coding DNAs could meet the above mentioned problems.

What is a non coding DNA?

Function of DNA has been associated mainly with the coding process, i.e. DNA which is transcribed into RNA which in turn is translated into proteins. Non coding DNAs (ncDNAs) have been considered as non-functional DNA by many authors. The genome can be divided into two main sections, the coding and non

coding portions. The coding section of the genome is generally what we talk about when we refer to genes. Genes and their products (proteins) are big, and easy to study. Therefore, they have garnered almost all of the scientific attention.

The technology to study non coding sequences is just now coming of age. Meanwhile it is clear that the greater the relative amount of ncDNAs an organism has the more complex it is. A correlation doesn't mean very much without data to support it. Genes make up only 2% of the genome, leaving over 98% of our genome which has been labeled as 'junk'. About 95% of haploid genomes in multicellular eukaryotes have been widely considered as a 'junk'.

Usually by ncDNAs mean introns, spacer DNA, potential genes, pseudogenes, DNA satellites and chromosomal heterochromatic regions.

Out of all known derivatives of ncDNAs only chromosomal heterochromatic regions (HRs) discovered as far back as in 20s of XX century [4] are well studied. The eukaryotic chromosomes contain two distinct types of chromatin: euchromatin and heterochromatin. Euchromatin contains genes and other unique sequences. Heterochromatin encompasses a smaller proportion of the chromosome, and is enriched in non coding, highly repetitive sequences. At present we have extensive information concerning features of organization and properties of chromosomal HRs. The best-known features of HRs are: (1) HRs are evolutionarily fixed in genome of all higher eukaryotes, (2) HRs are in a condensed condition during the whole of a cell cycle, (3) they are organized, as a rule, from short, non transcribed, tandemly joined sequences, (4) HRs are located in centric and telomere chromosomal domains, as well as in regions forming nucleolus-organizing regions (NORs), (5) HRs are replicated at the end of the S period of a cell cycle, and (6) wide interspecific and intraspecific variability on the quantitative contents. Speaking about properties of HRs the following is usually meant: (1) heteropycnosis as morphological expression of dense packing, (2) ectopic conjugation of HRs between homologous and inhomologous chromosomes in an interphase nucleus, (3) high frequency of breakage in domains with HRs or on a border of them by euchromatin regions, and (4) genetic inertness.

Why ncDNAs?

First of all because DNA is more plastic than was previously expected [5]. First of all they are capable of creation of higher forms of DNA organization. For example, highly repetitive regions of chromosomes adopt a heterochromatic chromatin structure, with distinctive properties and chromatin components [6]. At present we have extensive information concerning the features of organization and properties of chromosomal heterochromatic regions (for details see [7-11].

There is much evidence to show that the eukaryote genome is an epigenetic machine, besides being a genetic one [12]. Thus repeat sequences in euchromatin can lead to heterochromatinization.

Heterochromatinization can lead to position effect variegation (PEV). Constitutive heterochromatin induces PEV in euchromatic genes brought into contact with it by transposition [13-15]. This ability of constitutive heterochromatin can be extended to tandem repeats located within regions defined as euchromatin [16]. In this version of PEV, local 'heterochromatinization' can occur in the absence of any transposition. Sapienza [17] already pointed to an intimate relation between imprinting, heterochromatinization and PEV. Sequence repeats in euchromatin pair with constitutive heterochromatin through DNA looping. Thanks to DNA looping, repeat sequences in euchromatin join and pair with constitutive heterochromatin, even at considerable distances [18]. A gene's distance from stable heterochromatin affects of variegation [18,19]. Thus, an additional avenue for the evolution of gene regulation is provided through the introduction or loss of repetitive sequences. Of direct relevance here are the existence of different nuclear compartments, namely, the chromosomal territories and interchromatin compartments [20,21], and the fact that transcription and other processes occur in specialized and localized multiple 'factories', in each of which a particular type of RNA polymerase is bound to the nuclear matrix [22] (for details see [12]).

Nobody challenges the role of ncDNAs in formation of nucleosomas and chromatin. At the present time extensively are discussed that nucleus of eukaryotic cells, nucleosomes, chromatin, mitotic chromosomes, chromosome bands, heterochromatin regions, multicellularity, differentiation of somatic cells, sex, thermoregulation, adaptation, and also human being's naked skin and large neocortex result mainly from the evolution of ncDNAs [11,23-29].

It is difficult to imagine, that e.g. mitotic chromosomes, mono- and multicellular eukaryotes or higher vertebrates appeared resulting from prior forms of life accumulating great number of new genes. The share of coding DNA in the body of the mitotic chromosomes testifies to that. 'Each of us has roughly 30,000 genes, far fewer than the 100,000 that most researchers had expected. This is somewhat puzzling as some plants have 26,000 genes; clearly it is not merely the number of genes that determines the complexity of an organism' [30].

While paleontologists referred to 'the Cambrian explosion', those who studied cellular organization insisted that the real 'big bang' of biology occurred at least 1.8 billion years earlier when the eukaryote arose. With its membrane-bound nucleus and all the associated features, such as mitosis, and multiple chromosomes to package up to tens of thousands of genes per cell, it provided the organismic conditions for the differentiation of tissues, organs, and organ systems of plants and animals. Bacteria had only an unpackaged single strand of DNA, holding some four thousand genes. In this connection Mayr [100] insisted that 'all archaebacteria are nearly indistinguishable'; even if one took prokaryotes as a whole, he argued, the group 'does not

reach anywhere the size and diversity of eukaryotes'. Microbial phylogenists had so far described only about 200 archaebacterial species and only 10,000 eubacterial species, whereas Mayr suspected that within eukaryotes there were more than 30 million species. There were 10,000 species of birds alone, and of course hundreds of thousands of species of insects [100].

According to modern synthesis, rapid evolution is brought about by three main factors: high mutation rate; a short interval between generations; and large populations. Bacteria satisfy these factors but have remained rather stable in evolution. Prokaryotes have almost not changed for the last 2-2.5 billion years of history of the Earth. In contemporary evolution theory the biological species concept do not hold for the bacteria (sensu lato), among which horizontal gene transfer is rampant and evolution is reticulated [3]. So far there are no examples, which prove, that any species appeared exclusively owing to the gene changes. For example, the primates have existed for about 70 million years. The evolutionary studies carried out so far seem to indicate that the euchromatic regions of the chromosomes in the different species of primates analyzed are quite similar [31,32]. The main differences in these species are due to the different amounts and localization of heterochromatin [33]. The insignificant distinction between a human being and a chimpanzee at the level of DNA [34] and chromosomes [35] demonstrates, that the predominating role of structural genes in evolution has, probably, been strongly exaggerated. For example, the study of the amino sequences of proteins, and of DNA-DNA hybridization, shows that the genetic differences between the chimpanzee and humans are less than 1.1% [34].

While a tremendous amount of variation of proteins, enzymes, DNAs and chromosomes have been revealed, a satisfactory explanation of the origin and maintenance of such variation is lacking. Population genetic theory leads to conflicting conclusions about the forces operating on the variation, and it appears that current theory is inadequate to cope with the data. It is not by chance that Lewontin [2] urges that a theory needs to be developed which takes into account the evolution of the genome as a whole rather than the independent evolution of each gene. Such examples are many, therefore I would limit myself to the following question: whether ncDNAs are related to evolution?

Whether ncDNAs are related to evolution?

Obviously for correct understanding of the history of the development of organic forms it is necessary to clear out the mechanisms of origin of the main biological forms and functions on the basis of which all the cells, tissues, organs and organisms are constructed, and finally the overall biodiversity. Below some data are given, testifying that, probably, ncDNAs could play decisive role in the development of biological forms and functions.

1. The bulk of existing data allows to suppose, that mainly the following are related to ncDNAs: (1)

immobilization of chromatin fibers within so called "chromosome territories", but not as "spaghetti" in the interphase nucleus; (2) large genomes, which have an opportunity to separate in the groups of linkage (chromosomes), and thus they can pass through the mitotic cycle; (3) existence of chromosomes makes possible a differential condensation, replication and transcription both at the level of the whole chromosome (e.g., inactivation of the second X- chromosome with the female mammals), and their separate parts, by this creating the prerequisites for appearing of specialized cells, tissues, and organs; (4) both internal (repair, recombination, rearrangement, modification, restriction) and external (replication, transcription, packaging, organized movement) molecular activities of chromosome are realized outside the cytoplasm in a relatively isolated environment. In addition, Elgin and Grewal [36] assume that ncDNAs play an essential role in stable repression of large pericentric and telomeric domains, to prohibit deleterious recombination between repeated DNA sequences and have impact on higher-order chromatin assembly and genome regulation.

2. After the differential staining (C-, G-, Q- and R- techniques), the mitotic chromosomes in their length acquire the appearance of cross-streaked structures (bands), where the alteration of densely and weakly stained segments are strictly individual for each chromosome in the karyotype that allows their error-free identification [37]. Differential staining of metaphase chromosomes is a universal phenomenon for higher eukaryotes. In this phenomenon constant, fundamental elements of chromosome organization are manifested. The dense and weakly stained chromosome segments in the first place reflect different degrees of density of the DNA packaging [38,39]. It has been also established that in the G+ and Q+ bands the number of genes is much less than in the G-, Q- or R+ bands.

The significance of the G-, Q- or R- bands in development and evolution for higher eukaryotes remains completely unknown. We see the biological significance of these phenomena in selective inactivation of genes, which are mainly necessary at the early stages of embryogenesis with the help of the ncDNAs. In particular, with appearance of the G+ bands these genes are inactivated until the end of ontogenesis. The confirmation of this idea might be the assumptions, which were expressed more than once that the onco-genes are possibly the genes functioning at early stages of embiyogenesis, but they may became active after the G+ bands are damaged, or because of some forms of chromosome rearrangements in the somatic cells, as a result of which they are again available for transcription machinery – now in the differentiated cells. For example, analysis of leukemic cells from patients with chronic myeloid leukemia revealed that the material from the Philadelphia (PH[1]) chromosome (no. 22) was translocated to chromosome 9, not deleted [40]. Later was shown that the 9;22 translocation results in the movement of the ABL proto-oncogene on chromosome

9 next to a gene called BCR on chromosome 22 [41]. This gene was discovered only because of the translocation. The translocation results in a fusion mRNA and a fusion protein that is larger than the ABL protein in normal cells and his somewhat stronger tyrosine kinase activity. Analysis of the 8;14 translocation in Burkitt's lymphoma led to the paradigm (supported now by analysis of translocation in other leukemias/lymphomas) that the effect of translocation is to move gene that is centrally involved in growth regulation adjacent to a gene that is actively expressed in the particular type of cell in which the translocation occurs. These reports started a revolution in cancer biology that continues with increasing momentum. Of course, role of the chromosome bands in the mentioned above is far from being exhaustive.

3. It is difficult to explain such phenomena as cell division by the activity of the genes, as they are not being transcribed in the metaphase chromosomes. The ability of eukaryotic cells to delay segregation of chromosomes until long after their duplication distinguishes their cell cycle from that of bacteria, in which chromosome segregation starts soon after the initation of DNA replication. Furthermore mitotic chromosome condensation, without which large genomes cannot be partitioned between daughter cells at cell division, would not be possible if chromosome segregation coincided with DNA replication. A gap between S and M phases therefore made possible the evolution of large genomes. Despite its importance, the mechanism by which sister chromatids are tied together is poorly understood. Nevertheless there is no doubt that at the cell division, ncDNAs participates: a) in shortening and dense packaging of the chromatin fibres for formation of the body of the metaphase chromosomes; b) it keeps the sister chromatids up to the end of anaphase together; c) in repulsion of the sister chromatids at the stage of anaphase from each other; d) it gives chromosomes the necessary strength and flexibility so that they can pass the mitotic cycle (see [27]).

4. We have made a suggestion about a possible role of ncDNAs in cellular thermoregulation. Our hypothesis is guided by a concept of the cell thermoregulation (CT) and the role of the chromosomal heterochromatin regions (HRs) in the composition of the condensed chromatin (CC) in this process [23]. The essence of the CT is in the following: CC, being the densest domains in a cell apparently conducts heat between the cytoplasm and nucleus when there is a difference in temperature between them. The assumed heat conductivity effect of CC is stipulated by its principal features: condensed state during the interphase association with the lamina and the inner nuclear membrane, replication at the end of the S period of a cell cycle, formation of the chromocenter, genetic inertness and wide variability in the quantitative contents both within and between species.

The reality of the CT existence is shown at the organism level, although we still have to demonstrate its functioning also at the level of individual cells Experimentally we have managed to establish, that: a) individuals differ in populations on their body heat conductivity (BHC); b) human BHC is effected by sex, age and ethnic and racial origin; c) human morphophysiological characteristics such as height, weight, body constitution, blood pressure and pulse rate do not influence significantly on human BHC; d) apparently, human BHC depends mainly on the amount of chromosomal heterochromatin in his genome. As we suppose the level of heat conductivity peripheral layer of CC influences the speed of heat energy transferring inside the cells and then into intercellular space (for details see 11,27,42,43]).

5. Probably CT is directly related to another fundamental phenomenon. As is known, Lyon [44] proposed the single-active X chromosome hypothesis to explain the observation that in the mouse, females heterozygous for X-linked for color genes are patchy mosaics of two colors. According to the Lyon this mechanism provides dosage compensation for X-linked genes because each cell, male or female has only one X-chromosome that is transcribed. This generally accepted thesis connects the main reason of inactivation of one X chromosome in the normal female with possible undesirable genes' effects in case they are in double amount in the mammal's genome.

As I conceive, the hypothesis of gene dosage compensation may turn out to be not the only reason for 'lyonization'. It is possible that in this phenomenon the heat conductivity effect of the CC in the CT also plays quite an important role (for details see [11,23,24,27]. In short, the essence of our objections is based on the following facts:

a) the inactivation of one X-chromosome in the normal females occurs only with the mammals, which are able to support a relatively constant core temperature in the body;

b) the inactivation of X chromosome takes place early in embryonic development at an estimated 1000 - to 2000- cell stage of the blastocyst or possibly even earlier (for review see [99]). In other words, with the formation of a multicellular embryo the problems arise, which are connected with the intracellular thermoregulation, and we believe that for their solution the CC is of great importance [23,24]. As in the karyotype of the female mammals there is lack of the sex chromosome with a large block of HR, for example as Y chromosome with males, then it is possible that in the interest of the CT a considerable part of one of the two X-chromosomes with the female embryo is undergoing to heterochromatinization. This is proved by the physiological data on a relatively low heat conductivity of the female body in comparison with the males' one [28];

c) if compensation (double) dose of genes is an inevitable phenomenon for normal functioning of the mammals' genome, then why the inactivation of

genes on the homologous autosomes do not happen? The inactivation of autosomes was not found even in cases of trisomies;

d) '...the mammalian X chromosome is not specialized for sex determination. Although a rather large number of X-linked genes are known in mammals, a vast majority of them have nothing whatsoever to do with the process of sex determination and sexual development. On the contrary, many of the genes clearly involved in sexual development reside in autosomes'... 'Even the genes for hypothalamic releasing factors of gonadotropins are apparently on autosomes' [45].

Therefore, I assume that X chromosome is heterochromatized rather than inactivated to compensate for the lack of a large block of HR in the caryotype of females in the interests of CT [27].

6. There is a good reason to assume that the role of the ncDNAs in the cell differentiation may be significant. Though for the time being we do not know the concrete mechanisms of the ncDNAs influence on the cell differentiation, nevertheless the listed below facts justify to their possible participation at this important stage of development:

a) the specialized cells, tissues and organs appeared only after appearance of the cellular nucleus, i.e. the eukaryote organisms;

b) there are good reasons to believe that the eukaryote cell itself is the result of a long-term evolution of the ncDNAs [24];

c) with appearance of a nucleus isolated from the cytoplasm, the genes in the eukaryote chromosomes are no longer easily accessible to the transcription machinery, as in the prokaryote cells. For this it is necessary, somehow, to isolate the genes from the direct influence of the inductors in the cytoplasm. Apparently, such an isolating means is the nuclear envelope with a thick layer of peripheral CC of cells [27,24];

d) as a rule, the DNA of mitochondrions and chloroplasts in eukaryotes are outside the nucleus, and this situation, seemingly, is of an extraordinary importance. If they were inside the nucleus, then the energy supply of the eukaryote cells would be seriously under the threat, as these coding DNAs may be influenced by the condensed forms of the ncDNAs with well-known consequences (as in case of the position effect variegation);

e) apoptosis (programmed cell death) is peculiar only to the eukaryotes. Seemingly, it is the consequence of availability the ncDNAs in their nucleus genome. The point is that: the eukaryotes have global repression mechanisms for inactivation of genes, such as nucleosomes and histone-mediated chromatin structures [5]; in higher vertebrate genomes every cell cycle must be accompanied by genome compaction on the order of 10 - 40-fold [46]. All the above may mean with time, after a certain number of cell divisions in the nucleus genome there are no genes left, which are available to transcription machinery. Indirectly the

picture of apoptosis proves it: dissolution of nucleolus and chromatin condensation on the internal surface of nuclear membrane [47] accompanied by DNA fragmentation into large (about 50 kbp) blocks [48], membrane blebbing, dilation of the endoplasmic reticulum, swelling of mitochondria, cell shrinkage and nucleosomal DNA laddering [49]. Hence, the availability of the ncDNAs in the eukaryotes' genome is not permissiveness, but a strict responsibility to the individual development and evolution;

f) there are also other indirect data that prove a possible role of the ncDNAs at the earlier stages of embryogenesis. So, as an example, it is known that before the mitotic division of both the nucleus of spermium and the nucleus of the somatic cells (in the nucleus transplantation) in the egg, at the beginning they significantly swell [50]. When somatic nuclei are injected into *Xenopus* eggs (meiotic metaphase II), the nuclei swell up to 100-fold in volume within 1 hour, but they do not transcribe genes, reflecting physiological transcriptional silencing in eggs. When injected into oocytes (meiotic prophase), the nuclei swell more slowly, spending 3 days to accomplish the same 100-fold increase in volume [51], but they remain transcriptionally active during this period. The swollen nuclei in oocytes tend to show more active transcription than those that have not swollen, suggesting that the chromatin decondensation is not merely a morphological event but also linked with an increase in overall nuclear activity [52]. We assume that in this case there is the decondensation of the interphase chromosomes densely packed in the nuclei of the specialized cells with the ncDNAs. Obviously, without complete decondensation of chromatin in the spermium nuclei or the somatic cells the replication of the interphase chromosomes is hampered, without which the mitosis is impossible;

g) the picture of haemopoiesis clearly proves to the effect that the ncDNAs may relate to the cell differentiation. In this case it is obvious as nowhere else that the deeper the cells are differentiated, the smaller is the size of their nuclei. Sometimes such trend goes to extremes; the specialized cell loses the nucleus at all, as is the case with erythrocytes in the mammals. In other words, the larger the nucleus size is the more genes are transcribed, and vice versa. If this rule is correct than the greatest number of genes must be transcribed in cleavage of the fertilized egg, and the least number in the reticulocytes.

By these I do not at all insist that the ncDNAs are capable for specific reactions. Their non-specific molecular composition does not allow it. The only thing I want to say is that the non-specific reactions may be the basis for creation of specific forms of reaction, and this circumstance may be related to the differentiation in the multicellular organisms.

7. Epigenetic regulation of cell differentiation is surprisingly reversible. The most striking evidence of this reversibility is the establishment of fertile mouse

clones by using nuclei isolated from terminally differentiated lymphocytes and olfactory sensory neurons [53,54]. More and more data are being accumulated to prove that heterochromatin component can change, perhaps becoming rigid during cell differentiation. There has been proposed a rather substantiated hypothesis about the undifferentiated cells containing more loosely packed chromatin than their differentiated counterparts to maintain many genes in a potentially open state to prepare them for future expression [52].

There are certain mechanisms identified for the participation of some types of ncDNAs in epigenetic gene regulation. In particular, there is evidence that aggregation of pericentric heterochromatin is a general feature of terminally differentiating myotubes, and this major reorganization of nuclear topology can be induced by MeCP2 and MBD2 proteins. Furthermore, this rearrangement of heterochromatin is independent of the histone H3 trimethylation pathway and can occur throughout interphase [53].

Functional attachments to various nuclear landmarks are thought to organize the architectural folding of the chromosome fibre. The position of a gene within the nucleus can favor its silencing or activation and the efficiency with which its products are processed or transported to the cytoplasm. The stochastic properties of genome organization may contribute to cell-type-specific gene expression and to the dynamic responses that occur during differentiation and adaptation to the environment (see [54]).

8. There is one more example in the analysis of the cell differentiation, which as we believe is of interest itself: sex differentiation (SD) among animals. For the time being the mechanisms of the SD are not known. At present the balance hypotheses, worked out by Bridges [55] and Goldschmidt [56] are generally accepted. According to these hypotheses, the interaction of genes, located in the sex chromosomes and autosomes, underlie the SD. Thus, it is considered that sex is a polygenic feature.

In order to clarify the essence of our point of view, it is necessary to remind, that the sexual development in the mammals is a process consisting of at least three stages: the 1st stage is the chromosome determination of sex (XX or XУ); the 2" stage is SD (the development of testicles or ovaries); the 3rd stage is the development of the secondary sexual characteristics.

At the early stages of embryonic development a pair of undifferentiated embryonic gonads (UEG) and both rudimentary female and male reproductive system develop in the embryo. The UEG turn out to be of dual nature, or to be more exact they are indifferent concerning sex. They consist of the outer layer of tissue (cortex) from which the female tissue develops, and the inner layer, called medulla, from which the male tissue develops. In course of the 2nd stage of the sexual development, the progress of one of the germs and suppression of the other one takes place. In the male sex the medullary tissue, which suppresses the activity of the cortex layer, develops quicker; as a result the gonads turn into the testicles.

I assume that basically the SD is a "physical process", and at this stage of the sexual development the role of genes (a chemical process) is insignificant. The genes effects mainly determine the development of secondary sexual characteristics. As I conceive, the ncDNAs plays an important role in the SD.

Let's try to illustrate this assumption on the example of a human being. Until now the hypothetical genes responsible for the development of the male sex in the Y chromosome have not been revealed. The point is that the Y chromosome is largely a dummy [45]. Most likely from my point of view, the HR of the Y chromosome are responsible for the development of UEG towards formation of the testicles, and not some genes.

At first I give some initial prerequisites. (1). For lack of the processes causing the testicles development, the UEG develops invariably as an ovary. (2). SD at the level of gonads turned out to be a threshold phenomenon; to transform the germ cells of the gonads into the testicles some minimum "dose" of the factor switching over the direction of the sexual development is needed. (3). The sex "genotype" manifests its direct impact only at this stage of the UEG development transferring the further control over the corresponding development of the secondary sexual characteristics to different hormones.

Now let's try to ground our assumption. (1). The heat conductive effect of the CC especially strongly increases in conditions of mulicellularity [24]; (2). In a number mammals, including man, it has been shown that at equivalent gestational ages, males are developmentally more advanced than females [57,58]. By the 3th week of the embryo development in human, the HRs are completely formed [7], and they are able to exert their heat conductive effects in the cells. (3). Medulla, being located in the very middle of the UEG closed to aorta and surrounded with mesentery probably experiences the greatest problems with removal of the excessive heat in comparison with cortex. Obviously, the cortex having a relative advantage in supporting the intracellular temperature homeostasis than the medulla, other things being equal, has more chances to preserve and further develop into the female tissue (for details see [25,26].

Seemingly, the SD in animals and human is determined by the amount of cHR in the chromosomes of the UEG via cell thermoregulation. It is assumed the medulla and cortex tissue cells in the UEG are very vulnerable to the increase of the intracellular temperature. If the amount of the cHR is enough for efficient elimination of surplus heat in rapidly growing UEG cells the medulla tissue survives. Otherwise it doomed to degeneration and a cortex tissue will remain in the UEG.

It could be possible to test our hypothesis experimentally. At UEG with the karyotype XX to remove its cortical layer preserving the medulla tissue.

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If our hypothesis is true then a male with a female genotype will be developed (XX), which at usual crossing results only in females. Such experiments could give an answer to two interrelated question: 1) what does the SD depend on, either on the gene balance or on the "dose" of the HR?; 2) why does at genotype XX the medulla tissue preliminarily degenerate?, either from the "heat death" because of a small dose of the HR or from the impact of the gene products, produced by the cortex cells, on the medulla tissue?

9. In the process of evolution of the higher eukaryotes also the chromosome b a n d s (C → G → Q - b a n d s) have evolved. It is notable that the chromosome bands are best of all revealed by the existing methods of differential staining on the chromosomes in the mammals,
and especially clearly they become apparent in the higher primates [24]. About 15%-20% out of non coding part of human DNA represents constitutive heterochromatin (John 1988). There are two types of constitutive heterochromatin in human chromosomes: C- and Q- heterochromatin [37,59,60]. Chromosomal C-heterochromatin regions (C-HR) were detected in genome of all higher eukaryotes whereas Q-heterochromatic regions (Q-HRs) are presented in genome of only three higher primates (*Homo sapiens, Pan troglodytes and Gorilla gorilla*) [9,61,62]. However there is a fundamental difference between them: quantitative variability of chromosomal Q-HRs in the genome only exists in human population.
There are data available, which testify that in unprecedented by its speed and scales of adaptation of a human being to different climatic and geographical conditions of the planet chromosomal Q-HRs are more important than genes [11,23,63,64]. Results of extensive comparative population cytogenetic studies showed that populations of modern man differ significantly on the amount of Q-HRs in their genome. It can be maintained that these differences are mainly related to the natural environment of residence of the human population and not to racial or ethnic features. In particular, the amount of Q-HRs is considerably lower in the genome of populations living permanently at northern latitudes and high-altitude regions, as well as in newcomers well adapted to extreme natural conditions of high altitudes (mountaineers) and the Far North (drillers), than in populations living in temperate zones of lowland Eurasia and tropical Africa [65-73,101]. As we suppose, the *H. sapiens,* besides those inherent in all warm-blooded vertebrates, possesses an additional but very fine and simple mechanism of thermoregulation. In the present case, in order to preserve temperature homeostasis under different environmental conditions, in addition to physiological and biochemical mechanisms, the simple physical effect, such as body heat conductivity, was used. And value of this effect depends of the amount of chromosomal Q-HRs in genomes of individuals in a population. Evidently, in conditions of hot climate a high

level of intracellular heat conductivity is important in order to take out metabolic surplus heat from the cell, whereas in conditions of cold climate it is important to retain some heat energy by slowing down its transfer into intercellular space [11,27,42,43].

10. As Changeux [74] points out, the volume of the human brain continues to increase long after birth, whereas in the chimpanzee it augments only slightly. The same happens with the bipedal posture. Much needs to be learned about the development of the human brain and the way it is affected by the physico-chemical components of the environment [75]. I believe that the increase of the human brain size was not the result of dramatic changes of the structural genes. Most likely it was the consequence of more ordinary events, such as evolution of HRs in chromosomes, BHC and skin [64].
Naked skin was a result of long series of events, each depending on the other, and each unpredictable and unique. Apparently, the main reasons for appearance of hairless skin were the following factors: a) increase of BHC because of high Q-HRs and C-HRs content in the genome of the direct ancestor of modern human; b) quantitative and qualitative changes of the diet composition [76-78], which lead to increase of heat production in the organism demanding efficient heat loss from the body for preservation of temperature homeostasis; c) tropical climate of Africa, where the ancestors of the *H. s. sapiens* inhabited, had a strong selective influence on such organisms because their bodies have changed towards high heat conductivity and heat production. It is possible that in such conditions the best solution of the thermoregulation problems was modification of skin: loss of hairy cover, increase of its heat dissipation ability by increase of the amount of the eccrine glands, blood vessels, and other changes. Such skin, in addition provided with a great amount of sensory receptors, cannot but influence the postnatal development of the brain size because they have a close ontogenetic connection, since as in early embryogenesis the skin and brain are formed simultaneously from ectoderm.
It is believed that namely the skin has led to the formation of many more abundant microconnections and also to parts of the brain being connected, which had not been connected before. It would also lead to changes the rates of dendritic pruning during development and puberty, which are also important in determining the connectivity of the adult brain. Size alone of the brain is important in providing enough neuronal elements to interact to produce a complex network. But it is the richness and specifity of the fine connections of that network, which determine the complexity of the information processing which can occur [78]. Information from touch-sensitive nerve cells ultimately crosses the sensory cortex to the opposite side of the brain where it is processed. The amount of space needed by the cortex is related not to the size of the body part but to the nerve density: areas with more

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nerve endings, such as fingertips, tips and genitals, require more space in the cortex than the back, which has fewer nerve endings [79].

For unknown as yet reasons, at late stages of the evolution of life, in ancestor of contemporary three higher primates (*H. sapiens, P. troglodytes and G. gorilla*) there appeared a new type of HR – Q-heterochromatin. Thus, one can say with certainty that Q-heterochromatin originated in tropical Africa.

C-HRs is available in the genome of all higher eukaryotes, including great apes. But in the heterochromatin part of genome in the direct ancestors of modern human some changes occurred about 100-150 000 years ago; in addition to Q-HRs, on three pairs of autosomes (1, 9 and 16) unusually large C- HRs appeared, which do'not exist in karyotypes of chimpanzee and gorilla [61,62,80]. There are no C-HRs of such size on the chromosomes of chimpanzee and gorilla. Q- and C-HRs are also available on the Y chromosome of human and gorilla. However the size of constitutive heterochromatin in human Y chromosome is much larger than that in gorilla [37]. Thus, by the total amount of HRs, the human surpasses all other higher primates, as in his genome; in addition to Q-HRs on seven pairs of autosomes (3, 4, 13-15, 21 and 22) there are three pairs of autosomes (1, 9 and 16) with large C-HRs [37,61,62].

As we have demonstrated before, the amount of chromosomal Q-HRs in genome is connected with the human BHC [28]. We assume that assemblage of the greatest amount of HRs in the *H. sapiens* genome among the higher primates was the turning point in human evolution [63], as exactly this circumstance has lead to disappearance of hairy cover on his skin. The latter turned out to be the main factor responsible for increase of the brain size during the first years of life of the *H. s. sapiens* [64].

11. The longevity is surrounded by many mysteries; at least three of them are related to humans: (1) the infants who die in the first four weeks of their life, have low birth weight, complications of pregnancy and of delivery, and congenital malformations. Between the first four weeks and one year, respiratory and other infectious diseases take their toll, together with malformations, sudden infant death syndrome, and accidents; (2) the fact that women live longer than man; and (3) the shorter life span of males applies to most animals that have been studied.

The following observations testify to a possible role of ncDNAs in longevity. It is established that: (1) in a population there is a clear-cut tendency towards a decrease in the number of chromosomal Q-HRs with age, regardless of racial and ethnic features of the individuals; (2) of all the age groups the genome of neonates contains the greatest number of Q-HRs; (3) decreases in the number of Q-HRs with age are not due to the "loss" of Q-heterochromatin on individual loci or chromosomes, but occur simultaneously in all the seven Q-polymorphic autosomes [81,82]; (4) we also have demonstrated that the mean number of Q-HRs

per one individual (m) in newborn population were 3.16 in Kyrghyz and 3.59 in Russian, respectively. Neonates are characterized by a high range of variability in the distribution of Q-HRs (from 0 up to 7) in population. But died neonates, besides high value of m differs by extremely narrow diapason of variability of Q-HRs in population: number of Q-HRs in a karyotype changes from 4 up to 6, with m = 4.58 and m = 4.80 in Kyrghyz and Russian, respectively [83].

12. Chromosome rearrangement is a key event in speciation; new species almost always have a new karyotype [84-86]. On possible role of the satDNAs and HRs chromosomes in the evolution of plants and animals there is a vast amount of publications (see [5-8]).

13. Retrotransposable elements are frequently considered as "junk DNA", though they are the major constituents of genomes in all eukaryotes. These mobile ncDNAs sequences can disrupt genes, induce genomic rearrangements, influence gene expression and are driving forces of genome evolution. Some mobile sequences have been domesticated by the host and play important cellular roles (for details see [87]).

14. At present it is not known how introns originated and how exons were put together, i.e. what principles governed their assembly. The basic functions of introns remain enigmatic. There are assumptions that introns (1) could be used in the nucleus as a communication message between other genes, (2) can be part of a cascade type process of the regulation of gene expression, (3) could also regulate messenger RNA maturation, and (4) could be future sites of chromosomal evolution [5,38]. Gilbert [88] proposed that introns arose at the beginning of multicelluarity and played a major role during the Cambrian explosion in creating new genes by exon shuffling. However, everybody agrees with one thing: Introns could be future sites of chromosomal evolution. For example, Maynard Smith [89] believes that from a conceptual point of view the most important fact, which should be taken into consideration by us, is a wide distribution of genetic elements capable of multiplication within the genome. It is possible that for such multiplication short non coding sequences were used, which, with time, formed the basis of the satellite-like, and other highly repetitive sequences. Macgregor [90] believes that apparently one of the properties of the DNA is its trend for multiplication. The proposal was made that a general function of introns consists in their potential to help stabilize local high-order structures of chromatin in which genes, at times, have to be sequestered [91-93]. Anyway, the introns are in general much larger than the exons. The similarities between the introns and CC cannot be ascertained at present, but two classes of DNA do not need to be very different from each other [23].

We believe that after unwinding of DNA and its transcription, introns are attached to the inner surface of the nuclear envelope through CC. In other words, in the process of synthesis of primary RNA molecules the introns are used as binding sites for immobilization of the

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DNA of genes. Since the 1960s, this principle of synthesis of long polymeric molecules has been successfully used in organic chemistry, and it is known as solid phase synthesis [94]. The basis of this method is a temporary fixation of the polymer chain under synthesis (polypeptides, polynucleotides, polysaccharides, polyamides) on the insoluble polymer carrier (solid phase).

The first requirement for the solid phase synthesis is a suitable insoluble support. For these purposes, the chemists use the polystyrene and polyacrylamide resins. With this the synthesis reaction occurs in the heterogeneous compound with the surplus amount of all constituents of the polymer molecular components. It is possible that the same principle of synthesis of long polymer chains occurs in live nature. In the nucleus the primary RNA is assembled as a polymer chain in a stepwise manner where intron parts of DNA as a solid support are attached to the inner surface of the nuclear envelope through CC. After the full gene has been transcribed into primary RNA transcript intron-coded regions are deleted as exon-coded ones are spliced together. This second process of reunion is very important; otherwise the different pieces derived from the exons would not be aligned in perfect order but would be combined at random, giving different types of messages instead of always the same one. In this case, the introns promote successive and faultless binding of short sections of exons in mature RNA in the direction from the 5′ and to the 3′ end. In prokaryotic cells, one long, circular strand DNA serves as a chromosome. Yet, even in them, the genome is usually concentrated in one dense area of the cell called the nucleoid. Ultimately, an animal cell's need to adhere to a solid surface (anchorage dependence) is one of the most widespread features of live [24].

15. It is now clear, that major incongruities exist and that there is only a weak relationship between biological complexity and the number of protein coding genes. For example, using the protein-coding gene number as a basis for evaluating biological complexity would make urochordates and insects less complex than nematodes, and humans less complex than rice. However, Taft and Mattick [95] analyzed the ratio of non coding to total genomic DNA (ncDNA/tgDNA) for 85 sequenced species and found that this ratio correlates well with increasing biological complexity. The ncDNA/tgDNA ratio is generally contained within the bandwidth of 0.05 – 0.24 for prokaryotes, but rises to 0.26 – 0.52 in unicellular eukaryotes, and to 0.62 – 0.985 for developmentally complex multicellular organisms. Authors came to the conclusion that the observed non coding DNA increases and compositional patterns are primarily a function of increased information content. It is therefore possible that ncDNAs previously regarded as genetically inert may be far more important to the evolution and functional repertoire of complex organisms than has been previously appreciated.

Concluding remarks

Rose [96] talking about the three main problems – of the origin and persistence of variation, of adaptation and of speciation – that Darwin left to his followers to resolve, specifies that: '(1) The first was the mechanism of transmission of both similarities and variations; (2) The second was the classic argument from design: how could gradual change result in such seemingly perfectly adapted structures as a eye; (3) The third was the problem of speciation. Today, the first is no longer a problem, the second raises a number of important conceptual issues, and the third is still with us'.

As is known in the process of writing '*The Origin*' Darwin had some difficulties due to shortage of data on variability to prove his theory. Nowadays it is otherwise. We do not know how to explain the cause of polymorphic proteins, enzymes, DNAs, chromosomes origin and their role in evolution. Having seen millions of variable sites of human being's DNA Darwin would rather ponder: could natural selection choose the most adapted organism out of such tremendous variability in order to create new species? The matter is that up till now the question on how the degree of genetic differences between individuals in population influences on their biological fitness which, finally, should be expressed in longevity and number of descendants reached reproductive age is still open. This proved by results of persistent comprehensive researches of human adaptation to various extreme natural conditions [102]. 'With respect to identifying specific genetic loci contributing to high-altitude functional adaptation, efforts so far have not been successful' [97].

When the success of the Human Genome Project (HGP) celebrated (2001) several scientists proclaimed that the genome sequence represented 'the script of life'. However, as is known, results of HGP did not give both theoretical and practical results which had been promised by the Project initiators to the general public. This even is not the matter of fact. The lesson was useful in many ways including understanding of material basis of evolution. Nowadays we are not allowed to think that 'We are built as gene machines' [98]. If not genes then what? For a while nobody has ready answer. However it is not the way out to think only within the frames of modern synthesis conception because it was not able to solve even the problem of speciation.

Apparently ncDNAs had done real revolution in the history of life on the Earth. The appearance of eukaryotic cell, nucleus, mitotic chromosome, sex, multicellular organisms with specialized cells, tissues and organs, temperature homeostasis, adaptation, warm-blooded animals up to modern human being could be explained by the emergences of ncDNAs [11,23,24,27,63]. Sexual mode of reproduction made possible of evolution in Darwin's understanding – origin of biological species. Though at present all this do not mean that "master molecules" should be named as ncDNAs, and not genes. The synthesis of proteins and enzymes is impossible without genes, if there is no such involvement any types

of DNAs will remain the most inert and stable macromolecule known to science.

As far as I can see variation of genes (in the sense of favorable mutation) did not have substantial significance in evolution contrary to generally accepted opinion. Then, how would we imagine evolution without variability? We do not dispute the role of variability in evolution. The only case is types of variability. Probably it will be more correctly to distinguish two types of variability. The first type applies to genic   variability and its products (proteins and enzymes), and the second type is limited by ncDNAs variability. There are considerable reasons to think that genes could not play substantial role in evolution of eukaryotic organisms because new forms and functions are needed for their evolution. Thus genes are not able to create new forms and functions because, as it turned out, old classical notion of one gene, one protein and one function is exception rather than rule. Number of genes in genome and their products (e.g. polymorphism of proteins and enzymes) differ with tremendous diversity; it can complicate creative work of natural selection. It is obvious that in order to create new form or function the involvement of many genes not one is important. However the probabilities of coordinated favorable mutations for large number of genes in great number of individuals in population are extremely small.

The variability of ncDNAs radically differ from genes, it is less diversified but is able to cover considerable part of genome. The number of chromosomal HRs of individuals in human population or inactivation of one of X-chromosomes in genome of female animal may be shown as an example of such variability (see above). Variability of the ncDNAs can ensure more rapid changes in the genome than those that could be only achieved by mutations of structural genes. They apparently ensure genetic adaptation to changes in environment more rapidly as compared to the process of mutation. In order to survive and leave descendants in a new environment, the organism utilizes different mechanisms, and this does not always require the participation of genes.

What does the gene actually do? The role of genes according to one of the known critic of new-Darwinism is as follows: (1) The gene is relevant but of secondary importance. The gene does not create form and function, it only fixes one of the alternatives; (2) Darwinism and neo-Darwinism start from the wrong end of evolution, i.e. from its terminal products. The origin of species and the dynamics of populations has been the main object of their studies. The mechanism of evolution is unknown at present. However, the mechanism of a phenomenon can only be revealed by investigating its primeval causes. Only by studying the origin and transformation of form, and the origin and transformation of function, can one elucidate with precision the mechanism of evolution. Any other approach is a start in reverse [38].

Currently theories of differentiation on genic level could be considered as disproved; although they (genes) are identical in all types of cells of an organism. That does not apply to ncDNAs; they vary considerably depending on the type of cells, stage of a cellular cycle and ontogeny, thus creating different microenvironments for functioning of genes with all the resulting consequences. Through high plasticity of different types ncDNAs the Nature reveals its amazing economy: regulating the most complicated and infinitely diverse life processes via a few simple physical and chemical principles. On the basis of the above I am inclined to consider, that evolution based on genes was stopped on prokaryotic level.   It is probably that ncDNAs, and not genes, play the main role in evolution of eukaryotes.

Acknowledgements

Referenceses

[1] Mayr E. (1970) *Populations, species, and evolution. Belknap Press of Harvard Univ. Press, Cambridge, Massachusetts.*

[2] Lewontin R.C. (1974) *The genetic basis of evolutionary change. Columbia Univ. Press, New-York and London.*

[3] Sapp J. (2003) *Genesis. The evolution of biology. Oxford Univ. Press.*

[4] Heitz E. (1928) *Jahrb Wiss Bot* 69, 762–818.

[5] Lima-de-Faria A. (1983) *Molecular evolution and organization of the chromosome. Elsvier, Amsterdam, New York, Oxford.*

[6] Elgin S.R.S. (1996) *Curr Opin Genet Dev* 6,193-202.

[7] Prokofyeva-Belgovskaya A.A. (1986) *Heterochromatic Regions of Chromosomes (in Russian).* Nauka, Moscow.

[8] John B. (1988) In: Verma RS (ed) *Heterochromatin: Molecular and Structural Aspects.* Cambridge, Cambridge University Press, pp 1-147.

[9] Verma R.S. (1988) *Heterochromatin. Molecular and Structural Aspects. Cambridge Univ. Press. Cambridge, New York, Sydney.*

[10] Bhasin M.K. (2007) *In: Bhasin V, Bhasin M.K (eds) The Anthropologist Today: Trends: Scope and Applications. Kamla-Raj Enterprises, India. pp* 435-506.

[11] Ibraimov A.I. (2010a) *In: Bhasin M.K, Susanne S (eds) Anthropology Today: Trends and Scope of Human Biology. Delhi: Kamla-Raj Enterprises,* pp 199- 224.

[12] Zuckerkandl E. (2002) *Genetica* 115, 105-129.

[13] Lewis E.B. (1950) *Adv Genet* 3, 73-115.

[14] Spofford J.B. (1976) In: Ashburner M, Novitski E (eds) *The Genetics and Biology of Drosophila. New York Academic Press, New York,* pp 955-1018.

[15] Weiler K.S., Wakimoto B.T. (1995) *Annu Rev Genet* 29, 577-605.

[16] Henikoff S. (1996) In: *Epigenetic Mechanisms of Gene Regulation. Cold Spring Harbor Laboratory Press,* pp 319-334.

[17] Sapienza C. (1995) *Dev Genet* 17(3), 185-187.

[18] Dorer D.R, Henikoff S. (1997) *Genetics* 147, 1181-1190.

[19] Lloyd V.K., Sinclair D.A., Grigliatti T.A. (1999) *Genetics* 151, 1503-1516.

[20] Schul W., de Jong L., Driel R. (1998) *J Cell Biochem* 70, 159-171.

[21] Cremer T., Cremer C. (2001) *Nature Rev* 2, 292-301.

[22] Jackson D.A. (1997) *Mol Biol Rep* 24, 209-220.

[23] Ibraimov A.I. (2003) *Complexus* 1, 164-170.

[24] Ibraimov A.I. (2004) *Complexus* 2, 23-34.

[25] Ibraimov A.I. (2008) *Int J Hum Genet* 8(3), 283-290.

[26] Ibraimov A.I. (2009) *Int J Hum Genet* 9(1), 39-47.

[27] Ibraimov A.I. (2010b) In: Bhasin M.K, Susanne S (eds) *Anthropology Today: Trends and Scope of Human Biology. Delhi: Kamla-Raj Enterprises,* pp 225-250.

[28] Ibraimov A.I., Kazakova A.K., Moldotashev I.K., et al (2010a) *J Hum Ecol* 32(1), 1-22.

[29] Ibraimov A.I., Kazakova A.K., Moldotashev I.K et al (2010b) *J Hum Ecol* 32(2), 69-78.

[30] Buchanan M. (2003) *Complexus* 1, 45-48.

[31] Dutrillaux B. (1979) *Hum Genet* 48, 251-314.

[32] Dutrillaux B., Counturier J., Viegas-Pequignot E. (1981) In: Bennet M.D., Bobaraw M., Herwitt G.M. (eds) *Chromosomes today, vol. 7,* New York.

[33] Clemente I.G, Ponsa M., Garcia M., Egoscue J. (1990) *Hum Genet* 84, 493-506.

[34] King M.C.., Wilson A.C. (1975) *Science* 188, 107-116.

[35] Yunis J.J., Prakash O. (1982) *Science* 215, 1525-1530.

[36] Elgin S.C.R., Grewal S.I.S. (2003) *Curr Biol* 13(23), R895-R898.

[37] Paris Conference (1971), Suppl. (1975) *Birth Defects* XI, 1-84.

[38] Lima-de-Faria A. (1988) *Evolution without selection. Form and function by autoevolution. Elsevier, Amsterdam, New York, Oxford.*

[39] Manuelidis L., Chen T.L. (1990) *Cytometry* 11, 8-25.

[40] Rowley J.D. (1973) *Nature* 243, 290-293.

[41] Groffen J., Stephenson J.R., de Klein A., et al (1984) *Cell* 36, 93-99.

[42] Ibraimov A.I. (2007b) In: Bhasin V, Bhasin M.K (eds) *Anthropology today: trends, scope and applications. Kamla-Raj Enterprises, Delhi, India,* pp 513-523.

[43] Ibraimov A.I., Tabaldiev S.K. (2007) *J Hum Ecol* 21(1), 1-22.

[44] Lyon M.F. (1961) *Nature* 190,372-373.

[45] Ohno S. (1983) In: Sandberg A.A (ed) *Cytogenetics of the mammalian X chromosome, Part A. Basic Mechanisms of X chromosome behavior. New York, Liss,* pp 76-82.

[46] Bird A.P. (1995) *Trends Genet* 11, 94-100.

[47] Wyllie A.H., Beattie G.J., Hargreaves A.D. (1981) *Histochem J* 13, 681-689.

[48] Oberhammer F.A., Hochegger K., Froeschl G., et al (1994) *J Cell Biol* 126, 827-831.

[49] Kerr J.E., Wyllie A.H., Currie A.R. (1972) *Br J Cancer* 26, 239-257.

[50] Harris H. (1970) *Nucleus and cytoplasm. Clarendom Press, Oxford.*

[51] Gurdon J.B., Partington G.A., De Robertis E.M. (1976) *J Embryol Exp Morphol* 36, 521-553.

[52] Tamada H., Nguyen Van Thuan., Reed P., et al (2006) *Mol Cell Biol* 26(4), 1259-1271.

[53] Hochedlinger K., Jaenisch R. (2002) *Nature* 415, 6408-6413.

[54] Pombo A.B. (2007) *Curr Opin Genet Dev Oct;* 17(5), 451-5.

[55] Bridges C.B. (1925) *Amer Nat* 59, 127-137.

[56] Goldschmidt R. (1955) *Theoretical genetics.* Berkeley and Los Angeles University of California Press.

[57] Mittwoch U. (1987) *Hum Reprod* 8,1550-1555.

[58] Burgoyne P.S. (1993) *Development* 117, 341-345.

[59] Caspersson T., Zech L., Johansson C. (1970) *Exp Cell Res* 60, 315-319.

[60] Arrighi F.E., Hsu T.C. (1971) *Cytogenetics* 10, 81-86.

[61] Pearson P.L. (1973) *Progress in Medical Genetics* 2, 174-197.

[62] Pearson P..L (1977) In: Caspersson T., Zech L (eds) *Chromosome identification techniques and applications in biology and medicine.* New York, London. Academic Press.

[63] Ibraimov A.I. (1993) *Hum Evol* 8, 81-91.

[64] Ibraimov A.I. (2007a) *J Hum Ecol* 21(2), 95-103.

[65] Lubs H.A., Patil S.R., Kimberling W.J., et al (1977) *Nature* 268, 631-632.

[66] Ibraimov A.I., Mirrakhimov M.M. (1982a) *Hum Genet* 62, 252-257.

[67] Ibraimov A.I., Mirrakhimov M.M. (1982b) *Hum Genet* 62, 258-260.

[68] Ibraimov A.I, Mirrakhimov M.M. (1982c) *Hum Genet* 62, 261-265.

[69] Ibraimov A.I., Mirrakhimov M.M., Nazarenko S.A., et al (1982) *Hum Genet* 60, 1-7.

[70] Ibraimov A.I., Mirrakhimov M.M., Axenrod E.I., Kurmanova G.U. (1986) *Hum Genet* 73, 151-156.

[71] Ibraimov A.I., Kurmanova G.U., Ginsburg E.K., et al (1990) *Cytobios* 63, 71-82.

[72] Ibraimov A.I., Axenrod E.I., Kurmanova G.U., Turapov O.A. (1991) *Cytobios* 67, 95-100.

[73] Kalz L., Kalz-Fuller B., Hedge S., Schwanitz G. (2005) *Int J Hum Genet* 5(2), 153-163.

[74] Changeux J.-P. (1985) *Neuronal Man. The Biology of Mind. Oxford University Press, New York.*

[75] Delbrück M. (1986) In: Stent G.S., Fisher E.P., Golomb S.W., Presti D., Seiler H. (eds) *An Assay on Evolutionary Epistemology. Blackwell Scientific Publications, Palo Alto/Oxford/London.*

[76] Crawford M.A. (1992) *Nutr Rev* 50: 3-11.

[77] Rose L., Marshall F. (1996) *Curr Anthropol* 37, 307-338.

[78] Horrobin D.F. (1998) *Medical Hypotheses* 50, 269-288.

[79] Schiffman H.R. (1990) *Sensation and Perception: An integrated Approach. Wiley, New-York.*

[80] Seuanez H.N. (1987) In: Obe G., Baster A. (eds) *Cytogenetics. Berlin, Springer.*

[81] Buckton K.E., O'Riordan M.L., Jacobs P.A. et al. (1976) *Ann Hum Genet* 40, 90-112.

[82] Ibraimov A.I., Karagulova G.O. (2006a) *Int J Hum Genet* 6(3), 219-228.

[83] Ibraimov A.I., Karagulova G.O. (2006b) *Int J Hum Genet* 6(4), 281-285.

[84] Nickerson E., Nelson D.L. (1998) *Genomics* 50, 368-372.

[85] Richard F., Dutrillaux B. (1998) *Chromosome Res* 6: 263-268.

[86] Haig B. (1999) *Philos Trans R Soc Lond B Biol Sci* 354, 1447-1470.

[87] Volff J.-N. (2005) *Retrotransposable elements and genome evolution. Karger.*

[88] Gilbert W. (1985) *Science* 228, 823.

[89] Maynard Smith J. (1982) In: Dover G.A., Flavell R.B (eds) *Genome Evolution. London, Academic Press,* pp 375-382.

[90] Macgregor H.C. (1982) In: Dover G.A., Flavell R.B. (eds) *Genome Evolution. London, Academic Press,* pp 85-94.

[91] Zuckerkandl E. (1981) *Mol Biol Rep* 7, 149-158.

[92] Beckman J.S., Brendel V., Trifonov E.N. (1986) *J Biomol Struct Dyn* 4, 391-400.

[93] Beckman J.S., Trifonov E.N. (1991) *Proc Natl Acad Sci USA* 88, 2380-2383.

[94] Merrifield B. (1992) In: Frängsmyr T, Malmström BG (eds) *Nobel lectures, Chemistry* 1981–1990. *Singapore, World Scientific Publishing Co, pp* 149–175.

[95] Taft R.J., Mattick J.S. (2003) *Genome Biol Preprint Depository* http://genomebiology.com/2003/5/1/P1.

[96] Rose S. (2003) *Lifelines. Life beyond the gene. Oxford Univ. Press.*

[97] Beall C. (2007) *Proc Natl Acad Sci USA* 104, suppl. 1, 8655–8660.

[98] Dawkins R. (1976) *The Selfish Gene. Oxford University Press.*

[99] Lyon M.F. (1974) *Proc R Soc bond B* 187, 243-268.

[100] Mayr E. (1998) *Proc Natl Acad Sci USA* 95, 9720-9723.

[101] Ibraimov A.I., Mirrakhimov M.M. (1985) In: Sandberg A.A. (ed) *Progress and Topics in Cytogenetics. The Y chromosome. Part A. Basic characteristics of Y chromosome.* Alan R. Liss, Inc., New York, USA, pp 213-287.

[102] Little M.A., Garruto R.M. (2000) *Hum Biol* 72(1), 179-199.