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Review Article

Why the mechanisms of biological evolution are still not revealed?

Abyt Ibraimov

Laboratory of Human Genetics, National Center of Cardiology and Internal Medicine, Kyrgyzstan

ABSTRACT
Since the days of Darwin, it is generally accepted that biological evolution rests on three pillars: variability, inheritance and selection. It is believed that main sources of variability, mechanisms of inheritance and forms of natural selection have been clarified. Nevertheless, for more than 150 years since the publication of "Origin of Species" no consensus as to the mechanisms of evolution emerged. It is highly likely that the main obstacle in elucidating the mechanisms of evolution is the incompleteness of our knowledge regarding the sources of biological variability. The following sources of variability are universally recognized: gene mutations, gene recombination during meiosis and gene duplication. However, the role of the non-genic part of the genome, which makes up the vast majority of DNA in eukaryotes, remains unclear. For example, in human chromosomes, about 98% of DNA is represented by non-coding nucleotide sequences (ncDNAs). Although no one excludes their possible role in evolution, nevertheless, studies aimed at elucidating the participation of the non-genic part of the genome in variability, inheritance and selection are extremely small. The possible role of ncDNAs in the origin of biological variability in the eukaryotic genome and their evolution is discussed.
Key words: mechanism of evolution; biological variability; noncoding DNAs; heterochromatin; origin of species.

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Author for correspondence: *A.I. Ibraimov, Laboratory of Human Genetics, National Center of Cardiology and Internal Medicine, Bishkek, Kyrgyzstan.*

Email: *ibraimov_abyt@mail.ru*

INTRODUCTION

The issue of the sources of biological variability has always remained the focus of evolutionists. On this occasion, Mayr [1-4] wrote: 'What is the source of this variability? Where does it come from? How is it maintained from generation to generation? This is what puzzled Darwin all of his life, but in spite of all his efforts he never found the answer'.

It is generally accepted that biological evolution rests on three pillars: variability, inheritance and selection. To date, the main mechanisms of inheritance, forms of natural selection and sources of variability have been clarified. Nevertheless, for more than 150 years since the publication of "Origin of Species" no consensus as to the mechanisms of evolution emerged. It is highly likely that the main obstacle in elucidating the mechanisms of evolution is the incompleteness of our knowledge regarding the sources of biological variability.

The following sources of variability are universally recognized: gene mutations, gene recombination during meiosis and gene duplication. However, the role of the non-genic part of the genome, which makes up the vast majority of DNA in eukaryotes, remains unclear. For example, in human chromosomes, about 98% of DNA is represented by non-coding nucleotide sequences (ncDNAs). Although no one excludes

their possible role in evolution, nevertheless, studies aimed at elucidating the participation of the non-genic part of the genome as a source of biological variability are extremely small.

The sources of biological variability

An understanding of the nature of this variability was finally made possible, after 1900, by advancements in genetics and molecular biology. Currently, genes are recognized as the main source of biological variability, namely their mutations, recombination (reshuffling of chromosome segments during meiosis) and duplication.

Indeed, the scale of gene variation that a population of sexually reproducing organisms can produce is enormous. 'Consider a single parent with *N* number of genes, each with only two alleles. This individual can produce 2^N genetically different sperm or egg cells. Because sexual reproduction involves two parents, each set can therefore produce an offspring with one of 4^N different genotypes. Thus, if each parent genotype has a mere 150 genes with two alleles each (a gross underestimate of the human genome), each parent can give rise to over 10^{45} genetically different sperm or egg cells, and a single set of parents can produce more than 10^{90} genetically different offspring (a number that comes very close to estimates of the total number of particles in the observable universe)' [5].

It would seem that with such a scale of genetic diversity, there is everything for selection that the population can adapt to any ecological environments. However, judging by the fact that this is not so, even the genetic mechanisms of adaptation of eukaryotic organisms have not yet been elucidated, not to mention their evolution as a whole, we have to admit the insufficiency of our knowledge about the sources of biological variability. Perhaps one of the reasons for this situation was the underestimation of the possibility of the non-gene part of DNA in the eukaryotic genome as an important source of hereditary variation. Indeed, if the existing variety of life forms on Earth is considered a visible manifestation of evolution, then what should be the role of ncDNAs, which make up the vast majority of the eukaryotic genome, for example, in the origin of biological species?

In spite of the fact that the speciation is a key issue in evolutionary biology, there is still debate about the "creative process" that leads to species diversity [6-8]. From the time of Weismann [9] it is generally accepted that "creative process" stands explicitly on proposal that sexual reproduction functions to provide variation for natural selection to act upon. However, the origin of the biological sex is still not known, including its material base, mechanism of origin, and selective value [10-12].

Even without taking into account the problem of the origin of biological sex its adaptive significance is still controversial; because the 50% "fitness cost" of meiosis which, in theory, should favor asexual reproduction [13]. For example, Kutschera and Niklas, [5] notice 'that during sexual reproduction, each parent contributes only 50% of its genome to its offspring. The resulting genomic variation thus introduced into a population can lead to maladapted individuals. In contrast, asexual reproduction ensures that new individuals are as adapted to their environment as their parents, since every individual in the population leaves progeny that are clones of itself. So why does bisexual reproduction abound?'

Thus, it is difficult to agree with the generally accepted position when genes are considered the main, if not the only, sources of biological variability. If things were this way, then for more than 150 years of the history of research, scientists would reveal the basic mechanisms of evolution, not to mention the emergence of sex, without which the origin of biological species is not possible.

Some controversial issues related to the gene-centric view on evolution.

Many scientists continue to explore and debate precisely how the mechanisms of evolution work [5]. However, they all share the gene-centric view on evolution. And, nevertheless, the exact genetic mechanisms of even the origin of the biological species are still not clear, not to mention the evolution as a whole. All this happens at a time when genetics and molecular biology have achieved impressive success.

What could be the reason for this discrepancy between knowledge of the work of genes up to the molecular level and their role in evolution? It seems highly probable to us that the gene-centric view suffers from attributing to the genes everything that may takes place in life, from the synthesis of the polypeptide chain to complex human behavioral reactions. Perhaps it is appropriate to cite Rose's fair remark [14]: 'To judge from headlines in daily newspapers, or the titles of academic papers in major

scientific journals … there are genes available to account for every aspect of our lives, from personal success to existential despair: genes for health and illness, genes for criminality, violence and "abnormal" sexual orientation – even for "compulsive shopping". And genes too to explain, as ever, the social inequalities that divide our lives along of class, gender, race, ethnicity'.

Discussion of controversial issues about the role of genes in evolution will start right with E. Mayr. In many of his writings, Mayr [1-4] rejected the idea of a gene-centered view of evolution. He rejected reductionism in evolutionary biology, arguing that evolutionary pressures act on the whole organism, not on single genes, and that genes can have different effects depending on the other genes present. Mayr advocated a study of the whole genome rather than of isolated genes only. He believed that a gene is never visible to natural selection, but rather its phenotype and evolution is not "a change in gene frequencies". The history of evolutionary biology reports numerous cases of evolutionary theories that were eventually rejected. The belief that a gene can be the direct object of selection is one such refuted theory.

To find out the mechanisms of evolution in Darwin's understanding (namely, the origin of species) it is necessary to find out how, where and why eukaryotes originated. Oddly enough, the question of the origin of eukaryotes has not yet been resolved. Without an answer to this question, one cannot be sure that the study of the mechanisms of the origin of biological species is going in the right direction? But this is not enough. We do not yet know the origin of the most fundamental features of eukaryotes, such as the cell nucleus, mitotic chromosomes, biological sex, multicellular and homeothermic organisms, including the human himself [12.15-17].

Symbiosis was apparently not involved in the origin of cell nucleus. The endosymbiotic hypothesis does not easily account for single membrane-bound organelles, the evolution of the endoplasmic reticulum, or the appearance of single membrane-bound organelle-like structures in prokaryotic cells. It is not yet understood how the nucleus originated, in which the chromosomes are placed within a membrane.

Genes, unlike ncDNAs, are very conservative, since they contain vital information for the cell that has arisen, been selected and fixed in the process of evolution. Conversely, ncDNAS can change rapidly without affecting the informative part of the genome. A more definite statement in favor of this issue was made by Prokofyeva-Belgovskaya [18]: 'Changes in the heterochromatin content of chromosomal heterochromatin regions in species are adaptive. They apparently ensure 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. Quantitative changes in heterochromatin could be of great importance'.

The question remains completely open, why did prokaryotes, like eukaryotes with genes, remain unchanged for the past 3.0 – 3.5 billion years of evolution? If the gene-centered view were true, then we would be witnesses to the unusually frequent evolution of microbes, which are distinguished by their multiplicity, short reproduction period and wide habitat. 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, co-existed 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. This fact suggests that the role of genes in speciation and evolution in eukaryotic organisms is apparently very limited [19].

The metabolism of organisms proceeds well only within narrow ranges of internal physical and chemical conditions. Many of the structures and mechanisms that organism possesses serve to maintain this relative internal constancy (homeostasis) even when there are large changes in the surrounding environment. Homeostasis depends on the organism's ability to respond to the environment by changing the rates of its internal reactions or processes – in short, to regulate its metabolism. However, it is difficult to imagine that, for example, physiological thermoregulation arose due to gene mutations, gene recombination during meiosis and gene duplication. Yes, all organisms respond to temperature stress by synthesizing heat- and cold shock proteins. But to assert that the system of physiological thermoregulation in homeothermic organisms arose as a result of favorable mutation of genes, borders on the abuse of human credulity [20].

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. The main differences in these species are due to the different amounts and localization of heterochromatin [21].

According to supporters of "Third Way scientists" 'The principal focus of dispute with Neo-Darwinists is over the source of variation on which Natural Selection can operate. Supporters of the Extended Synthesis deny that these arise from "random copying errors" in DNA replication'. They claim that 'The DNA record does not support the assertion that small random mutations are the main source of new and useful variations'… 'The goal is to take evolution beyond the gene-centered approach of population genetics to consider more organisms and ecology-centered approaches' [22].

And finally, is it even possible that the genes that make up about 1.5% of the genome DNA in such a complex organization species as *H. sapiens* could be responsible for those features that distinguish his from animals, including higher primates (see below)? If the above issues have a right to exist, then out of the three pillars on which evolution stands, the weakest point may be just biological variability, or rather its possible sources [23-25].

Do we need in a paradigm-shift?

Our answer is yes rather than no, when it comes to the evolution of eukaryotes. It is proposed to study in more depth the DNA variability of that part of the eukaryotic genome that does not encode proteins and enzymes known to science. The following are some examples that demonstrate the role of ncDNAs as the main source of biological variability in the evolution of eukaryotes using the example of humans.

First of all, ncDNAs is more plastic than was previously expected. They are capable of creation of higher forms of DNA organization. For example, it is generally known that highly repetitive DNA regions of chromosomes adopt a heterochromatic chromatin structure, with distinctive properties and chromatin components. Introns, transposons, middle repetitive DNA, highly repetitive DNA, and many other kinds of ncDNAs suggests different functions, but most of what these elements are and how they work together is still to be determined.

Of all the higher forms of ncDNAs organization, the so-called heterochromatin chromosome regions are best studied. We affirm that chromosomal HRs played a decisive role in the origin and evolution of modern man. To make our arguments clearer, it is necessary to give short information about chromosomal HRs. Details about the morphology, inheritance, variability and molecular structure of chromosomal HRs have been given in special reviews [26-31].

A fundamental feature of chromosomes in higher eukaryotes, including man, is the presence of two evolutionally consolidated types of genetic material: euchromatin and heterochromatin. Euchromatin, the conservative portion of the genome, contains transcribed structural genes, while heterochromatin, the variable portion of the genome, is predominantly composed of non-transcribed repeated DNA sequences.

Heterochromatin is universally distributed in the chromosomes of all the eukaryotes - plants, animals and man, accounting for 10% to 60% of their genome. Chromosomal HRs account for about 15% - 20% of the human genome [27-29]. To-date two types of heterochromatin are recognized: Q– and C– heterochromatin [29]. There are several significant differences between them: C-heterochromatin is found in the chromosomes of all the higher eukaryotes, while Q-heterochromatin - only in man (*Homo sapiens*), the chimpanzee (*Pan troglodytes*) and gorilla (*Gorilla gorilla*) [29,32,33].

C-heterochromatin regions (C-HRs) are known to be invariably present in all the chromosomes of man, varying mainly in size and location (inversion). Q-heterochromatin regions (Q-HRs) variability can be found in man only on seven autosomes (3, 4, 13, 14, 15, 21 and 22), as well as on chromosome Y. Chimpanzees have Q-HRs on five autosomes (14, 15, 17, 22 and 23), while in gorillas they are present on eight (3, 12, 13, 14, 15, 16, 22 and 23) and on chromosome Y [27-29]. Individuals differ in the number, location, size, and intensity of staining (fluorescence) of these specific chromosomal regions [29,31,34].

Chromosomal Q-HRs is subject to considerably greater variability in any population as compared to C-HRs. That chromosomal Q-HRs meets the requirements as a source of biological variation in human adaptation and evolution, say the following facts: a) although chromosomal Q-HRs exist in the genome of only three higher primates (*H. sapiens, P. troglodytes and G. gorilla*), their wide quantitative variability is characteristic only to human populations [32,33]; b) most chromosomal Q-HRs are present in the genome of gorillas and chimpanzees, and least of all in humans. Note that the orangutan has no such chromosomal segments [32,33,37]; c) individuals in human populations differ in the number, location, size, and intensity of chromosomal Q-HRs fluorescence in the genome; d) the results of extensive comparative population-cytogenetic studies show that the populations of modern man are significantly different, and that these differences are associated with the natural environment of permanent residence, and not with racial or ethnic characteristics [35, 47-52]; e) the amount of chromosomal Q-HRs in the population genome tend to decrease from low geographical latitudes to high ones, and from low-altitude to high-altitudes [38-46]; f) different age groups have different amount chromosomal Q-HRs: the greatest number of Q-HRs is characteristic of neonates, while the lowest - of elderly subjects [53]; g) individuals capable of successfully adapting themselves to the extreme high-altitude climate (e.g. mountaineers) and of the Far North (e.g. oil industry workers of polar Eastern Siberia) are characterized by extremely low amounts of Q-HRs in their genome [43-44]; h) all forms of purely human pathology (alcoholism, drug addiction, obesity) were associated with a wide quantitative variability of chromosomal Q-HRs. For example, individuals with a lower amount of Q-HR in their genome proved to be prone to alcoholism and obesity, while those with a greater amount of Q-HR - to drug addiction [54,55]; i) finally, unlike hypothetical adaptive genes, the amount of chromosomal Q-HRs in the human genome has a distinct physiological phenotype in the form of different body heat conductivity [56].

Of all the biological species that ever lived on Earth, only *H. sapiens* managed to populate the entire land of our planet. Nevertheless, it remains a mystery how exactly our ancestors managed to realize this global expansion. According to the new hypothesis, the basis of world domination of *H. sapiens* was laid by two unique human traits: the genetically entrenched ability to cooperate with unrelated individuals and the invention of highly effective throwing weapons [57]. But is it possible to believe that these unique traits have arisen only in the last 150,000 - 200,000 years and only in humans, on the basis of favorable mutations of genes, their recombination and duplication? If yes, then how to explain that all this did not happen with the genome of chimpanzees or gorillas, which are 6 million years older than us and exist in the same Africa? After all, it is known that these three higher primates have almost the same DNA for almost 99% of their DNA. Our nearly half a century experience of studying the genetic mechanisms of human adaptation to the high-altitude climate of the Pamir and Tien-Shan, as well as to the Far North of Eastern Siberia, argues in favor of the non-gene part of the genome [for more details see 33,42,44,58-60]. We also believe that the wide variability of chromosomal HRs may be directly related to the origin in humans of high physiological plasticity, hairless skin, large neocortex, reason and speech, as well as to the origin of 46 instead of 48 chromosomes [25]. As far as we know, no one has yet been able to explain all of the above-mentioned revolutionary innovations as a result of gene mutations.

From this list, here is just one example, testifying to the paramount importance of the wide variability of chromosomal Q-HRs in the emergence of modern man. Undoubtedly, perhaps the most important difference between *H. sapiens* and other higher primates is the presence in his karyotype of 46, instead of 48 chromosomes. In the end, it is this circumstance that provides the reproductive isolation of humans from other primates. At the same time, it is unlikely to expect that with this difference a man is obliged to favorable mutations of genes, their recombination or duplications.

We believe that the occurrence of 46 chromosomes can be rationally explained on the basis of Darwin's view of the origin of species. A hypothesis has been proposed that natural selection caused merger of two pairs of autosomes into one chromosome. In the changed climate of the East Africa individuals with less amount of chromosomal Q-HRs in genome were the most adapted. Two pairs of acrocentrics in the genome the common ancestor, which merged into a single chromosome, apparently, carried on their short arms of Q-HRs with a very high frequency, preventing the birth of individuals with a low number Q-heterochromatin. With the merger of these two pairs of acrocentrics into one, the number of autosomes bearing the Q-HRs reduced from nine to seven pairs, as in the modern human. Such chromosome rearrangement resulted in two important consequences: a) chromosomal Q-HRs distributed into seven Q-polymorphic autosomes, so that it was possible to give birth to the individuals with different, including the low, number of Q-heterochromatin; b) in the population individuals with low number of Q-

HRs appeared, able to adapt to new, harsher climatic conditions. With the lapse of time, these individuals formed a new population in the new territory, where individuals with a number of chromosomal Q-HRs like the modern natives of Africa, and with the number of 46 chromosomes in the genome began to dominate. Thus, the cause of the origin of the 46 chromosome karyotype from an ancestral 48 chromosome line was natural selection, and an effect was adaptation, i.e. individuals with different, including the low, number of Q-HRs, got the advantage to open up and to colonize new ecological zones of the East Africa [25].

Of course, the above data do not exhaust the role of ncDNAs as a source of biological variability in the evolution of eukaryotes. We stopped in more detail on chromosomal HRs variability only because experimental data were obtained from them. But, in fact, there are many other questions and they concern all eukaryotes, namely, the origin of nucleosomes, mitotic chromosomes, chromosome bands (C-, G+, Q + and T-bands), condensed chromatin, the cell nucleus, eukaryotic cells, sex, multicellularity, thermoregulation and homeothermic organisms.
We repeatedly discussed this issue and came to the conclusion that their origin can be rationally explained on the basis of the evolution of ncDNAs [23–25.61].

CONCLUSION

If we accept the generally accepted point of view that only genes are the basis of all evolutionary changes, then it should explain the mechanism(s) of the emergence of such revolutionary innovations as nucleosomes, mitotic chromosomes, the cell nucleus, eukaryotic cells, biological sex and species, multicellular and homeothermic organisms, without which it is not possible to imagine modern eukaryotes.

If we talk about human, then gene-centric theories should be able to explain the origin of modern man, including such biological features as high physiological plasticity, the ability to adapt to different climatic conditions, the presence of hairless skin, the existence of purely human forms of pathologies, large neocortex, mind and speech. As far as we know, no one has yet been able to explain all of the above-mentioned revolutionary changes as a result of gene mutations.

Of course, the study of possible sources of biological variability is important in itself. However, the purpose of this note is to seek an answer to an old question: the mechanism(s) of origin of evolutionary novelties? Another contemporary of Darwin J. F.W. Herschel wondered: but how could natural selections produce an entirely new structure? This question still has no answer. Mayr [4] indicates that 'there are two different pathways by which an evolutionary novelty can be acquired: by intensification of function or by the adoption of an entirely new function'. If so, then are genes enough for evolutionary novelties to emerge? Obviously, the problem is not so simple, because with the impressive achievements of modern developmental biology, we would know about it. Thus, there are two sources of biological variability and both are responsible for adaptation and evolution. However, their role in the evolution of eukaryotic organisms is still not entirely clear. But, if we are ready to admit that perhaps the obstacle in revealing the evolutionary mechanisms is the lack of our knowledge regarding the sources of biological variability, then our duty is to pay due attention to studies of the non-gene part of the eukaryotic genome. However, from the fact that we underestimate the possible role of ncDNAs as a source of biological variability in evolution, it will not become less significant from this.

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