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THE EVOLUTION OF MATERIAL BASIS OF EVOLUTION

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Abstract.

It is discussed, that: a) evolution is not only an the origin of various species of animals and plants, but the major transitions in life history on the Earth, such as the emergence of eukaryotic cells, mitotic chromosomes, mitosis, meiosis, biological sex, multicellular organisms, warm-blooded animals, including humans; b) the material basis of the origin and further evolution of the eukaryotic organisms were, apparently, non-coding DNAs (ncDNAs), while genes, though important, were of secondary importance; c) ncDNAs, due to their molecular structure (short, repeated thousands and millions times DNA sequences), behavior during the cell cycle (remain condensed through the cell), genetic organization (they do not encode polypeptide chains), cytological organization (an ability to dense packing in the cell), the localization features (centromere and telomeric sites, as well as the regions of nucleolar organizers of chromosomes) and wide genetic variation, were the main genetic material in the evolution of eukaryotic organisms.
Evolution of early forms of life and prokaryotes were carried out based on genes, but the origin of eukaryotic organisms and their further development were made possible by emergence and further evolution of ncDNAs, which led to the formation of chromosomal C-, G-, Q-, R - and T-bands. Some of the chromosomal bands underwent further evolution and formed two types of constitutive heterochromatin: C-heterochromatin that exists in the genome of all higher eukaryotes and Q-heterochromatin, existing only in three species of higher primates (*Homo sapiens, Pan troglodytes and Gorilla gorilla*). Among these three higher primates, only human populations have a wide hereditary polymorphism of Q-heterochromatin, and this genetic material may have played an important role in the origin of modern man and his adaptation to different climatic and geographical conditions of the Earth

Key words

material basis of evolution; non-coding DNAs; origin of eukaryotes; origin of chromosomes; Q-heterochromatin; C-heterochromatin.

Introduction.

The evolutionary synthesis of the 1930s and 1940s dealt with the evolution of plants and animals over the last 560 million years. At this evolution is understood in terms of gene pools and population genetics. Such accounts ignore studies of non-Mendelian heredity and of the other mechanisms of evolutionary change that lie outside Darwinian research traditions (Sapp, 2003).

The emergence of the eukaryotic cell type between 1.5 and 2 billion years ago provided all the organismic conditions for the differentiation of tissues, organs, and organ systems of plants and animals. Mitosis was crucial: it ensured that chromosomes were distributed to daughter cells and that the plane of cleavage was at right angles to the spindle , and it provided the opportunity for unequal distribution of cytoplasmic components, the basis for cell divergence and differentiation. Cell adhesion is, of course, a phenomenon in many protists (as well as bacteria) that form colonies, and the evidence indicated that cell-to-cell signaling is present among protisits as well (Maynard Smith and Szathmбry,1995).
It is known that in all eukaryotes, up to from fungi, there is an observed surplus of DNA in the nucleus as a kind of repeated sequences (Britten and Kohne, 1968). The significant part of this redundant DNA does not code any simple phenotypical function. Now it is obvious that in the investigated eukaryotes only an insignificant part of DNA is transcribed . However, the portion of them in the genome, frequency of repeatability and complexity of sequences in DNA vary over a wide range (for reviews, see Bostock and Sumner, 1978; Dover and Flavell, 1982; Lima-de-Faria, 1983).
But the question remains, what is the material basis for the evolution of eukaryotic organisms: the genes or non-gene (non-coding) parts of the genome? We believe that the material basis for the origin and further evolution of eukaryotes were non-coding part of genome that originated later of genes in some lines of prokaryotes. Genes, though were important and necessary, however, they played a secondary role in the history of life.

Evolution of the non-coding part of the genome.

In a very simplified form, we see some of the stages in evolution of non-coding parts of the genome (ncDNAs) as follows: genes → ncDNAs → mitotic chromosomes → mitosis → meiosis → biological sex → eukaryotic nucleus → condensed chromatin → cell thermoregulation → multicellular organisms → warm-blooded organisms → *Homo sapiens.*

The scheme above needs some additional comments. As the genes are known much more than non-gene parts of the genome, we will focus on the ncDNAs possible participation in the evolution of eukaryotic organisms.

Non-coding DNAs and origin of mitotic chromosomes.

We were unable to find special works dedicated to mitotic chromosome origin. The existing studies on this matter basically concern to molecular evolution and organization of the chromosome (Lima-de-Faria, 1983). The following model of mitotic chromosome origin seems highly probable. Formation of nucleosomes is the first step in DNA packaging into a minor

metaphase structure. We believe that it is connected with the availability in eukaryotic genomes intervening non-coding sequences of DNA, which has the ability to attach to histones (by DNA-protein recognition mechanisms). Lack of nucleosomes in prokaryotes in spite of the availability in the cells the histone-like proteins is possibly attributed to this important reason. In other words for formation in nucleosomes, chromomeres, chromosome bands and condensed chromatin it is necessary that in the DNAs should be nucleotide sequences with anchorage dependence features, due to which they will be inside the nucleus (Ibraimov, 2003; 2004).

At a certain stage of "naked" ring chromosome evolution of some lines of prokaryotes there start to emerge sites with ncDNAs. This led to: a) increase of the length of such chromosomes; b) delay of separation of already replicated DNAs because of mutual attraction of chromosome sections with ncDNAs (chromomere). As minimum, for the division of such ring chromosomes it is needed that they are shortened. This can happen only due to ncDNAs according to the principle, which has a place at mitosis prophase stage. When thickness of such "cylinder" reaches the certain limit «sister ring chromosomes» will start to repulse from each other and finally will divide in two (Ibraimov, 2004; 2009; 2010a; 2011b).
Virtually, a gap between S and M phases in mitosis and the fact that sister chromatids are tied together are connected to the formation of mitotic chromosomes themselves. In the cases when this division mode becomes difficult, ring chromosomes break. Perhaps, more favorable outcomes expect those ring chromosomes where breaks happened in the sections with considerable quantity of ncDNAs. As time goes by, these ends could be transformed into centromeres and telomeres, providing in addition the completeness of such sections of the former ring chromosomes (Lima-de-Faria, 1983). Thus, groups of genetic linkage of eukaryotes could occur in the form of telo-, acro- or metacentric chromosomes. There appeared possibilities for the endless combination of genes in the population of eukaryote organisms through meiosis, opening yet unknown prospects for their further development.

Origin of condensed chromatin and eukaryotic nucleus.

As it is known, the main difference of eukaryotes from prokaryotes is in the presence of the cell nucleus. However, the mechanism of the cell nucleus origin is still not clear. In particular, is it possible to be of opinion that the eukaryotic nucleus is the result of the evolution of genes, as for example, at the expense of the accumulation of favorable mutations and selection? This possibility seems to us unlikely only for the simple reason that between the number of genes and complexity of organisms there is no direct correlation.

The issue of 'how did eukaryotic cell with organelles arise in the first place' is still under discussion. The nucleus has no obvious ancestor. Where does it come from? No one seems to know. The nucleus has no evolutionary history or a very rudimentary one' (Lima-de-Faria, 1988). For this reason, there are no swiping hypotheses on its ancestry as there are for other eukaryotic organelles such as the mitochondria or the chloroplasts (Schwartz and Dayhoff, 1978; Dickerson, 1980).
We have proposed hypothesis that the eukaryotic nucleus is the result of evolution, not of genes, but accumulation of favorable mutations and selection of ncDNAs in some lines of prokaryotes (Ibraimov, 2003; 2004). It seems to us to form nucleus isolated from the cytoplasm, besides the biological membranes, it is necessary mitotic chromosomes to exist with sufficient quantity of ncDNAs, which due to their chemical features (highly repeated sequence of nucleotides) are inclined to be dense packaging with a lack of free space in the cell. In other words, the formation of the eukaryotic nucleus is possible only in the presence of mitotic chromosomes, the basis bulk of which consists of different types of ncDNAs, including the so-called heterochromatin regions of chromosomes, consisting of highly repeated ncDNAs (more details see Ibraimov, 2004; 2009; 2010a; 2011b).
We have postulated that: a) the redundant DNA originated in multiplication of ncDNAs in the cells of prokaryotes; b) condensed chromatin (CC) appeared from the redundant DNA because of the necessity of denser packaging of DNA in the cells, and the nuclear genome enveloped by membranes, i.e. eukaryotic cell; c) with origination of unicellular eukaryotes with dense layer of peripheral CC inside the nuclear envelope the cell thermoregulation appeared, and d) for the existence of the multicellular organisms with common outside cover, separating them from the external environment and maintenance of more or less constant internal environment, especially the temperature, are necessary, and an important role in the implementation of this condition is played by a dense layer of peripheral CC in the interphase nucleus, which is the constitutive basis of the cell thermoregulation (Ibraimov, 2003; 2004; Ibraimov et al., 2014; Ibraimov and Tabaldiev, 2007). The existing data on the redundant DNA, three-dimensional organization of the interphase nucleus, chromatin, chromosome segments and thermoregulation in the higher eukaryotes do not contradict this point of view (Ibraimov, 2015).
We know very little on how the condensation of chromosomes occurs, or how certain chromosome regions are being kept in the condensed state. Still less is known on how CC originated, and why it is in the condensed state during the whole cell cycle. In our opinion, CC appeared because of a strict limitation on the cell volume. The point is that rather strict physical restrictions are imposed on the increase of the cells' size, as the surface-to-volume ratio of a cell influence to its functioning. As a cell metabolizes, it must exchange material and heat with the environment. The requirement of denser packaging apparently has led to a situation where the eukaryotic chromosome is organized into nucleosomes. From this point of view the chromosomal heterochromatin regions (HRs) are a particular case of the differential packaging of the eukaryotic chromosome (van Holde, 1989).
Sutton (1972) believes, that the presence of repetitive (i.e. rather homogenous) DNA sequences may lead to more compact chromatin packaging. Assumptions that positive Q- and C-segments may serve as the centers of chromosome condensation of mammals have some experimental confirmations (Okada and Comings, 1974; Luciani at al., 1977). In the past years a rather promising data on the condensation of somatic chromosomes at mitosis were obtained. Particularly a number of proteins participating in this process were identified: 13S condensin complex, A-kinase anchoring protein, AKAP 95 (Collas et al., 1999; Hirano, 2000; Bomar et al., 2002).
It is possible that CC promotes the formation of the globular configuration of the nucleus and nucleolus. As is known, the

nuclear envelope with peripheral CC constitutes a more or less continuous layer, permeated by small pores, linking the central diffusive chromatin with the nuclear membrane. Often this CC layer is so dense (Bostock and Sumner, 1978) that it can form a sufficiently rigid structure by itself, which is able to support the spatial nuclear organization (Manuelidis, 1984). As assumed, in the muscle cells this is the dense layer of peripheral CC, which ensures the shape of the nuclei (Bostock and Sumner, 1978). Apparently, this mechanism is at the base of the formation of a spherical nucleolus, and its invariable location closer to the periphery of the nucleus in intimate connection with the peripheral CC. Finally, intuitively it seems to be plausible that CC have some relation to the cytoskeleton and cytoplasm mobility of the eukaryotic cells. As is known, the cytoplasm of prokaryotes is in principle immobile, and they have no cytoskeleton, which includes microtubules, microfibrils and microfilaments. There are reports suggesting that the highly repetitive super repeat structure has a direct function in the formation of a functional kinetochore region of the chromosome (Avila et al., 1983; Radic et al., 1987). In any case without support in the form of a dense CC carcass around the nucleus (exoskeleton of a nucleus), where the elements of a cytoskeleton can attach, it is difficult to imagine the movement of the cytoplasm and organelles.

Origin of multicellularity and thermoregulation.

Many eukaryotes today are multicellular. There is usually a division of labor among the cells; therefore, a multicellular organism has various types of cells that contain different proteins and are capable of performing different specialized functions.

It has been known for a long time that the majority and possibly practically all bacteria lead a life of multicellular organisms (Chapiro, 1988). Concerning the issue which is being discussed here, another thing is important: (1) despite the fact that prokaryotes ruled on the Earth for about one billion years, coexisted with eukaryotes for more than 2 billion years, and there is constant contact between the cells of prokaryotes proper, neither now nor before did the prokaryotes form multicellular organisms, and (2) among the multicellular organisms the prokaryotes are not found, despite the fact that in the colonies the specialization of bacterial cells and regulation of protein synthesis are performed by means of signals, i.e. as it is performed in multicellulars. We assume that inability of prokaryotes to form a multicellular organism with a common external cover is attributed to the absence of a mechanism for providing maintenance of a relative constancy of temperature in the cells located in the deep parts of body, which is impossible without CC (for more details see Ibraimov 2003; 2004; 2010a; 2011b; 2015; Ibraimov and Tabaldiev 2007).
As is known, the metabolism of organisms proceeds well only within narrow ranges of internal physical and chemical conditions. Many of the mechanisms that organisms possess serve to maintain this relative internal constancy even when there are large changes in the surrounding environment (homeostasis). Homeostasis depends on an organism's ability to respond to the environment by changing its metabolism. With the appearance of multicellularity, one serious problem emerged, that is the elimination of surplus heat from the cells located in the deep parts of the body. The point is that the cells convert energy from one form to another as they carry out the business of life. None of these energy conversions is 100% efficient – some energy is always lost as heat. All of these energy conversions are often accompanied by the production of heat, not all of which can be made to do work. Heat generated by the chemical reaction within cells must be dissipated for the organism to survive. However, by the mechanisms of heat loss the body and individual cells apparently differ. As is known, the external heat flow from a body performed by way of radiation, conduction, convection and evaporation of water. Apparently, of these mechanisms, the cell, in particular the cell nucleus can use only the heat conduction.
In our opinion, in the elimination of heat surplus from the cell the cytoplasm and nucleus are in different. The nucleus, in contrast to the cytoplasm, cannot conduct heat directly in the extracellular space, from where the heat is taken by the circulating flow of sap, lymph and blood. Thus, the nucleus can conduct heat only in the cytoplasm (in case the nucleus temperature, for this or that reason, exceeds the temperature in the cytoplasm). With this, the nucleus has two options for dissipation of heat surplus: either by increasing its volume, or increasing the heat conductivity of the nuclear envelope. As the first option is limited (see above), and the second one is hampered because of a relative constancy of thickness of the cell membranes, apparently the higher eukaryotes took advantage of the opportunity of a dense layer of peripheral CC as heat conductor for a more efficient elimination of the temperature difference between the nucleus and cytoplasm (Ibraimov, 2003; 2004).
It is possible that the DNA evolution process was performed in the following sequence: some sites of non-coding DNAs in some prokaryotes have started to constitute a significant part of their genome, having formed the redundant DNA due to the physical limit of a secure increase of the cell volume, the linear DNA molecules in such prokaryotes have transformed to the nucleosome structures for more dense packaging and with time they surrounded by a system of membranes from endoplasmic reticulum, having formed the eukaryote cell with formation of a dense layer of peripheral CC, adjacent to the internal layer of the nuclear envelope, the intracellular thermoregulation was formed, thus creating the prerequisites for the formation of the multicellular organisms. Finally we state the following: though during evolution the ncDNAs appeared later, it promoted the appearance of the CC, eukaryote cell, cellular thermoregulation, and multicellularity by way of the mitotic chromosomes, which are able to form the groups of genetic linkage and mitotic apparatus (for details see, Ibraimov, 2003; 2004; 2010a; 2011; 2015; Ibraimov and Tabaldiev, 2007).

Non-coding DNAs and origin of sexual reproduction.

We already discussed the possible role of ncDNAs in the origin of mitotic chromosomes (see above). On their basis the following possible model of sexual reproduction origin is proposed. For that it is required the availability of the following: a) mitotic (asexual) reproduction; b) chromomeres in mitotic chromosomes with sufficient amount of repeated ncDNAs capable of mutual attraction; c) changing conditions of external or internal environment influencing on the mitotic prophase stage duration. Apparently, the importance of availability of the first two conditions does not require additional argumentation. We will focus on the third one alone.

When at the stage of prophase a long delay of mitosis occurs under the influence of yet unknown factors of environment, sister chromatids often conjugate with chromatids of homologous chromosomes, forming bivalents. Obviously, at the same time there can have a place the chiasmata formation with well-known genetic consequences. As they are shortening and thickening, the centromere regions will start to separate first, and then the arms of homologous chromosomes will do (Sumner, 1991). Thus, in the anaphase of the first "meiotic" division there separate the homologous chromosomes of each pair, but not the sister chromatids of each chromosome. Probably, in the process of evolution such haploid cells have been merging into diploid organisms (see for details, Ibraimov, 2008; 2009; 2011b; 2012). Inasmuch as this mode of reproduction involves two individuals quite often with various sets of genes, then this could not help influencing on viability of such organisms. The advantage of this reproduction mode was proved by further evolution.
Thus, the sexual reproduction was an immediate consequence of meiotic division origin, but not a result of some specific structural gene emergences determining sex development. Sex related genes emerged later with higher eukaryotes, yet not for sex determination, but for stimulation of the secondary sexual character development with the help of hormones. The sex, even one of higher eukaryotes, develops from indifferent primordial gonads without gene interference (Ibraimov 2008b). On the basis of the foregoing we assume that probably the key role in sex origin and sexual reproduction of eukaryotic organisms belongs to ncDNAs, but not to structural genes. Apparently, sex and sexual reproduction have occurred as a result of the long ncDNAs' evolution, which successively led to the origin of mitotic chromosome, mitosis, meiosis, and sex determination and differentiation mechanisms (see below).

The possible role of ncDNAs in sex determination and differentiation.

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 appeared only after appearance of the cellular nucleus, i.e. the eukaryote organisms; b) the eukaryote cell itself is the result of a long term evolution of the ncDNAs (see above); c) apparently, for the differential activation of genes it is necessary that not all the coding DNAs be available to the transcription machinery of a cell. 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; 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) ncDNAs in the nucleus are not an amorphous mass or simple bulking agents: they have an aptitude for higher forms of physical organization of DNA, starting with nucleosomes and finishing with mitotic chromosome bodies (Ibraimov, 2004).

Germ cells in multicellular organism body belong to specialized cells. Sex development, as in the case of all other organism features, is defined with the help of genotype and environmental factors. Nevertheless, the role of specific structural genes and sex chromosomes in sex determination and differentiation is not clear yet. However, recently there has appeared information about the possible role of ncDNAs in individual development and evolution (Ibraimov 2003; 2004; 2008b; Ibraimov, Tabaldiev 2007), including the sex differentiation (Ibraimov 2008a). In particular, on the basis of the cell thermoregulation concept there was proposed a hypothesis of a possible sex differentiation (SD) mechanism. Seemingly, the SD in animals and human is determined by the amount of constitutive heterochromatin region (cHR) in the chromosomes of the undifferentiated embryonic gonads (UEG) via cell thermoregulation.
As is known, most widely the SD is studied in animals. For the time being the mechanisms of the SD are not known. At present the balance hypotheses, worked out by Bridges (1925) and Goldschmidt (1955) 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. However, almost nothing is known about concrete mechanisms and types of gene interaction at the SD. The problem also becomes complicated especially as: a) the number, localization, products, and types of these gene interactions are not determined; b) the role of the sex chromosomes in the embryo SD remains not completely clear; c) there are no ideas as regards the possible role of a great amount of cHR of the Y chromosome in the SD.
In order to clarify the essence of our point of view, it is necessary to remind, in brief, some generally known facts of the sexual development. In many animals, including us, the genetic sex is determined at fertilization by sex chromosomes carried by the father's sperm, X in the case of female and Y in the case of male. In birds, moths, and butterflies, males are XX(ZZ) and females are XY(XW). The sexual development in the mammals is a process consisting of at least three stages: the 1st stage is the chromosome determination of sex (XY or XX); the 2nd stage is SD (the development of testicles or ovaries); the 3st stage is the development of the secondary sexual characteristics. At the early stages of embryonic development a pair of UEG and both rudimentary female and male reproductive system develops 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. Whatever the nature of the factors determining the male sex may be, they are necessary in order that the UEG develop as the testicles, which is the first step in a male development. For lack of the processes causing the testicles development, the UEG develops invariably as an ovary.
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. 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.

The X chromosome of the mammals remains evolutionary stable; the genes located in it are homologous in all species of mammals (Ohno, 1983). It is known that the amount of constitutive HR in males at the level of population is on average two times more than in females (Paris Conference 1971; 1975; Ibraimov and Mirrakhimov, 1985). Most of the genes responsible for the development of the secondary sexual characteristics are concentrated not on the sex chromosomes, but on the autosomes (Ohno,1983). We 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 we conceive, the cHR 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 (Ohno, 1983). Most likely from our point of view, the cHR of the Y chromosome are responsible for the development of UEG towards formation of the testicles, and not some genes or the H-Y antigen. Now let's try to ground our assumption. (1). The heat conductive effect of the CC especially strongly increases in conditions of mulicellularity (Ibramov, 2004); (2). In a number mammal, including man, it has been shown that at equivalent gestational ages, males are developmentally more advanced than females (McLaren, 1988; McLaren and Southee, 1997). By the 3rd week of the embryo development in human, the HRs is completely formed (Prokofyeva-Belgovskaya, 1988), 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. (4). Sex may be determined by physical agents as temperature. For example as early as in the first decades of the XX century in the tests with the descendants of the triploid females of *Drosophila* itwas shown that at high temperature the flies with the female characteristics are being developed, and at a lower temperature - with the male sexual characteristics. Conover and Kynard (1981) have found that in the fish *Menidia menidia* (Atlantic Silverside fish) sex determination is under genetic and temperature control during a critical phase of larval development. The sex ratios of the progenies were highly skewed by this treatment. The eel (Anguilla) has no chromosomes that can be recognized as sex chromosomes and it shows the same skewed sex ratios as *Menidia* (Wiberg, 1983). There are many such examples in animals (Lima-de-Faria, 1983).

It is possible that the medulla of the UEG is more vulnerable to the temperature increase than the cortex tissue. The following data testify to this: a) the clinical consequences of cryptorchidism in boys; b) location of scrotum outside the body in the mammals. In other words, the direction of development of the UEG towards the male or female side is not something strictly fixed, it will depend on the environment in which it is being implemented. In our opinion, most likely this is the temperature influence on the UEG tissues, and seemingly on which it depends, whether the medulla tissue will remain or not. If cells of the medulla tissue are not provided with the timely and efficient removal of excessive heat, it will be doomed to degeneration having making for the cell from the cortex. Just in this meaning we understand the role of cell thermoregulation in SD, as efficient and simple means of medullar tissue protection against 'heat death'. As there is a wide intrapopulation polymorphism by the amount of cHR in the Y chromosome (Paris Conference, 1971; 1975; Ibraimov et al., 2000), no wonder that even insignificant deviation in the operation of the system ensuring the SD at the gonad level so often causes an incomplete development of the male phenotype in the organism with the male genotype (Vogel and Motulski, 1986).

According to Lyon (1992) "… the X-chromosome is clearly involved at some point in the sex determination pathway". The point that I am trying to convey is that: a) the SD is one of the most important examples of how the physical state of the DNA molecular (in this case the level of compacting of the peripheral layer of CC around the cell nucleus) influences to the cell differentiation; b) X-inactivation is not involved in the SD; c) X chromosome is not inactivated, but it is heterochromatinized to compensate the lacking big block of the cHR in the female karyotype in the interest of the CT.

To a possible role of ncDNAs through CT into SD testify also such clinical manifestations of Turner syndrome (XO), as rudimentary ovary, fibrous taenia at gonad place and primary amenorrhea. In this case, the main cause of the early stop of gonad development, apparently, is a 'thermal degeneration' of cortex tissue cells, because of absence of the second heterochromatinized X-chromosome in genome of that kind of patients. The reasons why the cortex tissue in the UEG is not subject to the heat degeneration, as the medulla tissue owing to the problems with the CC in addition to the above mentioned, are explained also by the facts that: a) it has been shown that at equivalent gestational ages, males are developmentally more advanced than females, even before the gonads form.So, for example, a detailed analysis of XX v. XY developmental differences in mice has shown that XY fetuses are indeed larger than XX fetuses prior to gonadal SD (Burgoyne et al., 1995). The human testicles are formed earlier (6-12th week) than the ovaries (14-16th week); b) by the time of formation of the ovaries the problems with heat removal from the deeper parts of the organs and embryo tissues become considerably easier, as by this time the blood circulation system of the fetus starts to function, - a long distance energy heat transfer in the body, - eliminating the hazard of cell heat degeneration including the cortex tissue; and, at last, c) in mammals and human beings the development towards the male sex is determined by availability of testicles, and to be more exact by the excreted by it hormone – testosterone, and the development towards the female sex is not induced, as it is not the consequence of the embryo ovary availability. It rather should be considered as the consequence of lack of the testicle (Ohno et al., 1971).

It could be possible to test our hypothesis experimentally. At UEG with the karyotype XX to remove its cortical layer preserving the medulla tissue. 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 cHR?; 2) why does at genotype XX the medulla tissue preliminarily degenerate?, either from the 'heat death' because of a small dose of the cHR or from the impact of the gene products, produced by the cortex cells on the medulla tissue? (for details see, Ibraimov, 2008a; 2009; 2010a; 2011b; 2012; 2013).

Non-coding DNAs and origin of homoeothermic organisms.

There are reasons to assume that in the evolution the cell thermoregulation (CT) preceded the physiological thermoregulation (PhT). We believe that the CT is one of the manifestations of numerous effects of the ncDNAs; this time in the form of the condensed chromatin (CC), which in its turn has also undergone deep changes in the process of the higher eukaryotes evolution (Ibraimov, 2003;2004; 2010a; 2011b; Ibraimov and Tabaldiev, 2007).

It is known that the temperature level in the homoeothermic organisms is set point (hypothalamus), and is regulated by the organ-based physiological mechanisms. However we assume that between the PhT and CT mechanisms should be interconnection for the following reasons: a) though the chemical heat production in an organism is provided by the cells, its efficiency in addition to the coming in the energy sources from outside depends on the temperature in the body, and the role of the PhT in its regulation is not replaceable; b) the PhT cannot directly participate in maintaining the intracellular temperature homeostasis as the cells of the body are surrounded by the tissue liquid, and is not in direct contact with blood; c) the CT mainly a physical process, and apparently it cannot actively set point the temperature level inside the cell. In this sense the CT completely depends on PhT. But it is not excluded, that the CT being most ancient type of the temperature homeostasis still possesses some mechanisms of self-regulation.

Apparently in appearing of the homoeothermic organisms the role of the CT was significant. As is known the basic metabolic machinery would apply to all the cells of the major groups of organisms. Sources of metabolic heat include metabolic thermogenesis, contractile thermogenesis, and the lipolysis with oxidation of fatty acid. Nevertheless, the points of view on mechanisms of maintaining the constant temperature in the body of the endothermic homoiotherms at a very high level of metabolic heat production remain amazingly conservative. It is accepted to believe that the homoiotherms maintain a constantly high temperature in a body due to availability in their organism a 4 chamber heart and lung breathing ensuring a high level of oxygenation of the arterial blood.

To the question on how the excessive heat is being removed from the organism, the physiologists answer: thermal loss comes from a variety of sources as well, including convection across mucous membranes or through sweating. We assume that such an answer to the asked question does not take into consideration one important circumstance: the known organ-based physiological mechanisms of heat removal, taking into account all their merits, cannot remove the excessive metabolic heat from the cell nucleus (Ibraimov, 2003; 2004), which is an important participant of a cellular metabolism.

We assume that exactly here the role of the CT is important which with the help of the CC ensures a high body heat conductivity of the homoeothermic organisms (Ibraimov, 2004; 2015; Ibraimov et al., 2014; Ibraimov and Tabaldiev, 2007), as without timely heat removal from the cellular nucleus the chemical thermogenesis will remain under threat. Homoiotherms maintain constant temperature in a body not so much they possess accelerated heat production as their ability to efficiently remove the excess heat from the deeper parts of the tissues and organs. A high heat conductivity of their bodies promotes this which are provided, in addition to constitutive heterochromatin, with availability of chromosomal G+ and Q+ bands, intensifying the compactization the peripheral CC layer in the interphase nuclei, thus accelerating the liquidation of the appeared difference between nucleus and cytoplasm in the cells (Ibraimov, 2003; 2004).

There is another interesting issue in the interrelations between CT and PhT. As is known, Lyon (1961) proposed the single-active X chromosome hypothesis to explain the observation that in the mouse, females heterozygous for X-linked fur color genes are patchy mosaics of two colors. To quote Lyon: "… (1) that the heteropicnotic X chromosome can be either paternal or maternal in origin in different cells of the same animal; (2) that it is genetically inactivated". According to 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 we 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 Ibraimov, 2003; 2004; 2008a,b; 2015; Ibraimov et al., 2014; Ibraimov and Tabaldiev, 2007). In short, the essence of our objections is based on the following facts: 1) the inactivation of one of the X-chromosome in the normal females occurs only with the mammals, which are able to support a relatively constant core temperature in the body; 2) if one X-chromosome could be enough, then women with chromosomal constitution XO would be absolutely normal; in reality, they are not quite normal (Turner syndrome); 3) 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; 4) "…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" (Ohno, 1983).

It is possible that the main reason of the 'lyonization' is not the gene dosage compensation, but the compensation of the 'dose' of the constitutive heterochromatin, missing in the genome of the mammals' females for efficient leveling of the temperature difference between the nucleus and cytoplasm that is very important for keeping the temperature homeostasis with the mammals. By the way, random X-inactivation of either the maternally – of paternally-inherited X chromosome in the mammal female more likely testifies to participation of the CT, and not in the dosage compensation of genes. Therefore we believe that the X chromosome is not inactivated, but heterochromatinized to compensate the lack of a large block of the cHR in the females karyotype in the interests of the CT. This is proved by physiological data on a relatively low heat conductivity of the female body in comparison with the males' one (for more details see Ibraimov, 2014; 2015; Ibraimov and Tabaldiev 2007).

Non-coding DNAs and adaptation – by the example of a human.

The bulk of the existing data testifies to a possible role of ncDNAs in human adaptation to various environmental conditions. There are some reasons to believe that, seemingly, the cell thermoregulation (CT) remains an important component of human physiological plasticity. In view of this it was found that a wide quantitative variability of the chromosomal Q-heterochromatin regions (Q-HRs) forms the basis of such intrapopulation physiological variability (Ibraimov, 2010b; 2011b; Ibraimov et al., 2013; 2014b).

Results of extensive comparative population cytogenetic studies showed that populations of modern man differ significantly. 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 (Ibraimov and Mirrakhimov, 1985). In particular, the amount of chromosomal 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 subequatorial Africa (Ibraimov 1993; 2003; 2007a,b; Ibraimov and Mirrakhimov 1982 a,b,c; Ibraimov et al. 1982; 1986; 1990; 1991; 1997).
The fact that in the genome of populations, permanently inhabiting the southern latitudes, the amount of chromosomal Q-HRs may be greater than in the population of the moderate Euro-Asia zones (Ibraimov et al., 1997) has been proved by the recent independent researches by Kalz et al., (2005). In particular, it was found that in the Indians the average number of Q-HRs per individual in the population (*m*) turned out higher than in the Europeans of Central Europe and Turks in Turkey. According to our data, the values of *m* in the Indians from the Northern India amounted to 3.7 (Ibraimov et al., 1997), were as Kalz et al., (2005) who examined the Indians from the Southern India (Bangalor) have obtained figure 5.2. It is interesting, that the authors did not know anything about our researches of chromosomal Q-HRs, including the researches concerning Indians. However the availability of a gradient towards the increase by the *m* values (from the North to the South) on the Indian continent is a very important fact as it is. The same is proved by the data of Lubs et al., (1977) on prevailing the amount of chromosomal Q-HRs in the genome of the “black” over the “white” populations in the USA.
There are rather many observations indirectly justifying our assumptions on a possible role of the Q-HRs in human adaptation. For example, it is known that with age the number of women in a population begins to prevail over men. Such a change in the sex ratio is usually explained by the fact that men are more subject to the effects of harmful factors (smoking, alcohol, etc.) or are more frequently engaged in professional activity with increased risk for life. Without calling in question the opinion of most people we suppose that a change in the sex ratio with age in favor of women is related to the amount of chromosomal Q-HRs in their genome. The point is that the overall amount of Q-HRs in the genome of women is on average twice smaller than in men, for women have no Y chromosome containing the largest block of Q-HRs in the human karyotype (Paris Conference 1971; 1975). It is possible that a certain advantage of women is explained by their relative resistance, as compared with men, to cold, hunger and even loss of blood because they have less body heat conductivity (Ibraimov, 2014; Ibraimov and Tabaldiev, 2007; Ibraimov et al., 2010; 2014a,b). In order to be convinced of the relative resistance of women to some forms of stress, we shall give several known examples: a) pearl-divers in Korea are exclusively women – “ama” (Folk, 1974); b) women succeed best in swimming across the cold water of La-Manche (Folk, 1974); c) during the period of the Leningrad blockade during the World War II about 80% of the women survived despite the fact that being in the rear they had a lesser access to food; d) at the reproductive age women, without detriment to their health lose every month from 120 to 300 ml of blood during menses and about 300-500 ml of blood even during normal labor. Men could hardly tolerate these losses of blood without detriment to their health. Thus, the known thesis that males seem to be less resistant to environment stress is also somewhat explained from our point of view.
In this connection another observation deserves to be remembered. For example, observations made in world of sport that, as we suppose, deserve attention. In recent years more and more developing countries in southern latitudes are taking part in the world sportive movement. This made us pay attention to the following aspects: individuals of the southern continent began to achieve remarkable successes in sports requiring, in addition to other things, effective heat losses in the organism. That is football, professional boxing and Marathon races. At the same time, athletes of northern countries dominate in aquatic and winter sports, as well as in mountaineering. As we understand, these phenomena could be explained by the fact that prevalence of individuals with a large amount of chromosomal Q-HRs in their genome is characteristic of native residents of tropical and subequatorial zones. Therefore their bodies with relatively high heat conductivity promote more successful sport employment that in addition to the things require effective heat losses in the body.
Apparently, the most important physical factor of the environment in adaptation of a modern man to the Euro-Asian climate was, seemingly, the temperature, and especially cold. The physiological and biochemical mechanisms of adaptation of a human organism to cold are known. Some authors believe that, possibly, some adaptive genes or gene complexes form their basis, though numerous attempts to find these hypothetical genes of adaptation were not successful (Little and Garruto, 2000). Nevertheless, a quick (on the evolution scale) and efficient mastery of the whole oikumene by a man is a really unique phenomenon, that makes ponder that here it is possible that the structural genes were not affected, but some, very mobile, non-conservative part of genome was used. So, our data suggest that, in addition to everything else, *H. sapiens* for adaptation to cold has used a heterochromatin part of its genome (Ibraimov 1993; 2007; 2010b; 2011b; 2015; Ibraimov et al., 2014b).
The assumption that natural selection during adaptation could only superficially affect the genotype of various human populations is not new in itself (Harrison et al., 1977; Baker, 1978). Little and Garruto (2000) while summing up the results of the researchers of the genetic bases of human adaptation noted: “Adaptation and adaptability have genetic and evolutionary bases, whether at the molecular level or at the complex physiological, morphological, developmental, and behavioral levels where plasticity is common. Yet there has been limited success in identifying genetic and hence evolutionary evidence for adaptation and adaptability in human population”. However, we believe that, concerning the *H.*

s. sapiens the search of the genetic bases of adaptation at the structural genes is hardly promising. Actually this does not mean a complete denial of the role of the genes in human biological adaptation. If in the adaptation process some structural genes were really involved, then, possibly, their effects would be restricted within the framework of the epigenetic variability (Zuckerkandle and Pauling, 1965).

Non-coding DNAs and origin of the modern man.

In the process of further evolution of ncDNAs the ancestors of the presently existing three higher primates (*Homo sapiens, Pan troglodytes and Gorilla gorilla*) got a new type of constitutive heterochromatin – Q-heterochromatin – which is different from the other type of constitutive heterochromatin (C-heterochromatin), on a number of physical and chemical properties (Prokofyeva-Belgovskaya, 1986; Verma, 1988; Ibraimov, 2015). Regarding the issue under discuss here, it is important to emphasize that among the three higher primates only *H. sapiens* has a wide intraspecies genetic polymorphism in chromosomal Q-heterochromatin regions (Q-HRs) (Pearson, 1973; 1974).

We feel that chromosomal Q-HRs could have played a decisive role in the origin of modern humans. This statement is based on the following facts: a) in terms of genetics Q-heterochromatin is an entirely inert material, i.e., Q-HRs do not contain any structural genes and, consequently, changes in them have no impact on the information portion of the genome and can occur extremely rapidly; b) the amount of Q-HRs in the genome plays an important role in the adaptation of individuals to unfavorable environmental conditions **(**(Ibraimov 1993; 2007; 2010b; 2011a,b; 2015; Ibraimov et al., 2014b). This unique feature was apparently duly taken advantage of by our ancestors when climate in the savannah began change and from the time they attempted to leave it in search of new habitats and when adaptation to a new, more rigorous environment became necessary.
Individuals with a smaller amount of chromosomal Q-HRs and hence, a low body heat conductivity, who had a certain advantage as to survival, could form new populations with a small amount of Q-heterochromatin material in the genome, and, although segregation of individuals "burdened" with a large amount of Q-HRs continued, the pressure of selection on such populations was on the whole not as great as on the initial ones. Therefore, these populations had at least one significant advantage: without changing the informative portion of the genome and only "using" the inert, most variable quantitatively portion of the genetic material they acquired a body with various heat conductivity (Ibraimov, 1993; 2011a).
It is hard to say why the ancestors of *P. troglodytes* and *G. gorilla* were unable to use the same route. However, the assumption which we feel is likely is the following one: initial Q-HRs frequencies on all the Q-variable loci proved to be high enough to produce of individuals with significantly different numbers of chromosomal Q-HRs and, hence, the appearance of individuals with a various body heat conductivity who would be able to survive under unfavorable conditions was quite improbable. In other words, the chimpanzee and the gorilla were initially unable to vary the amount of Q-HRs of their genome as much as man could. The following facts are in favor of this assumption: 1) the range of variability in the number of Q-HRs in the chimpanzee genome is from 5 to 7**,** whereas in the human population it is from 0 to 10, i.e., considerably wider**;** 2) in the gorilla and the chimpanzee, but not in man, a special type of Q-heterochromatin was found, located on the distal ends of certain chromosomes (7, 11, 20, and 23 in the gorilla; 20, 21, 22, 23 in the chimpanzee), and that itself makes hard to produce of individuals with different amount of Q-HRs in the karyotype less probable (for more details see, Ibraimov, 1993; 2011a).

Why non-coding DNAs?

DNA is more plastic than was previously expected (Lima-de-Faria, 1983). First of all they are capable of creation of higher forms of DNA organization (see above). For example, highly repetitive regions of chromosomes adopt a heterochromatic chromatin structure, with distinctive properties and chromatin components (Elgin, 1996). At present we have extensive information concerning the features of organization and properties of chromosomal HRs. The best-known features of HRs are the following: (1) HRs are fixed by evolution in the 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 jointed, highly repetitive DNA (hrDNA) sequences; as now established, HRs can consist not only of satellite sequences (satDNA), but also of other types of hrDNA; (4) HRs are located in centric and telomere chromosomal domains, as well as in the regions forming nucleolus-organizing regions; (5) HRs are replicated at the end of the S period of a cell cycle and (6) a wide variability in the quantitative contents within and between species.

When properties of chromosomal HRs are discussed the following are usually meant: (1) heteropicnosis is a morphological expression of dense packing (condensed chromatin), (2) ectopic conjugation of HRs between homologous and non-homologous chromosomes in an interphase nucleus, and (3) high frequency of breakage in HRs domains or on their border with euchromatin regions (for review see Prokofyeva-Belgovskaya, 1986; John, 1988). High plasticity of HRs is also proved by the following: chromocenters in fact vary with cell type and stage of development, both within and between species (Schmid, 1967); marked variability of HRs, not only within but also between species, commonly occurs with no phenotypic effect. Even significant changes in the contents of satDNA in genome cause insignificant somatic effects (Miklos, 1982); lability of the replication features constitutes a most important peculiarity of HRs, displayed in ontogenesis and phylogenesis. The HR contents in different tissues vary, and are controlled by their underreplication and overreplication (Prokofyeva-Belgovskaya, 1986).

Discussion

The existing literature data do not contradict to our point of view. Thus, for example, concerning the biological role of ncDNAs a number of hypotheses have been put forward. Britten and Kohne (1968) assumed that satDNA plays an evolutionary role. They believe that the satDNA was the initial product of "saltation" replication that was the reason for the appearance of the redundant DNA, which increases the evolution potential of an organism. The authors assume that the

satDNA itself has no definite function, but as a result of numerous mutations, translocations and recombinations with other gene sequences it may increase the ability of an organism to form the new genetic information.

According to Hatch et al., (1976) the satDNAs are the means for promoting a rapid change of karyotype, which may have a selective advantage in evolution in cases when rapid divergence or adaptation is required. The hypothesis of Hatch et al. is in agreement with the data of Wilson et al., (1974; 1975), who stated that amphibians and mammals had the same rate of evolution of primary protein structure. From this it follows that these animals accumulate the point mutations of structural genes at approximately with the same rate. With this, the mammals demonstrate a higher rate of evolution concerning the anatomical features as well as a higher rate of karyotype change in comparison with amphibians. Consequently, rapid evolution correlates with significant changes in the chromosome structure. If the conclusions of these authors are related to the peculiarities of the satDNA, it follows that it also promotes rapid evolutionary changes.
In Flavell's opinion (1982) the changes in the structure, organization and composition of repetitive sequences, as well as the chromosome size all contribute to a certain degree to evolution of the genome. The number of such 'macromutations', which are preserved as they do not have any influence on the expression of the genes, is most likely related with the total content of the DNA. It is possible that for species with large genomes, i.e. with a significant portion of non-coding, 'secondary' DNA, a greater amount of 'macro-mutations' is allowable. Therefore the genomes of the organisms with high DNA content may diverge in different populations more quickly than the genomes with lower DNA content.
Manuelidis (1982) has postulated after the repetitive sequences the following constitutive functions: 1) determination of the chromosome structure or their parts; 2) determination of a specific three-dimensional location of chromosomes in the interphase nucleus, and 3) contribution to defining the morphological variety of chromosomes observed in different species of plants and animals. The presence and organization of the repetitive sequences may, to a certain degree, participate in the more general properties of the nucleus, such as ability for regulated heterochromatinization of some chromosome segments in different types of cells.
Microbial phylogenists had so far described only about 200 archaebacterial species and only about 10,000 eubacterial species, whereas Mayr (1988) 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. He remarked that, "… the eukaryote genome is larger than the prokaryote genome by several orders of magnitude. And it is precisely this part of the eukaryote genome that is most characteristic for the eukaryotes. This include not only the genetic program for the nucleus and mitosis, but the capacity for sexual reproduction, meiosis, and the ability to produce the wonderful organic diversity represented by jellyfish, butterflies, dinosaurs, hummingbirds, yeasts, giant kelp, and giant sequoias. To sweep all this under the rug and claim that difference between the two kinds of bacteria is of the same weight as the difference between the prokaryotes and the extraordinary world of the eukaryotes strikes me as incomprehensible."
According to Modern Synthesis the speciation is the central problem of the evolution issue in general and the gene is the sole source of development and evolution (Mayr, 1970). Dobzhansky et al., (1977) put forward the hypothesis that the speciation requires genetic reconstitution. However, Lewontin (1974) 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". And Mayr (1970) recognizes that until now the perfection of the concepts on the gene and mutations origin has not added much in understanding of the evolution phenomena. Indeed, it is difficult to imagine that eukaryotic cells, mitotic chromosomes, mitosis, meiosis, sex, sex differentiation, multicellular organisms, cytodifferentiation, thermoregulation and homoeothermic organisms, including modern human appeared resulting from prior forms of life accumulating great number of new genes. Therefore, we suppose that the material basis of the aforementioned main transitions, there were evolution of non-gene parts of the genome.

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