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Adaptive Phenotypes: Their Material Bases, Criteria and Proofs: A Review

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Abstract

The term adaptation is used to refer to a feature of structure, function, or behavior that is beneficial and enables survival in a specific environment. Most often, they talk about genetic adaptation. There is no generally accepted definition of adaptive phenotype (AP). Since natural selection "sees" only AP, and not a gene or genotype, there is a need to clarify existing concepts. It seems that the time has come to determine objective criteria that would allow to decide which morphological, physiological or behavioral trait to take for AP. Criteria are proposed on the basis of which it would be possible to decide whether this trait meets the requirements for AP. Genomics studies for high-altitude populations have identified 169 genes that the authors believe are under positive natural selection. However, they did not help to find a high-altitude AP that would be "visible" to natural selection. The issues concerning the material bases, criteria and methods of proving AP on the example of human adaptation to a high-altitude climate are discussed.

Keywords: Adaptive Phenotype, Human Adaptation, High-Altitude Genomics, High Altitude Adaptation, Chromosomal Heterochromatin Regions

Introduction

Biological adaptation usually refers to the adaptation of an organism to external conditions in the process of evolution with the help of morphological, physiological, biochemical and behavioral reactions. Successful adaptation can ensure the survival of an organism in new habitat conditions, its resistance to the effects of abiotic and biological factors. The concept of adaptive phenotypes is discussed below using the example of human high-altitude adaptation.

Here we deliberately do not consider the concept of adaptive genotype, referring to the opinion of Ernst Mayr [27], who repeatedly 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”.

There is no generally accepted definition of adaptive phenotype (AP). The term adaptation is used to refer to a feature of structure, function, or behavior that is beneficial and enables survival in a specific environment. Most often, they talk about genetic adaptation. The term genetic adaptation is applied to a heritable feature that was produced by natural selection altering allele frequencies over time [28]. Since there is still no agreement on the concept of adaptive phenotype, it seems that the time has come to determine more or less objective criteria that would allow us to decide which morphological, physiological or behavioral trait to take for AP.

Criteria

We believe that AP, if it really has an adaptive and hereditary character, then it must meet some reasonable criteria. Below, based on the literature data and human high-altitude adaptation's own research, a number of criteria are proposed on the basis of which it was possible to decide (determine) whether the studied trait meets the requirements for AP:

a) AP must have a morphological, physiological, biochemical or behavioral manifestation that can be quantified or objectively evaluated;

b) AP should be characterized by hereditary variability in the population;

c) Individuals in the population should differ in their adaptability to new conditions of existence depending on the level of AP

expression;
d) AP at the population level should have different frequencies in different age groups;
e) In the population, individuals should differ in morbidity and mortality depending on whether they have AP. For example, in high-altitude conditions, children who died in the first days, months or years of life should be distinguished by the absence or low expression of AP;
f) According to the degree of AP expression in an individual, it is possible to predict whether he/she, born and raised in the low mountains, for example, will be able to adapt to a high-altitude climate without compromising his/her health.
At the same time, a prerequisite for recognizing a morphological, physiological, biochemical or behavioral trait as AP is that it meets all of the above criteria without exception.

Facts and Commentaries

Researches on human adaptation to the high-altitude climate have a long history. A number of major, including international scientific programs have been implemented [2-6,26,29-35]. As expected, these studies, first, aimed at searching for genes and adaptive genotypes in the genome of permanent residents of the highlands. Certain successes have been achieved in this regard. A detailed analysis of the results of these studies is not part of our task.

Here we will confine ourselves to discussing the main results and conclusions obtained by analyzing the DNA genome of human populations living in the highlands of Tibet, the Andes and the Ethiopian Highlands. To this end, we decided to rely mainly on one review, which is the most recent and complete summary of this problem [31]. We also took into account the results of genomic scanning obtained on both SNAP and WGS [1,7,29,33].

Collectively, genomics studies high-altitude populations like Tibetans, Andeans, Ethiopians, and Sherpas have identified 169 genes under positive natural selection. Interestingly, the genes identified for these populations to date majorly belong to oxygen-sensing pathways under the regulation of hypoxia-inducible factor (HIF). In particular, comparing of high-altitude Tibetan and Sherpa with matched low landers have identified a positive selection of *EPAS1*, which encodes the HIF-2α subunit of HIF complex, and *EGLN1*, which encodes PHD2, members of the HIF-oxygen-sensing pathway. Population genetic studies have identified that *EPAS1* and *EGLN1* variants is unique to Tibetans and Sherpas as compared to Andeans. Also, examining of positive selection of Himalayan populations, including Tibetan, Sherpa, and Nepalese genomes for hypoxia adaptation, have reported candidate gene loci like *PPARA, HBB, MTHFR, SLC52A3, ANKH, ZNF532, COL4A4, MKL1,* and *GRB2* genes to name a few.

Genomic investigations for Andean highlanders have identified positive selection for multiple genes, along with EGLN including *EDNRA, PRKAA1,* and *NOS2A, BRINP3, NOS2,* and *TBX5*. These studies suggest that positive selection in the Andes has focused on the nitric oxide pathway and cardiovascular system, unlike the HIF pathway of Himalayan highlanders. Studies comparing Andean highlanders with and without chronic mountain sickness further identified additional genes that seem to protect against chronic disease at high altitude, including *ANP32D, SENP1, PRDM1, AEBP2, CAST,* and *MCTP2*.

Analysis of high-altitude Ethiopia has identified candidate genes *CBARA1, VAV3, ARNT2,* and *THRB*, distinct from those identified in Andeans and Tibetans. Interestingly, two genes (THRB and ARNT2) are part of the HIF-mediated oxygen-sensing pathway indicating independent convergent evolution of hypoxia adaptation responses [29].

Thus, genomics studies for high-altitude populations like Tibetans, Andeans, Ethiopians, and Sherpas have identified 169 genes that are believed to be under positive natural selection. Of course, this figure is impressive. Nevertheless, no this helped to get an answer to the most important question: has the desired high-altitude AP been identified, which would be "visible" to natural selection? Unfortunately, from the analyzed review and the study of the publications cited there, we could not find indications of the detection of any AP. In other words, none of the 169 genes either detected, individually or collectively, met the criteria set out above for AP.

We do not know why none of the genes or genotypes found in the genome of high-altitude populations like Tibetans, Andeans, Ethiopians, and Sherpas had an adaptive morphological, physiological, biochemical, behavioral or other phenotype. Perhaps this circumstance is explained the fact that:
a) The identified genes were not "visible" to natural selection because they are part of oxygen-sensing pathways in both normal and new environmental conditions. Their high frequencies in the genome of native high-altitude populations are simply associated with the increased load imposed on the body by hypobaric hypoxia during acclimatization to a high-altitude climate;
b) The emergence of complex morphological, physiological and behavioral AP cannot be meaningfully explained "at the level of individual genes". It is hardly possible to explain the complex processes of adaptive development by the work of individual genes, since the relationship between the genome and the environmental conditions that give the phenotype output is very complex;
c) Apparently, mutation alone cannot create AP (although used);
d) Genes are only rearranged to be switches of changes in ontogenesis that occur in response to changes in the environment. At the same time, important evolutionary innovations often have to rely on pre-existing genes;
e) The high frequencies in the population, if not all, then most of the 169 genes, may be the result of acclimatization (reversible process), rather than genetic adaptation (non-reversible evolutionary process) to a high-altitude climate.
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 Siberia, the Pamir and Tien-Shan high-altitudes) and Africa (Ethiopian Highlands) shows

that, apparently, chromosomal heterochromatin regions (HRs) are the sought genetic material. Details about the morphology, inheritance, variability and molecular structure of chromosomal Q-HRs have been given in special reviews [10,24].

Our own data of human adaptation to the high-altitudes of the Pamirs, Tien Shan, and Ethiopian Highlands, as well as the Far North of Siberia support the hypothesis of a possible selective value of chromosomal Q heterochromatin regions (Q-HRs):

a) Consistent interpopulation differences in the quantitative content of chromosomal Q-HRs in the genome have been established. These differences have proven to be related to features of the ecological environment of permanent residence, and not to racial and ethnic composition [9,10,24];
b) The quantity of chromosomal Q-HRs in a population's genome tends to decrease from low to high geographical latitudes and from low- to high-altitudes [8-11,24];
c) Different age groups have different quantities of chromosomal Q-HRs: the greatest number of Q-HRs is found in neonates, while the smallest is found in the elderly [15,18];
d) In the first few years of life, ceteris paribus, infants that die among healthy children often have the greatest number of Q-HRs in their genome [16];
e) Individuals capable of successfully adapting to extreme high altitude climates (e.g. mountaineers) and the Far North (e.g. oil workers of Eastern Siberia) are characterized by extremely low quantities of Q-HRs in their genome [11-13];
f) High altitude pulmonary edema can develop in an individual who has a large number of Q-HRs in his genome [22];
g) All forms of purely human pathology (obesity, alcoholism, drug addicts and atherosclerosis) are associated with a wide quantitative variability of chromosomal Q-HRs [19-24];
h) Finally, unlike hypothetical adaptive genotypes, the quantity of chromosomal Q-HRs in the human genome has a clear physiological phenotype expressed in the form of variable body heat conductivity [18,23,24].

That the amount of chromosomal HRs in the human genome may have selective value, we explain through the hypothesis of cell thermoregulation (CT) [14]. We suggest that condensed chromatin (CC) is likely to relate to the thermoregulation of cells. CC, being the most densely packed material, appears to have the greatest heat conductivity in the interphase cell with all the ensuing consequences for the whole body [14,21,24].

Here, without going into details, we will note only some features of CT. 20 years ago, based on a study of the distribution of one of the forms of ncDNAs, chromosomal HRs in norm and pathology, the hypothesis of CT was put forward [14,25]. The essence of CT hypothesis is elimination of the temperature difference between the nucleus and cytoplasm when the nucleus temperature becomes higher than 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 blood and lymph. Thus, the nucleus can transfer surplus heat only in the cytoplasm. With this, the nucleus has two options: either by increasing its volume or increasing the heat conductivity of the nuclear envelope. As the first option is limited, and the second one is hampered because of the vulnerability of the cell membranes to temperature changes, apparently the higher eukaryotes took advantage of the opportunity of a dense layer of peripheral CC as heat conductor for a more efficient elimination of the temperature difference between the nucleus and cytoplasm. The CC localized between a nucleus and cytoplasm is made of chromosomal HRs, which are one of the forms of higher organization of ncDNAs. The higher eukaryotes use a dense layer of peripheral CC as heat conductor for a more efficient elimination of the temperature difference between the nucleus and cytoplasm. Thus, CT is a product of the evolution of a part of ncDNAs that formed the highest form of organization of highly repetitive sequences of nitrogenous bases in the form of chromosomal HRs [25].

In essence, the idea of CT refers to the process of equalizing the temperature difference between the cytoplasm and the nucleus and then the entire cellular part of the body. Ultimately, we are talking about the body heat conductivity (BHC). The simplest idea of the BHC can be represented on the basis of the known laws of physics. It follows from the second law of thermodynamics that heat transfers from a hot body to a cold one until the temperature difference disappears. It is also obvious from general theoretical considerations that the same substance, depending on its density, should have different heat conductivity. The higher the density, the higher the heat conductivity, that is, the higher the rate of transfer of heat. CC is the densest area in the interphase cell; therefore, all other things being equal, it should have the highest heat conductivity. It turned out that there is a link between the amount of chromosomal HRs and level of human body heat conductivity BHC: the larger the amount of HRs, the higher of human BHC [18,24,25].

The data on the influence of human BHC on its life activity in norm and pathology was established on the population level: 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 of southern latitude differ on the average by higher BHC than population of high mountains and northern latitude [23,24].

In conclusion, we would like to note that perhaps the material base of a high-altitude and the Far North AP could not be genes or genotypes, but chromosomal HRs in the genome of a population, which at the organism level manifests itself in the form of wide variability of human BHC. From our point of view, human BHC level is a physiological phenotype of the amount of chromosomal HRs, which are characterized by a wide inter- and intra-population variability with all the ensuing consequences both in normal and pathological conditions.

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Conflicts of Interest

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Statement of Consent/Ethical approval

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