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Review Article

The origin of the human karyotype: its uniqueness, causes and effects

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ABSTRACT
As is known, the diploid number of human chromosomes is 46, while in other higher primates, such as chimpanzees and gorillas, this number is 48. It has been established that a decrease in the number of chromosomes by two in humans is a result of the fusion of two autosomes into one chromosome in his karyotype ancestors. However, why such changes in chromosomes occurred among the highest primates in humans, their uniqueness, causes and consequences have not yet become the subject of special studies. We believe that the transition from 48 to 46 chromosomes, as well as changes in the composition, localization and amount of chromosomal heterochromatin regions in the karyotype of the ancestors of modern man turned out to be crucial in his formation as a biological species with all the ensuing consequences.
Key words: human karyotype, chromosomal Q-heterochromatin, human adaptation, human evolution.

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INTRODUCTION

It has been established that there is no direct relationship between the number of chromosomes in the karyotype and the complexity of the body structure. The amount and location of chromosomal euchromatin regions in the karyotype of a species is constant and are under strict control of natural selection. Biological variability at the level of karyotype relates mainly to chromosomal heterochromatin regions (HRs).

It is curious that the question of why a man has 46, and not 48 chromosomes, like other higher primates, the cause of their origin and biological consequences is still not the subject of special studies [1]. Perhaps this circumstance is connected with the deep-rooted gene-centric view on evolution.

We believe that not the decrease in the number of chromosomes, but the composition, localization and number of HRs in the karyotype was the main cause of the origin of modern man. The generally accepted view that the origin of a biological species is not necessarily accompanied by a rearrangement of the karyotype, we believe, does not have a serious reason: either they are not visible under a microscope, or the methods used are not sensitive enough to detect subtle chromosome rearrangements. So, for example, when comparing the chromosomes of humans and chimpanzees using the G-technique, many differences were detected (translocations and inversions) [2]. But since this applies to chromosomal HRs, it is considered not significant, because traditionally the heterochromatin component of the genome is considered as selectively neutral structures of genome.

Prerequisites for the origin of the human karyotype: its uniqueness, causes and effects.
As far as we know, for more than 60 years from the time the establishment of the exact number of chromosomes in the human karyotype and other higher primates [3-5], no attempts have been made to investigate the causes and effects of this drastic change. As for the known morphophysiological differences of a human (high physiological plasticity, ability to adapt to different climatic and geographical conditions,

hairless skin, large neocortex, reason, speech, etc.), their occurrences are attributed to favorable gene mutations, their recombination and duplications.

We held a different point of view, namely, changes in the composition, amount and localization of chromosomal HRs in the human karyotype led to the fact that he became a unique biological species, with all its distinctive features. Moreover, all this became possible, not because of a change in the number of chromosomes (from 48 to 46), but because of the special localization, distribution and composition of chromosomal HRs in the human karyotype. And well-known human features are result of the simple physiological effect of the amount of chromosomal HRs (see below), and not the function of structural genes [1,6,7]. To clarify the above, it is necessary to give a brief overview of the data about chromosomal HRs in the genome of higher eukaryotes.

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 [8-12; 13-33]. To-date two types of constitutive heterochromatin are recognized: C- and Q-heterochromatin. 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*) [8,9,13,14].

Although chromosomal Q-heterochromatin regions (Q-HRs) exist in the genome of three higher primates, their wide quantitative variability is characteristic only to human populations. 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. Individuals in population differ in the number, location, size, and intensity of staining (fluorescence) of these specific chromosomal regions [8,13,15-33].

C-heterochromatin regions (C-HRs) are known to be invariably present in all the chromosomes of man, varying mainly in size and location (inversion). Chromosomal Q-HRs is subject to considerably greater variability in any population as compared to C-HRs. Erdtmann [34] emphasized that "recent analyses... show a great population and evolutionary stability of C-band heterochromatin... From interpopulation comparisons, C-band means show a tendency to maintain a constant amount of constitutive heterochromatin". Therefore, we display here some the additional facts, concerning peculiarities of distribution of chromosomal Q-HRs in the genome of populations of the modern human.

In particular, it is established: 1) Chromosomal Q-HRs is detected on certain loci of only seven autosomes (3, 4, 13, 14, 15, 21 and 22) in both sexes, as well as on the Y chromosome of males. On the seven autosomes and the Y chromosome there are only 13 loci where Q-HRs potentially can be detected; 2) Despite the fact that in the human karyotype there are 13 loci in which Q-HRs can be detected (3cen, 4cen, 13p11, 13p13, 14p11, 14p13, 15p11, 15p13, 21p11, 21p13, 22p11, 22p13, Yq12), i.e., there could theoretically exist individuals with 25 Q-HRs in their genome, but such cases have not as yet been reported; 3) In individuals of a population the number of Q-HRs usually ranges from 0 to 10. Both complete absence and the maximum number of Q-HRs in the genome have no visible phenotypic manifestations. The presence of individuals in the population with different numbers of Q-HRs in the karyotype (from 0 to 10) is due to the fact that Q-HRs are unevenly distributed on seven potentially Q-polymorphic autosomes; 4) Comparative analysis of the native human populations of Eurasia and Africa convinces that the distribution of chromosomal Q-HRs in seven potentially Q-polymorphic autosomes far from accident. In particular, at the level of human populations each of the seven Q-polymorphic autosomes contains comparable "portion" of the overall amount of Q-HRs in population genome irrespective of their race, ethnic, sex and age peculiarities. Indeed, more than a half of Q-HRs are localized in autosomes 3 and 13, and the rest are distributed in autosomes 4, 14, 15, 21 and 22 (29.9%, 32.0%, 2.6%, 6.5%, 10.4%, 10.8% and 7.6%, respectively). Hence, if Q-HRs frequencies to be expressed in relative numbers (in percentage from the overall number of chromosomal Q-HRs found in a sample), then it became obvious that interpopulation heterogeneity is formed due to proportional increase or decrease of the absolute number of Q-HRs in all potentially Q-polymorphic loci of seven autosomes simultaneously [13-35].

Distribution of chromosomal Q-HRs on Q-polymorphic autosomes in population of a chimpanzee and a gorilla are absolutely the other. In chimpanzee Q-HRs have been found at the proximal region of the short arm of the

acrocentric chromosomes, Nos. 14, 15, 17, 22, and 23. 'The frequency of brilliant polymorphisms in the chimpanzee is considerably higher than in man; in man their incidence averages from about 2.9-4.2 [27], while in the chimpanzee it has been estimated to be equal to 8.77 [36], and to 8.85 [37].

Concerning the quantity of chromosomal Q-HRs in a gorilla it is known, that: 'In this species, autosomal brilliant Q-band polymorphisms have been found in the centromere region of chromosome 3, the terminal satellites of the acrocentric chromosomes 12, 13, 14, 15, and 16, and at the proximal short arm regions of chromosome 22 and 23. Variations accounts for change in size and/or fluorescent intensity' [38]. The frequency of brilliant autosomal polymorphisms accounted for 14.8 in specimens of gorilla, which is approximately five times the number observed in man [37].

That chromosomal Q-HRs may be subject to natural selection and 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 three higher primates (H. sapiens, P. troglodytes and G. gorilla), their wide quantitative variability is characteristic only to human populations [13,14]; 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 [38]; 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 [18-26]; 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 [18-26]; 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 [39,40]; 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 [23,24]; 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 [41,42]; 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 [43]. Details about the morphology, inheritance, variability and molecular structure of chromosomal HRs have been given in special reviews [26-31].

The causes of the origin of the human karyotype

At present several areas uncertainty exist regarding the precise origin of the 46 chromosome karyotype from an ancestral 48 chromosome line. It is assumed that the common ancestor described had 48 chromosomes and therefore ancestral man must have lost two chromosomes. Early proposals [44,45] pointed out that this might have occurred by centric fusion of two acrocentric chromosomes. Turleau et al., [46] suggested the idea that the human chromosome 2 has originated *de novo* from centric fusion of two nonhomologous acrocentrics.

We think it highly probable, that the causes of origin of individuals with 46 chromosomes were climate in the East Africa. Middle and Late Miocene ecology was far from being uniform, and such climatic changes as cooling, aridity, seasonal and diurnal temperature fluctuations gradually became dominant environmental factors [47]. Thus, even before they left Africa our ancestors were probably faced with the problem of adaptation to new, more rigorous natural conditions differing from those of the savannah.

As the amount of food decreases, populations of the common ancestor of the modern man began to expand the territory of their habitat to more severe, including cold areas (see above). Perhaps, just at this stage in the life history of our ancestors, the adaptive changes appeared in their karyotype, which, ultimately, resulted to the emergence of the modern human. In particular, the individuals with a number of chromosomal Q-HRs in the karyotype closest to the modern Africans became adapted better in the new climate conditions [48-52].

But wherefrom there are individuals with different, including with a low number of chromosomal Q-HRs in the population of our ancestors? Obviously, some of these individuals, as before, were born from parents with 48 chromosomes. However, due to their low number they could not form a new population, even if they had some adaptive advantage in the new environmental conditions. Here, a fundamentally new solution of the

problem was required. Namely, it is the merger of the two pairs of acrocentrics bearing Q-HRs with a very high frequency into one chromosome.

To substantiate such possibility we need to recall the long-established facts in human cytogenetics. In particular it was discovered that the acrocentric chromosomes are inclined to association. This means that in the interphase nuclei these chromosomes are joined together with HRs of the short arms. It is known that such associations of acrocentric chromosomes are associated with the formation and functioning of nucleolar organizers (NORs) in the nucleus. As, the ectopic pairing of HRs between homologous and non-homologous chromosomes in interphase nucleus and high break frequency in HR sites or at their border with euchromatin regions are integral properties of constitutive heterochromatin, why not to assume that such processes could result in the merger of the two pairs of acrocentrics with Q-HRs on the short arms of the common ancestor? In this case, the merging of two pairs of ancestral acrocentrics allowed to birth the individuals with different, including the low, number of Q-HRs.

We postulate that two pairs of acrocentric chromosomes in the genome of the ancestral population, which generated the chromosome 2 of the modern human, were bearers of Q-HRs with a very high frequency. In the genome of the population of the modern human only two pairs of autosomes (3 and 13) are the high frequency, and for more than half of the total amount of chromosomal Q-HRs belongs to their share, and the rest amount of Q-heterochromatin is distributed on the other Q-polymorphic chromosomes (4, 14, 15, 21 and 22) with frequency from 3% to 10% (see above). Apparently, our ancestors had the number of high Q-polymorphic chromosomes by two pairs more than the modern human. But it wasn't enough.

It is imperative that chromosomal Q-HRs was not distributed equally to all potentially Q-polymorphic autosomes. If the population have uniform distribution of chromosomal Q-HRs with high frequency as in modern chimpanzees and gorillas, then it will be difficult, if not possible, to birth the individuals with different numbers of Q-heterochromatin in the karyotype. The presence of individuals in human population with different numbers of Q-HRs in the karyotype (from 0 to 10) is due to the fact that Q-HRs is unevenly distributed on seven potentially Q-polymorphic autosomes [15,48,49]. As an analogy, we gave the example with banknotes on the example of the US dollar. Banknotes of denominations of 1, 2, 5, 10, 20, 50 and 100 are in free circulation and use, that is, as many as autosomes, in the human genome that can potentially have a chromosomal Q-HRs. Obviously, they came from common sense, if to print seven banknotes in varying proportions (that is, the most is 1 and less of all the 100 dollar bills), then the number of possible combinations at cash transactions be virtually unlimited [1].

It is possible that, sometime in the ancestral population individuals, as the 48, and the 46 chromosomes could coexist. But with the lapse of time the latter began to prevail over the first, and gradually they were replaced. Most likely, it's happened in the new territory, when the individuals with the 46 chromosome, having some adaptive advantage over individuals with 48 chromosomes in the new climates became dominant in the population numbers.

Then the question is appeared, what is the main at this: a number reduction of the chromosomes from 48 to 46 or something else? We believe that the correct answer will be: both. The modern human could exist with 48 chromosomes in the karyotype, if two pairs of acrocentric chromosomes in the genome of the ancestral populations, wherefrom the later chromosome 2 was formed, did not have at all or had Q-HRs with a very low frequency. However, it was that it was. Just, the existence on their short arms of chromosomal Q-HRs with a very high frequency made it difficult (but not excluded) to give birth in the population to individuals with different, and in particular a very low number of Q-heterochromatin in the genome.

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 variable loci proved to be high enough, as in two modern higher primates, to produce of individuals with significantly different numbers of chromosomal Q-HRs and, hence, the appearance of individuals with a various numbers of Q-HRs who would be able to survive under unfavorable conditions was quite improbable.

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 [13,14], whereas in the human population it is from 0 to 10, i.e., considerably wider [15]; 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. The nature of these bright distal Q-bands that are only

present in the chimpanzee and the gorilla is unclear, however, they are stained by quinacrine mustard and show intense fluorescence, suggesting that this is also chromosomal Q-heterochromatin [53].

Of course, we are far from thinking that in the karyotype of our ancestors the other chromosomal rearrangements did not take place, including those, which related to chromosomes without Q-HRs. They, apparently, took place. But in the process of adaptation only those rearrangements preserved that were not eliminated by natural selection.

Thus, the essence of our hypothesis is 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.

A natural question arises: why exactly the broad variability of the number of chromosomal HRs was so important in the origin of modern man, and what is the mechanism of its implementation? There are several reasons for this. In addition to the foregoing, the following were significant: a) chromosomal HRs are localized in regions forming nucleolar organizers (NORs); b) ectopic pairing of HRs between homologous and non-homologous chromosomes in interphase nucleus; c) chromosomal HRs are involved in the formation of chromocenters, and where they exist, B-chromosomes; d) in the interphase nuclei chromosomal HRs in the composition of condensed chromatin are located under a layer of nuclear envelope. Together these structures form the material basis of cell thermoregulation, the phenotypic manifestation of which in humans is different levels of heat conductivity of his body [43,54].

The consequences of the origin of a unique human karyotype

In our opinion, the main consequences of all these complex chromosomal rearrangements are their effect on human cell thermoregulation (CT). Based on investigations of chromosomal HRs variability in human populations, condensed chromatin (CC), interphase nucleus and redundant non-coding DNAs in the genome, an attempt is made to justify the view of possible participation of CC in CT. 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: a 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 nucleolus, chromocenters and B-chromosomes, genetic inertness, and wide variability in the quantitative contents both within and between species [54].

The mechanism of CT is presented to us as follows. Chromosomes have both internal (repair, recombination, rearrangement, modification, restriction) and external (replication, transcription, packaging, organized movement) molecular activities, which are accompanied, inter alia, by some heat output. If for any reasons the temperature in a nucleus begins to exceed than in cytoplasm there is a need for dissipation of surplus heat outside the nucleus. To do this the nucleus has two options: increasing its volume or increasing the heat conductivity of the nuclear membrane. The first option is limited for obvious reasons. The second option is the more promising one should the heat conductivity of the nuclear membrane be increased somehow. Since the nuclear envelope consists of double-membraned extension of the rough endoplasmic reticulum, the nuclear membrane cannot essentially change its structure. But it is necessary to remove the surplus heat from the nucleus somehow.

Apparently Nature chose a very simple and effective solution: it increased heat conductivity of the nuclear areas where excess heat is produced into temporary structures in the form of CC around the nucleus, chromocenters and nucleoli. The essence of the proposed hypothesis is the assumption that the CC, nucleoli, chromocenters and B-chromosomes participate in cell thermoregulation. Namely, they are involved in the removal of excess heat from the "hot" areas of the interphase nucleus through a dense layer of peripheral condensed chromatin in the cytoplasm.

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. The role of the circulatory systems (CS) has not been discussed here in maintaining temperature homeostasis. The thing is the CS cannot influence directly the temperature inside the cells, as they are linked with the CS indirectly through the intercellular space. The only exception may be endothelial cells lining the inner surface of blood vessels. Thus, the CS influence on inner cellular temperature homeostasis is limited. That is why it seems that the problem of maintaining the inner cellular temperature homeostasis is solved by cells themselves, and we call it the cell thermoregulation [54-56].

Certainly, CT hypotheses should be checked on the cell level. But till present no one had the opportunity to evaluate CT at the level of individual cells. Nevertheless, we have checked this hypothesis on the level of human organism assuming that CT is the basis for heat conductivity of whole cell part of body. It turned out that the level of human body heat conductivity (BHC) really depends on the amount of chromosomal HRs in the genome. Results obtained show that individuals in population truly differ from each other in BHC and its level depends on the amount of chromosomal HRs in human genome [43].

Relevant studies have shown that: a) individuals in a population differ from each other on the level of BHC; b) on the average BHC of males is higher than that of females; c) individuals differ in BHC from different age groups, on the average human BHC level is steadily changed decreasing with age; d) natives of low altitude regions differ on the average by higher BHC than population of high altitude ones; e) natives of low latitudes differ on the average by higher BHC than populations of high latitudes [43,56-59].

High physiological plasticity of a human usually means his ability to adapt to different climatic and geographical conditions. Human uniqueness in addition to all his known characteristics is that he is the only who managed to populate the whole Earth surface including such extreme areas as Far North and high altitudes remaining single tropic biological species. Moreover, all this took place in a short period of time (around 30,000 - 50,000 years), an unprecedented fact in life evolution [60].

Unlike many animal species, man is unstable to live in an extreme cold environment. He is basically a tropical homoeothermic. Naturally, all three effector thermo regulating systems mobilize: heat production, heat loss and thermoregulatory behavior. Though being important, they cannot be effective at long-term perspective. We suppose that *H. sapiens*, besides those inherent in all mammals 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, behavioral and biochemical mechanisms such as wide intra population variability by BHC was used [54-62].

On the whole, we see efforts for maintaining temperature homeostasis under conditions different from climate of the Eastern Africa as follows: 1) an individual with less chromosomal Q-HRs in the high latitudes maintain more effectively temperature homeostasis in organism because of low BHC, permitting to preserve additional amount of produced heat in organism longer and slow down the body cooling rate from external cold; 2) an individual with high BHC in the high latitudes, constantly loosing additional amount of metabolic heat through conduction which is necessary for organism in terms of cold climate and exposing to relatively fast cooling because of cold, has to produce larger amount of heat and/or consume more high calorie food for heat production, which is not always simple; 3) an individual with low BHC in the low latitudes (where environment temperature is higher than body temperature) besides his own internal heat production receives additional heat from environment by means of conduction, which, as it is known, is not used in useful physiological work. That is why these individuals' bodies overheat faster and they have to return heat surplus (through sweating, polypnoe, forced rest, behavioral reactions and etc.) to environment at the cost of significant decrease of physical and mental activities that finally negatively influences on their adaptation to hot climate; 4) an individual with big amount of Q-HRs in genome in the South having body with high thermal conductivity perhaps adapts better to high temperature of environment, more effectively leveling temperature differences in different parts of the body and faster directing surplus heat flow from organism to environment, including the way of heat radiation.

As we suppose, during his evolution man, possibly owing to chromosomal Q-HRs, had an additional and very flexible tool to ensure more effective thermoregulation, allowing him to master almost all the oykumene [1,61,62]. *H. sapiens* is not only devoid of a more or less large anatomic structure, but also has no protein or enzyme that has no analogue in the animal world. The fundamental structural characteristic of man is the presence of chromosomal Q-HRs in its genome which he has inherited together with the chimpanzee and the gorilla – from one common ancestor. 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 [63,64]. The main differences in these species are due to the different amounts and localization of heterochromatin [65]. These data are in agreement with those of Dutrillaux et al. [64] according to which heterochromatin is not distributed at random in the chromosomes, but is usually found in the same regions, depending on the species or genera studied.

What is unusual about the human brain is that we are the only largish mammal whose brain size kept pace with our growth in body size. The plausible reason of this phenomenon is his skin, when after having lost its hair it became the largest and almost universal organ of sense, which begins functioning as early as in the prenatal period of human development.

In the heterochromatin part of genome in the direct ancestors of modern human some changes occurred; in addition to Q-HRs, on three pairs of autosomes (1, 9 and 16), and on the Y chromosome unusually large C-heterochromatin regions appeared, which do not exist in karyotypes of chimpanzee and gorilla. Thus by the total amount of chromosomal HRs the genome of the *H. sapiens* turned out to be richest one. We assume that assemblage of the greatest amount of chromosomal HRs in the *H. sapiens* karyotype among the higher primates was the turning point in human evolution, as exactly this circumstance has led 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* [66].

Apparently, the main reasons for appearance of hairless skin were the following factors: 1) increase of BHC because of high Q-HRs and C-HRs content in the genome of the direct ancestor of modern human; 2) quantitative and qualitative changes of the diet composition [67-69], which lead to increase of heat production in the organism demanding efficient heat loss from the body for preservation of temperature homeostasis; 3) climate of Africa, where the ancestors of the *H. 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. Given this, the heat-protection function of hair passed over to the layer of subcutaneous fat. Such skin, in addition provided with a great amount of sensory receptors, cannot but influence the postnatal development of the brain size [66].

We believe that loss of hair was beneficial for human in the sense that if he were not naked, he would not begin to manufacture clothes, which is impossible without availability of fine instruments like awl, needle, and other instruments, production of which is connected with fine coordination of hands' movements. Fire striking and dwelling construction is also impossible without skillful hands even with availability of high Intellect.

A human, instead of his hair that he has lost, acquired clothes, which is more important in sense that in addition to body protection from cold (physiology) it has an important ethnical and cultural, psycho-emotional, social and economic importance that promotes the scientific and technical progress. In addition the latter facilitates functioning of the temperature homeostasis in human. Therefore in reply to the old question, namely: 'has a human survived because he became intelligent, or, he became intelligent only because he managed to survive', we have chosen the second version [61].

Humans tend to tropicalize their environment virtually everywhere they go. They do this by hands for the most part (clothing, tools, buildings, heating). Apparently, transformation of the frontal extremities into skillful hands, bipedality and erect walking are connected with appearance of hairless skin. All the above, in its turn and to a variable degree they have an influence on the human brain size. Thus the whole evolution of the BHC, skin and brain size is a result of adaptation to constantly changing temperature conditions of the environment.

We assume that namely the skin has led to the formation of many more abundant micro connections 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 [69].

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 nerve endings, such as fingertips, tips and genitals, require more space in the cortex than the back, which has fewer nerve endings [70]. Young children depend on touch for learning about the world including the quantities of temperature, texture, shape, softness, sharpness, elasticity and resilience. Children also learn safety from touch such as avoiding stoves, sharp objects or frostbite, and they may learn how to write through touch if given hand-over-hand assistance in handwriting classes. Touch is not only critical for growth, development, and communication and learning but also serves for comfort, reassurance and self-esteem [71]. In the words of Schanberg: 'Touch is ten times stronger than verbal or emotional contact, and it affects damned near everything we do. No other sense can arouse you like touch. We always knew that, but we never realized that it had a biological basis. If touch did not feel good, there would be no species, parenthood or survival. …We forget that touch is not only basic to our species but the key to it' [72]. The role of touch in culture, health and caring for infant is well known.

Schematically the evolution of the BHC, skin and brain size may be roughly presented as follows: in the karyotype of one of the branches of the hominid together with Q-HRs large segments of C-HRs on three autosomes and Y chromosome appear → in such organisms the BHC significantly increases → problems appear with the heat loss from the body in conditions of tropical heat and heat protection of the organism when the environmental temperature decreases → in such conditions in order to keep the temperature homeostasis, the organisms with high BHC were deprived of hair for improving the heat loss, and under new skin a layer of subcutaneous fat for heat protection instead of the hair cover was formed → gradually the hairless skin has transformed into the largest sense organ → with falling of temperature of the African savanna the need in tropicalization of the microenvironment around the body started to increase that is impossible without a skillful hand → with switching the frontal extremities for the needs of tropicalization the bipedal locomotion became the bares necessity → naked skin with a great amount of the different nerve receptors, skillful hands and bipedal locomotion have promoted, and is being promoting the postnatal increase of the human brain size with all the ensuing consequences, including the emergence of conceptual thinking and speech. Therefore, we believe that the increase of the human brain size was not the result of drastical changes of the structural genes. Most likely it was the consequence of more ordinary events, such as evolution of constitutive heterochromatin in chromosomes, BHC and skin.

Thus, *H. sapiens* became the possessor of the largest brain with neocortex among the primates after he has lost hair on his skin. Apparently skin became hairless as a result of evolution of chromosomal HRs in the karyotype of the direct ancestors of a modern human. In particular in their karyotypes together with chromosomal Q-HRs three pairs of autosomes and Y chromosome became the carriers of unusually large C-HRs, which have led to significant increase of body heat conductivity. In conditions of tropical Africa, where our ancestors inhabited, availability of skin covered with hair became a serious obstacle in keeping the temperature homeostasis, particularly in dissipation of excessive heat from the organism that finally has led to hairlessness. Given this, the heat protection function of the hair cover was taken over by a large amount of subcutaneous adipose tissue. As for the possible role of chromosomal Q-HRs, they, providing a wide variability of the BHC level in individuals in the population (phenotype), turned them into an object for natural selection.

The influence of chromosomal HRs is not limited to their role in the origin of the large brain with newcortex in the evolution of *H. sapiens*. The participation of chromosomal HRs as part of the CC in CT is extremely important in the life of a modern human. In the end, the brain consumes more fuel than modern internal combustion engines: this body, whose mass is only 2% of the total body weight, accounts for 20% of the body's energy. If the adult brain consumes about 20% of the total energy of the body, then the baby's brain is almost 50%. With a relatively small brain mass, the use of such a huge amount of calories will inevitably lead to dangerous. The question is not simple, what kind of efforts: genetic or non-genetic, are required to ensure the safe functioning of brain cells? We believe that for this the greatest effort is required not from the genes, but from the chromosomal HRs in the CC. This is because for the normal functioning of genes in the brain it is extremely important to remove excess heat from neurons. It is no accident that the brain has an autonomous thermoregulation system many details of which are not yet known. Here, for the removal of excess heat, one circulation system is not sufficient, since it does not directly contact the cells of brain tissue, with the exception of the endothelium, the lining walls of blood vessels [52.56]. Here, the involvement of the CT system, which selectively removes excess heat from the cell nucleus, is necessary [73].

The uniqueness of the human karyotype

By the uniqueness of the human karyotype, we mean not so much the number of chromosomes, but something more. In fact, nothing special is hidden behind the number 46. With so many chromosomes, there are animals and plants. Here, in our opinion, the composition and broad quantitative variability of chromosomal HRs in the karyotype are important. The uniqueness of the human karyotype is as follows: 1) unlike other higher eukaryotes, only humans and two other higher primates contain both types of constitutive heterochromatin – C- and Q-heterochromatin; 2) among the higher primates, the largest amount of chromosomal C-HRs is in the human karyotype, and they are localized on his three autosomes (1, 9 and 16) and on Y chromosome.

It is to this circumstance that a human owes the highest heat conductivity of the body; 3) unlike chimpanzees and gorillas, the number of chromosomal Q-HRs in individuals in a population is different and it ranges from 0 to 10; 4) such a wide quantitative variability is associated with an uneven distribution of the number of chromosomal Q-HRs on seven Q-polymorphic autosomes; 5) the phenotypic manifestation of such biological variability is the difference between individuals in the population from each other in the levels of BHC, with all the ensuing consequences for the body.

CONCLUSION

It is possible that chromosomal HRs, which is highly mobile, primarily respond to environmental changes. A more definite statement in favor of chromosomal HRs was made by Prokofyeva-Belgovskaya [74]: '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'.

If all of the above really reflects the picture of the emergence of the karyotype of modern man, then we may have come closer to elucidating the mechanisms of the origin of biological species. In this case, the role of genes in speciation, contrary to popular belief, may not be so important. In the above speciation pattern, changes of the heterochromatin rather than the euchromatin component of the genome, which contains genes and is highly conservative, were of significant importance.

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