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B-chromosomes and cell thermoregulation**AI Ibraimov**

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Abstract

B-chromosomes have been studied for over a hundred years. Thousands of works are devoted to the study of morphology, distribution, inheritance and molecular structure of B-chromosomes. However, the biological role of these additional to the main set of chromosomes is still unknown. The main directions of researches aimed at elucidating the biology of B-chromosomes are related to the study of their molecular structure using the latest methods of molecular biology and genomics. Without disputing the importance of such researches, we suggest paying attention to the physiology of cells as well. We believe that B-chromosomes may be involved in maintaining the organism's temperature homeostasis under different environmental conditions by actively incorporating into the process of cell thermoregulation.

Keywords: B-chromosomes; Cell Thermoregulation; Heterochromatin; Condensed Chromatin; Adaptation B-chromosomes and cell thermoregulation

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Introduction

B-chromosomes (Bs) are chromosomes that are additional to the normal set of chromosomes (called A- chromosomes or As). They have been detected in numerous fungi, plants and animal species. Hundreds to thousands of reports have described the distribution of B-chromosomes among diverse eukaryote groups. The evolutionary origin of Bs is obscure, but presumably they must have been derived from heterochromatic regions of As in the remote past. In general 'we may regard supernumeraries as a very special category of genetic polymorphism which, because of manifold types of accumulation mechanisms,

does not obey the ordinary Mendelian laws of inheritance' [1]. The morphology, distribution in the population, peculiarities of inheritance and molecular structure of Bs were studied in sufficient detail. However, the role of Bs on biology of the organism remains largely unknown [2-7].

Hypotheses about the possible biological role of B-chromosomes

There are many hypotheses about the possible biological role of Bs. Their detailed analysis is not our task. Here we will limit ourselves to just a few of them, which point to areas of research in the search for a possible biological role of B-

chromosomes. So, many authors, paying attention to the fact that B chromosomes can persist without providing any measurable benefit to the body, offer to investigate them as genome parasites. Although the parasitic model for B chromosomes appears plausible and has been observed worldwide, the mechanisms that regulate Bs maintenance and segregation during the cell cycle remain enigmatic. With rare exceptions, attempts to find an adaptive value for Bs at the level of the individual ran into virtual dead-end and attention was redirected toward two areas. One was the co-evolution of the host-parasite relationship itself and the other was a description of sequence organization on Bs. Valente et al (2017) [6] note, that the most recent knowledge obtained from omics analyses, which is associated with a systemic view, has demonstrated that B chromosomes can influence cell biology in a complex way, possibly favoring their own maintenance and perpetuation. The accumulated data suggests that Bs can act by manipulating the entire cell system to benefit its own survival. However, the mechanism by which this is accomplished remains completely unknown. Rubtsov and Borisov [7], do not exclude that natural selection favors Bs with valuable genes. The discovery of protein coding genes in Bs of the fungus *N. haematococca* [8] was followed by a lot of reports describing the presence of copies of protein-coding genes, rRNA genes, pseudogenes, and transcriptionally active sequences on Bs. The constant increase in the number of such studies shows that in solving the mystery of Bs high hopes are placed on molecular biology. However, the major problem confronting any study of the biology of Bs is that they are not present in all individuals of a species and not always present in all tissues.

B-chromosomes and cell thermoregulation

The basis for the proposed hypothesis was two circumstances: 1) accumulated experience and data on the morphology, distribution, variability, molecular structure and some effects of human chromosomal heterochromatin regions (HRs), which can be

used to study the biology of Bs; 2) there are many fundamental similarities between Bs and chromosomal HRs. It is established that there are two types of constitutive heterochromatin in the eukaryotic genome: C- and Q-heterochromatin. Heterochromatin is universally distributed in the chromosomes of all plants, animals and man, accounting for 10% to 60% of their genome. Here we are mainly interested in the second type of constitutive heterochromatin, namely chromosomal Q-heterochromatin regions (Q-HRs). Chromosomal Q-HRs were for the first time found in human chromosomes [9]. To date, the following facts about morphology and distribution of human chromosomal Q-HRs have been established:

- 1) 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 can be detected [10];
- 2) despite the fact that in the human karyotype there are 13 loci in which Q-HRs can be detected, i.e., there could theoretically exist individuals with 25 Q-variants in their genome, but such cases have not as yet been reported. In individuals of a population the number of Q-HRs usually ranges from 0 to 10 [11-14]. Both complete absence and the maximum number of Q-HRs in the genome have no visible phenotypic manifestations [15];
- 3) distribution of the number of Q-HRs in individuals of a population is almost normal [14,16-20];
- 4) the amount of Q-HRs in the genome of human population is best determined by the value of their mean number per individual in a population [11,12,14,16-19,21-24];
- 5) 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 [25];
- 6) chromosomal Q-HRs does not change during ontogenesis and are inherited in a regular manner as discrete mendelian traits.

For the problems discussed here the greatest interest represents evidences of the possible selective value of chromosomal Q-HRs:

- a) consistent interpopulation differences in the quantitative content of chromosomal Q-HRs in their genome were established [12,14,16-19,21-23,26-31];
- 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 [13,25,32,33];
- c) 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-altitude ones [16-19,21-23];
- 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 amount 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 [34,35];
- e) the overall amount of Q-HRs on autosomes in females is higher than in males. The increasing number of Q-HRs on autosomes in females at the population level is 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 [35];
- 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 [26,36,20];
- 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 [37];
- 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 [14,16,17];

- i) high-altitude pulmonary edema can develop in an individual who has a large number of chromosomal HRs in his genome;
- j) all forms of purely human pathology (alcoholism, drug addiction, obesity) were associated with a wide quantitative variability of chromosomal Q-HRs. So, 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 [38-41];
- k) finally, unlike hypothetical adaptive genes, the amount of chromosomal Q-HRs in the human genome has a clear physiological phenotype in the form of different body heat conductivity [24];

That the amount of chromosomal HRs in the human genome may have selective value, we explain within the framework of the hypothesis of cell thermoregulation (CT) [42,43]. We have been suggested a hypothesis of 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 consists of chromosomal 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 [42,43].

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. The most interesting for our hypothesis are the results of studies on the variability of chromosomal Q-HRs obtained in human populations. Table 1 shows some similarities between Bs and human chromosomal Q-HRs.

Table 1: Similarities between B-chromosomes and human chromosomal Q-heterochromatin region.

Main features	B-chromosomes	Chromosomal Q-HRs
Mainly or entirely heterochromatic.	Yes	Yes
DNA sequences are repetitive and non-coding.	Yes	Yes
Show genetic polymorphisms.	Yes	Yes
Usually genetically inert.	Yes	Yes
They are not present in all individuals of a species. A population would consist of individuals with 0, 1, 2, 3 (etc.).	Yes	Yes
They are dispensable for normal growth.	Yes	Yes

But this Table cannot fully reflect the similarities between Bs and human chromosomal Q-HRs. The fact is that for reasons independent of researchers, many data obtained at the level of human populations cannot be collected on fungi, plants and animals in which Bs are found. There are some observations that can be interpreted in favor of our hypothesis, although they are obtained under other hypotheses and programs. For example, Shaw and Hewitt [44], demonstrated that the British grasshopper *Myrmeleotettix maculatus* has two structural types of B-chromosomes; metacentrics and submetacentric. The Bs, which have a satellite DNA, occur in warm, dry environments, and are scarce or absent in humid, cooler localities. Vujos'evic' and Blagojevic' [45], observed that the frequency of Bs increased with altitude and was positively correlated with extreme climatic conditions. Zima and Machola'n (1995) [46] did not detect correlations with altitude, but found a slightly increasing trend in B-

chromosome; frequency from central to eastern and southeastern Europe. Clinal increase in the number of Bs (from 1 to 14) in West-East direction was found in Siberian roe deer [47]. Shellhammer [48], claimed for a general increase in genetic variability towards the periphery of species distribution as the most reasonable explanation for Bs frequency variation in *Reithrodontomys megalotis*. It has just been discovered in rye that the presence of Bs determines the over expression of the activity of the genes that defend plants against thermal shocks, which can be a mechanism of adaptation to heat [49]. Thus, the main problem in clarifying the biological role of Bs, in our opinion, is related to the establishment of their phenotype, without knowledge of which it is difficult to determine their possible adaptive value. Data on molecular structure, for all their importance, did not contribute to the clarification of the Bs phenotype, without which it is difficult to determine their biology for the organism. 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' [50]. 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-HRs is the sought genetic material. All these facts have found their rational explanation in the framework of the hypothesis of cell thermoregulation [51]. We suggest that CC, which includes chromosomal 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 [42,43].

Certainly, CT 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 developed a method, which allows estimating the level of human body heat conductivity (BHC). 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 [35]. We now view the

human BHC level as a phenotypic manifestation of the amount of chromosomal Q-HRs in the genome, which have selective value, with all the ensuing consequences for the body.

Since there is no direct evidence to support the hypothesis that Bs are involved in maintaining the body's temperature homeostasis through cellular thermoregulation, what conceivable experiment could be proposed to ensure that they are not inferior to the data obtained in humans? It seems to us that there is nothing unexpected in the assumption that Bs can participate in cell thermoregulation. This is to be expected for the simple reason that the material basis of all Bs is heterochromatin. For this reason, all Bs in the interphase nucleus will be associated with condensed chromatin, and they will inevitably participate in the processes in which chromosomal HRs participate in the cell.

Therefore, future experiments should be based on the assumption that Bs persist in a species because of their possible selective value. Such researches should be aimed at finding:

- a) existence of consistent interpopulation differences in the quantitative content of Bs;
- b) seek evidence that the amount of Bs in the population genome trend to decrease from low geographical latitudes to high ones, and from low-altitude to high-altitude ones;
- c) these differences should indicate that they are related to features of the ecological environment of the place of permanent residence;
- d) find out if there are differences in different age groups in the population by the number of Bs in the genome;
- e) are there differences in mortality rates by age according to number of Bs in genome at the population level?
- f) and finally, it would be ideal with the help of the existing methods for nanothermometry of cells [52-55] to carry out *in vivo* measurements of the rate of thermal energy transition from the nucleus to the cytoplasm depending on the number of Bs in the genome of the individual.

The answer can be considered satisfactory if it turns out that there is a positive correlation between the number of Bs in the genome and the level of thermal conductivity of the body of the individual. In other words, if individuals with low BHC are better able to survive cold and/or food shortages in a population and individuals with high BHC are resistant to heat or drought, then the primary cause of persistence in a species of B-chromosomes is their selective value. The problem is the discovery among plants and animals that have Bs in the genome of model species on which it would be possible to conduct the necessary experiments and observations to get an answer to the desired question, what do B-chromosomes do in the body?.

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