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Review Article

Alimentary Obesity: Genes or Heterochromatin?

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Abstract:

Obesity is excessive fatty deposits in the subcutaneous tissue, organs and tissues. It is believed that the development of obesity contributes to: inactive lifestyle, genetic disorders, nutritional errors, endocrine pathologies, stress, etc. Obesity of different types have a similar general symptomatology; differences are observed in the presence or absence of endocrine or nervous system damage. In alimentary obesity, body weight increases gradually and there are no symptoms of endocrine gland involvement. The possible role of hereditary factors in the development of nutritional obesity is discussed here. This is usually understood as genes. We will consider the possible role of the non-genic part of the genome in the development of alimentary obesity.

Key words: alimentary obesity; chromosomal Q-heterochromatin; cell thermoregulation; human body conductivity

Introduction

Obesity is excessive fatty deposits in the subcutaneous tissue, organs and tissues. In adults, obesity corresponds to a body mass index greater than or equal to 30. A number of factors contribute to the development of obesity: inactive lifestyle; genetically determined disorders of enzymatic activity (increased activity of lipogenesis enzymes and decreased activity of enzymes that break down fat (lipolysis); brain injuries; errors in the nature and mode of nutrition (excessive consumption of carbohydrates, fats, salt, sweet and alcoholic beverages, eating at night, etc.); some endocrine pathologies; psychogenic overeating; physiological conditions (lactation, pregnancy, menopause); stress, lack of sleep, taking psychotropic and hormonal drugs (steroids, insulin, birth control pills), etc.

Obesity of different types has a similar general symptomatology; the differences are observed in the pattern of fat distribution and the presence or absence of signs of endocrine or nervous system damage. In alimentary obesity, body weight increases gradually, fat deposits are uniform, sometimes predominate in the thighs and abdomen. There are no symptoms of endocrine gland involvement.

Despite the fact that substantial advances have been made towards identifying the components of the systems that regulates body weight, we are still far from the full understanding of the pathogenesis of alimentary obesity. This is evidenced by: 1) during the last decades obesity has become on extremely wide spread occurrence with serious medico-social aftereffects. Besides the detriment to health, such as hypertension and heart disease, obese people are often stigmatized socially; 2) that the existing methods of treatment and other forms of control of obesity are insufficiently effective is indicated by the following fact: more than 90% of individuals who lose weight by dieting eventually return to their original weight [1].

The bulk of the ongoing research in this field focuses on the molecular mechanisms of appetite and satiety regulation, energy metabolism, nutrient partitioning, and adipose cell differentiation and enlargement. It is supposed that this is likely to provide geneticists with a whole new generation of candidate genes to explore for DNA sequence variation and relationships with body fat content and proneness to become obese with age.

The possible role of heredity in the development of alimentary obesity, i.e., in the absence of endocrine damage, is discussed here. The role of hereditary factors is usually understood to be genes. Indeed, progress has been made in this regard. Studies have identified variants in several genes that may contribute to weight gain and body fat distribution, although only in a few cases are genes the primary cause of obesity [2-8].

However, there are a number of circumstances that are directly or indirectly indicative of the scantiness of molecular approaches of studies, including the search for a hypothetical gene (or genes) involved in the development of obesity in man. Thus, for instance:

1) the results of numerous epidemiological studies carried out in many countries and regions have unequivocally shown that the frequency of obesity in females is two times higher than in males;

2) the global medico social problem of obesity only emerged in the last decades and we consider the functional derangements in the neuroendocrine and central nervous system in preserving energetic homeostasis in the contemporary man very doubtful just because of an

improved diet and life conditions despite the fact that corresponding homeostatic systems act in nature have been acting for a long time. Moreover, our bodies are better adapted to combat weight loss than to combat weight gain, since for thousands of years our species evolved in circumstances where nutrients were in short supply and therefore, the increasing rates of obesity cannot be explained exclusively by changes in the gene pool;

3) The role of genes in evolution, heredity and development is now being seriously reconsidered. In connection of the aforementioned facts, we suppose that possibly exist other hereditary factors predisposing to obesity in man.

Without contesting the importance of these studies, we have chosen a somewhat different approach to the search for hereditary factors predisposing to the development of alimentary obesity. It is based on studying the phenomenon of wide quantitative variability of chromosomal Q-heterochromatin regions (Q-HRs) in the human genome in certain purely human pathologies [11,12]. The point is that quantitative chromosomal Q-HRs variability only exists in man, though this type of constitutive heterochromatin is present in the genome of two other higher primates: *Pan troglodytes* and *Gorilla gorilla* [9,10].

Facts.

Almost a decade ago, we were able to show for the first time that variability of the amount of chromosomal Q-heterochromatin regions (Q-HRs) is relevant to the development of so-called purely human forms of pathology, including alimentary obesity [10,11]. In particular, individuals with alimentary obesity in two ethnic groups living in Bishkek, Kyrgyzstan were studied. It was shown that obese individuals differ from controls in the extremely low number of Q-HRs in their genome.

Our sample included women of Kyrgyz and Russian nationality of reproductive age, whose weight exceeded 20% or more of the norm, and physicians diagnosed them as an alimentary form of obesity. Phenotypically healthy women of the same ethnic groups of reproductive age with normal weight were taken as controls. Inclusion of only female individuals in our sample was due to two reasons: 1) women lack the Y chromosome, which differs with the content of the largest block of Q-HRs in the human karyotype; 2) women, unlike men, including in our country, try to maintain a normal weight. Data on the distribution and mean number of chromosomal Q-HRs per individual in the samples studied are presented in Table.

Number of Q-HRs	Obese females		Controls	
	Kyrgyz (n = 56)	Russians (n = 44)	rgyz = 100)	Russians (n = 100
	1	2	3	4
0	11 (19.6)	5 (11.4)	2 (2.0)	4 (4.0)
1	24 (42.9)	18 (40.9)	11 (11.0)	7 (7.0)
2	19 (33.9)	19 (43.2)	32 (32.0)	24 (24.0)
3	2 (3.6)	2 (4.5)	19 (19.0)	33 (33.0)
4			22 (22.0)	31 (31.0)
5			11 (11.0)	1 (1.0)
6			2 (2.0)	
7			1 (1.0)	
Total number of Q-HRs	68	62	294	283
Mean number of Q-HRs	**1.21 ± 0.11**	**1.41 ± 0.11**	**2.94 ± 0.14**	**2.83 ± 0.11**
Statistics	$t_{1,2}$ = 1.29 $t_{1,3}$ = 9.72 $t_{1,4}$ = 10.41 $t_{2,3}$ = 8.59 $t_{2,4}$ =9.13 $t_{3,4}$ = 0.62			
	df = 99 df = 156 df = 144 df = 140 df = 123 df = 189			
	P > 0.20 P < 0. 000 P < 0.000 P < 0.000 P < 0.000 P > 0.50			

Table : Distribution and mean number of chromosomal Q-HRs per individual in groups of obese females and in control samples.

As can be seen from this Table, females with obesity, regardless of their ethnic origin, are characterized by a consistently low value of the mean number and by narrow range of variability in the distribution of Q-HRs numbers in the samples as compared with controls.

Genes or heterochromatin?

Little progress has been made with respect to the genetic basis of human obesity. Let us mention at once that a number of mendelian disorders are known to exist in humans, but no specific genes have yet been identified for them [13,14]. Although several single gene defects are known that produce obesity in animals and all of these have been cloned for understanding obesity [15-19]. Nevertheless, the question still remains open: why then are some individuals obese and others not in the absence of neuroendocrine disorders? We searched for the answer by investigating the wide hereditary variability (polymorphism) of human chromosomal Q-heterochromatin regions (Q-HRs) in norm and pathology [10,11,20].

A remarkable feature of human chromosomal Q-HRs is their wide quantitative variability characterized by the fact that individuals in a population differ in the number, location, size and intensity of fluorescence of these specific fluorescence areas. The existence of population Q-HRs variability in twelve polymorphic loci of seven autosomes and on the distal portion of the long arm of chromosome Y is well-established fact [20,30-39]. By studying chromosomal C- and Q-HRs variability in the human populations permanently living in various climatic-and-geographic conditions of Eurasia and Africa, in norm and pathology we have obtained the data indicating possible participation of chromosomal Q-HRs as part of the condensed chromatin (CC) in cell thermoregulation (CT). 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 [20,40,42].

To better visualize this viewpoint, it is necessary to recall what chromosomal HRs, condensed chromatin and cell thermoregulation are. Briefly, chromosomal HRs are the highest form of organization of non-coding DNAs, consisting of short repetitive sequences of nucleotides, which constitute the bulk of DNA in the genome of higher eukaryotes. In humans, non-coding DNAs make up about 98% of their genome and 15%-20% of them form chromosomal C- and Q-HRs. In the interphase cell, chromosomal HRs form a layer of CC around the nucleus, which is

characterized by the highest density [20,40]. The essence of hypothesis of CT is elimination of the temperature difference between the nucleus and cytoplasm when the nucleus temperature becomes higher than in the cytoplasm. 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. The phenotypic manifestation of CT is the level of body heat conductivity (BHC) of the individuals in the population with all the ensuing consequences for the organism [20,40,42,43].

We believe that the pathogenesis of alimentary obesity (AO) is somehow related to the peculiarities of CT. Thus, in patients with AO and therefore with a low BHC (even assuming that they use the same number of calories as people with normal weight), we believe that a part of the calories accumulates in the body in the form of adipose deposits due to inadequate heat dissipation. The point is that excess heat energy is not effectively eliminated from the organism of individuals with low BHC, but accumulates in the form of fat deposits due to the low content of chromosomal Q-HRs in their genome. If we take into account the use of high-calorie, easily digestible foodstuffs, hypodynamia and, possibly, the use of energy-intensive drinks (alcohol), the accumulation of excess energy in the body of individuals with AO becomes obvious.

And finally the answer to the raised question: "Why are some individuals lean or some obese?" instead of the existing points of view that obesity is either the result of fundamental lack of discipline on the part of affected individuals or that the answer to this question will be found by the identification of genes that a responsible for human obesity, we would answer that obesity is not simply a personal failing or the result of abnormal functioning of some structural genes (here we mean only AO). We suppose that in a human population there is a very great variety in the functioning of the system of energy homeostasis involved in the regulation of food intake, fat stores and energy expenditure related to the number of Q-HRs in the genome. In individuals with a low BHC, even with a same consumption of food as in people with a normal weight, in comfortable conditions of life, more fat will be deposited than in individuals with a medium or high BHC, as their heat losses are lower due to a lesser BHC [20,43].

AO are individuals in whose cells chromosomal HRs are unable to form a sufficiently dense layer of CC around the nucleus to remove excess heat in a timely manner due to their small number of Q-HRs in the genome. This means that such individuals become unable to efficiently eliminate excess metabolic heat outside the body. There will always be excess energy in the body of such individuals, which over time can lead to the accumulation and deposition of fat cells with all the resulting harmful consequences for the host. It is this circumstance, as we believe, that is the decisive factor of heredity in the development of AO.

We tend to believe that the role of genes in vulnerability of individuals to AO, apparently, is not great. In addition to the lack of data directly pointing to a specific gene (or genes) in the development of AO, new theoretical ideas have emerged, prompting us to reconsider the established ideas about the role of genes in evolution, heredity, and development [44,45]. It is not our task to analyze their arguments in detail, and we will limit ourselves to quoting the main ideas of the supporters of the new movement in theoretical biology. It is noteworthy that their views became especially convincing after realization of the Human Genome Project and the failure of its promises of a revolutionary breakthrough in practical medicine.

One of the leaders of the new direction in theoretical biology D. Noble [45] writes: "The widely promised health benefits of genome sequencing have simply failed to materialise. We now need a careful rethink of priorities since it is clear that meeting the looming challenge of ageing populations manifesting diseases that are notoriously resistant to genetic explanations will require resources to be devoted to higher-level studies of the causes of health and disease. …Since the articles in this issue of the Journal were published, the case has been supported by the discovery that polygenic scores based on GWA fail to predict major diseases, including cardiovascular disease and cancer. Despite spending some US$8 billion by NIMH, no gene responsible for schizophrenia has been identified either".

"I stand by the central claim that the primary functional element in the cell is not the gene/genotype but the cellular phenotype, represented by the process of gene product interaction, in today's terminology, a gene product interactome. …I propose that the evidence dictates that the phenotype is the governor and regulator of the cell, which is the basic 'building block' of the organism. …genes are not responsible for common disease traits. …the failure of the candidate gene approach (based largely on classical genetics) ought to be a signal that something is very wrong: evidence has comprehensively rejected theory. …My argument is that the cellular phenotype, not the gene/genotype, plays the leading role in both inheritance and evolution [44].

Apparently, E. Mayr [46] was right when he wrote: '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-centred view of evolution, insisting 'a gene is never visible to natural selection and in the genotype'.

Thus, we concluded that, among the heredity factors, not genes but the number of chromosomal HRs play a decisive role in human susceptibility to AO. In particular, individuals with a low number of chromosomal Q-HRs in the genome, the phenotypic manifestation of which is a low level of heat conductivity of their bodies, are vulnerable to the development of AO, all other things being equal. Individuals due to low heat conductivity of their bodies are not able to effectively dissipate excess heat from the body and this circumstance may be accompanied by accumulation and deposition of fat cells, characteristic of alimentary obesity. In any event, the study factors implicated in weight gain and obesity is crucial for predictions about the future impact of the global epidemic of obesity, and provides a unique opportunity for the implementation of preventive actions.

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