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Human adaptation: why only genes?

Ibraimov AI

Laboratory of Human Genetics, National Center of Cardiology and Internal Medicine, Bishkek, 720040, Kyrgyzstan

Correspondig Author: Ibraimov AI, Laboratory of Human Genetics, National Center of Cardiology and Internal Medicine, Bishkek, 720040, Kyrgyzstan. Email: ibraimov_abyt@mail.ru

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Abstract: Adaptation of a human to different climatic and geographical conditions has two principal features: a) only man managed to master the entire land of the Earth, while remaining a single, tropical biological species (*Homo sapiens sapiens*); b) in contrast to animals, human colonization of all climatic-geographical provinces, including the extreme ones (Far North and high-altitude), occurred in a very short period of time. It remains unclear how it all was managed by a human. Regarding genetic mechanisms, the main question is not clarified: did a human adapt only with the help of genes, like all other living organisms, or did he use a means inherent only in *H.s.sapiens*? 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.

Keywords: Human adaptation; Cell thermoregulation; Hypobaric hypoxia; Chromosomal Q-heterochromatin; Human body heat conductivity

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Introduction

It is thought that beings undistinguishable from modern man appeared in Africa about 150 000 - 200 000 years ago, 50 000-60 000 years ago they reached Europe, Asia and Australia, and more than 20 000 years ago - North and South America [1]. During this time, man was able to populate the entire earth's land, from Africa to Patagonia, including the Far North and the high-altitude.

Human adaptation to different climatogeographic conditions has two fundamental features: a) only man managed to master the whole land of the Earth, while remaining a single, tropical species (*H. s. sapiens*); b) unlike animals, human settlement of all climatogeographic provinces, including extreme zones (Far North and high-altitude),

occurred in a very short period of time. If animals have adapted to their permanent habitat for hundreds of thousands and millions of years, it took a human from 700-1000 years (Pamir and Tien Shan) to 10 000-25 000 years (Andes and Tibet). The purpose of this note is to discuss some controversial issues regarding the genetic mechanisms of human adaptation.

To date, numerous studies have been carried out to find out the genetic basis of human adaptation to the high-altitude climate. First, we briefly present the results of studies aimed at detecting the gene bases of human adaptation. The history of the study of genetics of human adaptation to some extreme natural conditions, including the high altitudes, originates from the International Biological Program (IBP). However, results of the IBP indicate that attempts of a number of investigators to reveal certain systematic differences from features of the distribution of genetically polymorphic systems (blood group, electrophoretic variants of proteins and enzymes, anthropological traits, etc.) between human populations living permanently under different environmental conditions of the terrestrial globe, including extreme ones, were unsuccessful [2]. Almost the same results have also been obtained during the realization of "the Multinational Andean Genetic and Health Program" in aboriginals of high- and low-altitude regions of South America [3,4].

However, the search for specific genes of adaptation, to high-altitude climate in particular, continues, now using new methods of DNA analysis. Researchers have applied different genomic strategies to samples to uncover these mechanisms. Most studies that aim to understand the genetic basis for adaptation to high altitude rely on statistical association between the gene(s) and phenotype. While this is an important first step towards understanding the complexity of phenotypes, ultimate tests (functional tests) must uncover causal relationships. Here, as an illustration, we present the results of only a few researches, while limiting ourselves to references to review articles.

So, for example, Hancock et al., [5], scanned the human genome using data for about 650,000 variants in 61 worldwide populations to look for correlations between allele frequencies and 9 climate variables and found evidence for adaptations to climate at the genome-wide level. In addition, authors detected compelling signals for individual SNPs involved in pigmentation and immune response, as well as for pathways related to UV radiation, infection and immunity, and cancer. A particularly appealing aspect of this approach is that they identify a set of candidate advantageous SNPs associated with specific biological hypotheses, which will be useful for follow-up testing.

Jeong et al., [6], combined approaches for detecting polygenic adaptations and for mapping the genetic bases of physiological and fertility phenotypes in approximately 1000 indigenous ethnically Tibetan women from Nepal, adapted to high altitude. The results of genome-wide association analyses and tests for polygenic adaptations showed evidence of positive selection for alleles associated with more pregnancies and live births and evidence of negative selection for those associated with higher offspring mortality. Lower hemoglobin level did not show clear evidence for polygenic adaptation, despite its strong association with an EPAS 1 haplotype carrying selective sweep signals.

Genomic analysis of high-altitude populations residing in the Andes and Tibet has revealed several candidate loci for involvement in high-altitude adaptation, a subset of which have also been shown to be associated with hemoglobin levels, including EPAS1, EGLN1, and PPARA, which play a role in the HIF-1 pathway [7-12]. On the other hand, Scheinfeldt et al., [13], highlight several candidate genes for involvement in high-altitude adaptation in Ethiopia, including CBARA1, VAV3, ARNT2 and THRB. Although most of these genes have

not been identified in previous studies of high-altitude Tibetan or Andean population samples, two of these genes (THRB and ARNT2) play a role in the HIF-1 pathway, a pathway implicated in previous work reported in Tibetan and Andean studies. Authors suggest that the genes and genetic variants contributing to high-altitude adaptation in Ethiopia are largely distinct from other high-altitude regions and arose independently through convergent evolution due to the strong selective force of hypoxia. To date, dozens of genes have been found, which, as the authors believe, may be related to the genetic adaptation of a human to hypobaric hypoxia. However, as can be seen from the above examples, much remains unclear.

So, do the results of these molecular biological (gene) studies meet the requirements of the modern theory of evolution? Our answer is probably no, then yes. Without going deep into the theory, let us limit ourselves to the fact that, for all their importance, none of these studies provides evidence of their selective value. In addition, there is no data: a) what are the phenotypic expressions of these adaptive genes; b) when, where and who have these adaptive genes; c) what are the frequencies of these adaptive genes in individuals from different age groups in the population where such studies have been conducted; d) whether these genes are available in all high-altitude human populations, if not why; e) whether such adaptive genes are found in animals permanently living at high-altitudes; f) whether they are related to the development of pathologies that occur in high-altitude conditions, etc.

There must be literally hundreds of definitions of adaptation in the literature. Ultimately, most agree that a trait is adaptive if it enhances the fitness of an organism, that is, if the trait contributes to the survival and/or better reproductive success of an individual or social group. In many of his writings, E. Mayr 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. He rejected the idea of a gene-centered view of evolution, insisting ‘a gene is never visible to natural selection and in the genotype’. In particular, he wrote: ‘Evolution deals with phenotypes of individuals, with populations, with species; it is not "a change in gene frequencies." ‘It is the phenotype that is exposed to natural selection, and not individual genes directly’…’Not its genes or genotype, because these are not visible to selection, but rather its phenotype. The word phenotype refers to the totality of morphological, physiological, biochemical, and behavioral characteristics of an individual by which it may differ from other individuals’ [14].

If not genes, then what? Our experience in the search for the genetic basis of human adaptation to some extreme natural conditions in Eurasia (the Extreme North of Eastern Siberia, the Pamir and Tien-Shan high-altitudes) shows that, apparently, chromosomal Q-heterochromatin regions (Q-HRs) is the sought genetic material. Details about the morphology, inheritance, variability and molecular structure of chromosomal Q-HRs have been given in special reviews [15-20]. The fact that it is possible that chromosomal Q-HRs meets the requirements of modern theory, say the following facts:

a) consistent interpopulation differences in the quantitative content of chromosomal Q-HRs in their genome were established [1,16,21-33].
b) these differences proved to be related to features of the ecological environment of the place of permanent residence, and not to their racial and ethnic composition [16,20,34,35].
c) the amount of chromosomal Q-HRs in the population genome tend to decrease from southern geographical latitudes to northern ones, and from low-altitude to high-altitude ones [1,16,24-30].
d) the Q-HR on the Y chromosome is the largest in the human karyotype, and its average size is at average twice greater than all the Q-HRs on

autosomes taken together. The size of Q-HR on the Y chromosome influences the number of Q-HRs on autosomes, for example in males with large blocks of Q-heterochromatin on the Y chromosome, the number of Q-HRs on their autosomes is lower and *vice versa* population [36,37].

e) the overall number of Q-HRs on autosomes in females is higher than in males. The increasing number of chromosomal Q-HRs on autosomes in females at the population level can be explained by the existence of some evolutionary established mechanism that "compensates" the difference in the "dose" of Q-heterochromatin material in the female genome due to the lack of chromosomes in their karyotype, which carries largest Q-HR, as Y chromosome [38].

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 [21,39,40].

g) in the first days, weeks, months and years of life, ceteris paribus, among healthy children the infants often die with the greatest number of Q-HR in genome [41].

h) 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 the Jamal peninsula of polar Eastern Siberia) are characterized by extremely low amounts of Q-HRs in their genome [1,28,29].

i) with high-altitude pulmonary edema ill individuals who have in their genome a large number of chromosomal Q-HRs [42].

j) 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 [42-45].

k) 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 [40].

In addition to the above facts, indicating the selective value of chromosomal Q-HRs, there are other data that speak in favor of our hypothesis:

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 [46-48].

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 [48].

c) Q-HRs, in genetic terms, is completely inert material, that is, these specific regions of chromosomes do not contain structural genes, and therefore their quantitative changes have no consequences for the informative part of the genome and can be carried out at an extremely high rate [17].

d) individuals in human populations differ in the number, location, size, and intensity of chromosomal Q-HRs fluorescence in the genome;

e) 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 [1,21-33,49-52].

All these facts have found their rational explanation in the framework of the hypothesis of cell thermoregulation [35,53,54]. We have been suggested a hypothesis of cell thermoregulation (CT), which was formulated based on studies, mainly on the distribution of chromosomal Q-HRs in human populations. We suggest that condensed chromatin (CC), which includes chromosomal Q-HRs of higher eukaryotes is likely to relate to the thermoregulation in a cell. CC, being the most densely packed material, apparently has the greatest heat conductivity in the interphase cell [35,53].

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 that 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. Since the proposed idea is based on cell phenomena, apparently Nature 'found' a very simple and effective solution: it increased its heat conductivity through compression of the internal layer of the nuclear membrane by CC.

In essence the idea proposed is reduced to the evolution of the genome structure and the physiology of the whole organism in higher eukaryotes going in parallel to counteract changes of temperature in the ambient environment for more effective preservation of constancy of temperature of the internal environment. The outcomes of such a parallel evolution were: (1) the appearance of different kinds of CC (C- and Q-heterochromatin, G+ and Q+ bands), at a genome level the effect of which is generally subject to the laws of physics, and (2) formation at an organism level of a complex organ-based (hypothalamus) physiological system of thermoregulation. This is why redundant DNA in the form of chromosomal HRs has no phenotypic expression and bears no specific function because chromosomal HRs in CC participate in thermoregulation at the level of individual cells.

Certainly, cell thermoregulation hypothesis should be checked *in vivo* on the cell level. But we have not had such opportunity till present. 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. Through trial and error, we have identified areas of the body and the thermal load mode, which allows to roughly estimating the level of human body heat conductivity (BHC): high, medium and low. A hypothesis that number of Q-HRs in genome is possibly connected with human body thermal conductivity has been proved. Results obtained show that individuals in population truly differ from each other in BHC and its level depends on the number of chromosomal Q-HRs in human genome (for more details see: Ibraimov et al., [40].

Human adaptation

Human adaptation to cold and high-altitude hypoxia, in general, is presented to us as follows. Man, chimpanzees and gorillas in the process of evolution inherited from a common ancestor, among other things, and chromosomal Q-heterochromatin. However, it was subsequently distributed differently in their genomes, possibly as a result of random population-genetic processes that took place in the early stages of divergence of these species [34,42]. We can hardly hope to learn anything about the nature of these processes in the foreseeable future. However, we know that the ancestors of *H. sapiens* received Q-heterochromatin on seven autosomes and Y chromosomes, and the *P. troglodytes* on five autosomes only, and the *G. gorilla* on eight autosomes and Y chromosomes [46-48].

In the future, each of these species evolved independently. However, it is possible that the unusual success was only accompanied by *H. sapiens* for the following reasons. The ecology of the Middle and Late Miocene was far from smooth, and such climatic changes as cooling, dryness, seasonal and daily temperature

fluctuations gradually became the dominant environmental factors. Thus, our ancestors, perhaps even before leaving Africa, faced the problem of adaptation to new, more severe natural conditions, different from the Savannah climate.

According to our model of adaptive human evolution, it all began with the time when individuals with different amounts of Q-heterochromatin regionsl (as it happens now) began to be born in the populations of modern *H. sapiens* [33]. This was possible because: 1) the number of Q-polymorphic loci in the karyotype was big enough to allow for the appearance in populations of individuals with different numbers of Q-HRs (25 loci); 2) the relative frequencies of Q-HRs at these loci were different, so that the same number of Q-HRs in the genome in different individuals could be provided by a variety of combinations of chromosomal Q-HRs [33,42]. Thus, we are dealing with a complex self-supporting genetic system, which is unique among the classical genetic objects is hard to call. This unique feature of the chromosomal Q-HRs was taken advantage of by our ancestors with the onset of climate change in the Savannah and especially when they tried to go beyond it in search of new habitats.

It's hard to say why the ancestors of *P. troglodytes* and *G. gorilla* are unable to use this path. However, the following assumption can be made; the initial frequencies of chromosomal Q-HRs at all Q-polymorphic loci were high, so that individuals with different Q-HRs numbers in the karyotype were born in the populations of these two higher primates. Therefore, the probability of occurrence of individuals with different, including, and with low heat conductivity of bodies was simply excluded. In other words, chimpanzee and gorilla populations were initially unable to vary the number of chromosomal Q-HRs in the genome as widely as human populations [33,42]. In favor of this assumption is evidenced by the following facts: 1) the range of variability in the number of Q-HRs in the chimpanzee genome - from 5 to 7, whereas in human populations-from 0 to 10; 2) in gorillas and chimpanzees, but not in humans, found a special type of Q-heterochromatin, located at the distal ends of some chromosomes (7, 11, 20 and 23-in gorillas; 20, 21, 22, 23 -in chimpanzees), which eliminates the possibility of birth individuals with different numbers of Q-HRs in populations.

How, then, does a person with a relatively low body heat conductivity (BHC) adapt to the high-altitude climate? Obviously, chromosomal Q-HRs cannot directly affect the ability of Hb to bind molecular oxygen in the alveoli. However, we believe low BHC helps man more effectively deal with hypoxia at high altitude conditions indirectly through heat-, energy- and oxygen saving.

The essence of heat saving is that individuals with low BHC to maintain temperature homeostasis in the body are able to retain some of the metabolic heat in the body, which is usually lost in the environment through conduction, radiation and evaporation. As is known, the increase in temperature reduces the possibility of binding hemoglobin oxygen. The temperature in the tissues is higher than in the lungs. In this case, the warmer the body of the individual, the better will be the oxygen supply to his body due to the more facilitated dissociation of oxyhemoglobin, as a result of which the blood gives the oxygen released from the chemical compound into the tissue liquid (oxygen saving). Speaking of energy saving, we mean that to maintain a constant temperature in the body, individuals even with a comparable body weight will require different amounts of energy. Consequently, individuals with low thermal conductivity of the body will have some advantages in the high-altitudes, known for their limited natural and food resources.

The views expressed here are best illustrated by the example of birds whose adaptability to the extremely low partial pressure of oxygen in the

atmospheric air is not in doubt. Of the two groups of homoiotherms (birds and mammals) the highest core temperature (>41°C) have the birds. In birds, the structure of the respiratory organs differs significantly from mammals, namely, the lungs of birds are small, little stretchable, and they communicate with large thin-walled air bags that do not participate in gas exchange. According to their functional purpose, air bags are divided into two groups: front and rear, through which air, respectively, enters the respiratory system (lungs) and leaves it. In addition, these air bags are located in the abdominal cavity between the internal organs, some grow beyond it - between the muscles and, finally, inside the bones. This complex respiratory system provides a unidirectional flow of air - from the rear bags through the lungs to the front bags, and then out. During the flight, there are no breathing movements of their own, and breathing occurs passively, due to periodic compression of the armpits and chest bags with each lowering of the wing. During the flight, ventilation is enhanced as a result of powerful contractions of the chest muscles. Together, this kind of respiratory system leads to the fact that the residual air in birds is limited mainly by air bags, where the air is heated to body temperature.

Traditionally, the adaptive value of air bags in birds is reduced to the following: they play the role of furs, blowing air through the lungs, because during the flight of the chest wall should be fixed to create a support for the action of the muscles of the wings. It seems to us that the presence of a system of air bags in the deep parts of the body is not limited to the above effects. The adaptive value of air bags in hypobaric hypoxia seems to be much wider, and it is to increase the temperature of the air in the body to create the best physical and chemical conditions for the dissociation of oxygen from hemoglobin. This may indicate that in the genome of birds for 130 million years of their existence on Earth and did not appear directed, favorable mutations, contributing to an increase in affinity Hb to O_2 in hypobaric hypoxia. Instead, the birds chose an indirect way - to facilitate the dissociation associated with Hb oxygen - by increasing the blood temperature in the tissues. In addition to the low BHC, the indigenous people oppose the extreme high-altitude climate with effective forms of behavior. For example, the highlanders unless absolutely necessary (for example, the Sherpas who accompany climbers) rarely rise to great heights, as their daily life of the farmer is at an altitude below 5000 meters above sea level. To overcome long distances or high terrain highlanders use yaks or horses. In addition, the highlanders are measured, closely related to the rhythm of Nature, a way of life, avoid performing heavy physical work and use their energies sparingly, creating a false image of lazy and slow people for travelers.

Therefore, we believe that *H. s. sapiens*, from the physical environmental factors limiting his life, could genetically adapt mainly to the influence of low temperatures as it faced in East Africa. It is difficult to assume that in such a short time of existence at high-altitudes for the effective supply of human cells with oxygen, appeared, and then successfully spread to the genome of highlanders, directed favorable mutations in the genes involved in the long chain of oxygen transport from the alveoli to the tissues. This is indirectly evidenced by the known fact; places of permanent human settlement do not exceed 4200 m above sea level.

Discussion

The essence of our note is reduced to one question: what part of the human genome - genic or non-genic -is involved in the process of its genetic adaptation? Because on the side gene (genes) in adaptation human are worth all or almost all researchers, then in short we shall state here our "anti[genes]" theses:

1) structural genes occupy only a small proportion of DNAs in human chromosomes (about 1.5 - 2.0%). The possible involvement of

non-coding DNAs, including constitutive heterochromatin, remains unclear;
2) in humans, no protein or enzyme has been found that would, in one form or another, be completely absent from animals to talk about its genetic exclusivity;
3) the man was and still is a single tropical biological species;
4) fully formed man originated in Africa around 150 000 - 200 00 years ago, and permanent populations of high-altitude areas even less, about 20 000 years;
5) the ancestors of man for more than a million years in their evolution existed in low-altitude tropical Africa and never, in the past, lived in conditions close to the high-altitudes or the climate of the Far North, and, nevertheless, they were able to master all the climatogeographic provinces of the Earth. Inevitably, the question arises when hypothetical adaptive genes could appear? The problem is complicated by the fact: was there such genes (such as preadaptation) before man began to penetrate the extreme for tropical species ecological areas or else, they appeared every time again, when the human population was trying to adapt to the new conditions. If we recognize the possibility of re-emergence of specific adaptive genes in the human genome, do they relate to the same genes? Leaving open the question of the possibility of the existence of such a highly mutable gene or genes, let us ask another question: how did such favorable mutations spread in the genome of the inhabitants of high-altitude populations? After all, high-altitude populations, even within one mountain province, are often isolated.
7) the existence of some" high ceiling " (about 4,200 m above sea level) for permanent human habitation indirectly indicates the absence of specific adaptive genes in the genome of modern highlanders.
I, a native of one of the most high-altitude villages of the Eastern Pamir, do not quite understand why hypobaric hypoxia, and not, for example, cold, is taken out of all the harmful physical factors of the environment in the high-altitudes? On the human body in the high-altitudes in addition to hypoxia affects piercing cold, sharp seasonal and daily temperature fluctuations, dry air, frequent winds, ultraviolet radiation, high terrain, etc. In addition, life in the high-altitudes, as nowhere else, requires high-calorie food, warm homes and clothing, which is not always available to everyone. All medical and biological studies show that living in the high-altitudes permanently does not contribute to good health, as evidenced by the high infant mortality rate and their lagging in physical development, cold-related diseases (ranging from colds to pneumonia), as well as malnutrition [2].

In highlanders chronic mountain diseases are not the most common forms of pathology and they do not have a significant impact on their demographic indicators. All chronic mountain diseases originate from the common cold. We tend to believe that the main harmful physical factor for human survival in the high-altitudes is still cold, not hypobaric hypoxia. After all, if there is not enough oxygen, a person can stop climbing and go down. But life in the conditions of high-altitude cold with sharp seasonal and daily temperature changes is a constant struggle for existence, especially for the tropical species, which is a man.

Concluding remarks

Unlike many animal species, man is unstable to live in an extreme cold environment. He is basically a tropical homoiotherm. The question is why exactly *H. sapiens* managed to master the entire land, while remaining a single tropical species, still unclear? We believe that this is a highly probable response; in adapting to a climate different from that of East Africa, humans have used a non-genic part of their genome, known for its high mobility and non-conservatism in individual development and evolution. Moreover, we believe that man as a species owes its origin primarily to chromosomal Q-HRs, rather than specific structural genes [33].

Ignoring the results of almost half a century of studies of chromosomal Q-HRs in human populations living in different ecological zones of Eurasia and Africa, individuals from different racial-ethnic and age groups, in norm and pathology, only because these works are made by authors from Third World does not seem fair. This reminds us of the irony in the story of A. Saint-Exupery “the Little Prince” when they didn't believe in the existence of an asteroid from which the little prince arrived just because there was a turban on the head of the Turkish scientist who announced this.

As is known, “The little prince has ideas which were very different from of the grown-ups". In particular, he believed that: “The thing that is important is the thing is not seen." In humans, chromosomal HRs does not manifest itself in a visible way either, namely through body heat conductivity, which we consider to be their physiological phenotype. “And no grown-ups will ever understand that this is a matter of so much importance!” But ..."one never knows." To refute our hypothesis, it will be enough to check at least one of the above facts, indicating the possible selective value of chromosomal Q-HRs in the human genome.

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