

## Chromosomal Q-heterochromatin Regions in Alcoholics and Drug Addicts

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### Abstract

We studied quantitative variability of chromosomal Q-heterochromatin regions (Q-HRs) in alcoholics and drug addicts in various racial and ethnic groups. It was found that in the genome of alcoholics the amount of chromosomal Q-HRs is significantly lower than in control samples and drug addicts, whereas the latter have the greatest number of chromosomal Q-HRs.

**Keywords:** Chromosomal Q-heterochromatin; Alcoholism; Drug addiction

### Introduction

Despite the fact that human chromosomal Q-heterochromatin regions (Q-HRs) have been studied for 45 years, their biological role and nature remain unclear. The existence of Q-HRs variability in twelve Q-polymorphic loci of seven autosomes and the distal portion of the long arm of chromosome Y in populations is a well-established fact [1]. A remarkable feature of human chromosomal Q-heterochromatin regions is that individuals in a population differ in the number, location, size and intensity of fluorescence of these specific fluorescent areas [2-12].

Results of our extensive comparative population studies show that modern human populations differ considerably from each other. These differences are undoubtedly related to environmental factors rather than to racial or ethnic features. Specifically, the mean number of Q-HRs is considerably lower in the genome of populations living permanently in northern latitudes and high-altitude regions as compared to permanent residents of temperate zones of Eurasia and low-altitude regions of subequatorial Africa [9,13-21].

The problem of alcohol abuse is exclusively human. Produced and consumed since at least the sixth century, surrounded by wonder and regulation, alcoholic beverages have played a central role in all cultures to-date. There are large individual differences in the rate of ethanol metabolism, and a single dose may have widely different effects within a population. Indeed, there has been very strong evidence that ethanol metabolism varies among racial groups [22]. According to data of certain authors, there is a tendency towards an increase in the consumption of strong alcoholic beverages from southern regions to northern ones [23-25]. An analogous trend was traced within one state and even territorial region [26].

Taking into account the well-known role of alcohol and drugs in metabolism, we have carried out a pilot study in order to detect possible relations between the tendency of individuals to consume strong alcoholic beverages, as well as drugs, and the amount of chromosomal Q-HRs in their genome taking into account their racial and ethnic features.

### Materials and Methods

Using identical methods, we were the first to examine patients undergoing treatment in a narcological dispensary (in Bishkek, Kyrgyzstan) in connection with alcoholic and narcological intoxication. It is difficult to unequivocally label them as sick people, for, as we have ascertained, at present, at least under conditions of the medical service functioning in our country, various interpretations of "alcoholism" and "drug addiction" do not allow us to adopt a unified system of their classification and diagnosis. Since our sample included subjects receiving medical care of their own free will or at the urgent request of their relatives, we cannot call them sick in the strictly clinical sense of the word. Therefore, we conditionally call them alcoholics and drug addicts.

In order to study chromosomal Q-HRs variability in alcoholics we selected those of both sexes belonging to two ethnic groups (Kyrgyz and Russians). However, the group of drug addicts included all those who received medical care regardless of their racial and ethnic affiliation, since narcomania appeared in our country as a medico social phenomenon just recently. But owing to a number of social and psychological factors women with narcomania either conceal it or do not seek medical care. That is why our sample included male drug addicts. The age of the subjects studied ranged from 18 to 60 years.

Chromosomal preparations were made using short-term cultures of peripheral blood lymphocytes. The cultures were processed according to slightly modified [27] conventional methods [28]. The dye used was propylquinacrine mustard. Calculation and registration of chromosomal Q-HRs variability was performed using the criteria and methods described in detail elsewhere [16,18].

To describe Q-HRs variability in our samples we used three main quantitative characteristics of this cytogenetic phenomenon: (1) the distribution of Q-HRs in the populations studied, i.e., the distribution of individuals having different numbers of Q-HRs in the karyotype regardless of the location (distribution of Q-HRs), which also reflected the range of Q-HRs variability in the population genome; (2) the derivative of this distribution, an important population characteristic, i.e. the mean number of Q-HRs per individual; (3) the frequency of Q-HRs in seven Q-polymorphic autosomes in the population.

The  $\chi^2$  test was used to compare distributions of Q-HRs. The mean numbers of Q-HRs per individual were compared using the Student t-test.

## Results

Table 1 shows the distribution of the numbers and mean number of Q-HRs on autosomes in alcoholics and drug addicts, as well as in the control groups (residents of Bishkek). To begin with, let us note that the appropriate statistical analysis showed that alcoholics representing

two different ethnic groups did not differ significantly in all the quantitative characteristics of chromosomal Q-HRs variability, and this admitted to pool them into one group. As it follows from the Table 1, alcoholics are characterized by the lowest value of the mean number of Q-HRs per individual in the population ( $\bar{x}$ ) and by the narrowest range of variability of the number of chromosomal Q-HRs among all the samples studied. Although subjects with drug abuse typically had the highest  $\bar{x}$  value, nevertheless it should be noted that the range of variability of the number of Q-HRs was as narrow in the as that in alcoholics.

Number of Q-HRs	Alcoholics		Drug addicts	Controls	
	Kyrgyz (n=48)	Russians (n=57)	(n = 100)	Kyrgyz (n=202)	Russians (n=556)
	I	II	III	IV	V
0	7 (14.5)	10 (17.5)		18 (8.9)	46 (8.3)
1	23 (47.9)	17 (29.8)		37 (18.3)	119 (21.4)
2	12 (25.0)	22 (38.5)	12 (12.0)	72 (35.6)	194 (34.9)
3	6 (12.5)	6 (10.5)	13 (13.0)	35 (17.3)	122 (21.9)
4		2 (3.5)	36 (36.0)	29 (14.4)	57 (10.2)
5			30 (30.0)	9 (4.5)	16 (2.9)
6			9 (9.0)	2 (1.0)	2 (0.4)
Total number of Q-HRs	65	87	411	459	1193
	$\chi^2_{I,II}=2.40$	$\chi^2_{I,III}=78.39$	$\chi^2_{I,IV}=21.50$	$\chi^2_{I,V}=21.78$	$\chi^2_{I,III}=57.21$
	df=1	df=1	df=1	df=1	df=1
	P>0.50	P<0.001	P<0.01	P<0.01	P<0.001
	$\chi^2_{II,IV}=8.34$	$\chi^2_{II,V}=7.52$	$\chi^2_{III,IV}=33.29$	$\chi^2_{III,V}=39.65$	$\chi^2_{IV,V}=0.43$
	df=1	df=1	df=1	df=1	df=1
	P<0.05	P<0.001	P<0.001	P<0.001	P>0.05
Mean number of Q-HRs	1.35 ± 0.128	1.53 ± 0.135	4.11 ± 0.113	2.27 ± 0.094	2.15 ± 0.51
	$t_{I,II}=0.96$	$t_{I,III}=16.17$	$t_{I,IV}=5.79$	$t_{I,V}=5.81$	$t_{II,III}=4.66$
	df=103	df=118	df=106	df=64	df=112
	P>0.300	P<0.000	P<0.000	P<0.000	P<0.000
	$t_{II,IV}=4.50$	$t_{II,V}=3.76$	$t_{III,IV}=12.52$	$t_{III,V}=15.81$	$t_{IV,V}=1.12$
	df=118	df=611	df=232	df=143	df=328
	P<0.000	P<0.000	P<0.000	P<0.000	P>0.200

**Table 1:** Distribution and mean number of Q-HRs per individual in alcoholics, drug addicts and controls.

Table 2 presents data regarding the comparative analysis of alcoholics with subjects suffering from narcomania. As noted above, we were unable to divide our sample of drug addicts according to their ethnic affiliation because it was too small to carry out an adequate statistical analysis, and therefore, we just indicated their number. Nevertheless, in determining the value of the mean number of Q-HRs ( $\bar{x}$ ) in all the ethnic samples of drug addicts we invariably found  $\bar{x}$  to

amount to four (these data are not presented here). In any case, according to our data the content of chromosomal Q-HRs in the genome of drug addicts proved to be considerably greater in drug addicts than in the controls and especially in alcoholics.

Table 3 shows the frequency of the Q-HRs in seven Q-polymorphic autosomes in the samples studied. As can be seen from this Table, another quantitative relationship exists between Q-HRs frequencies on

seven autosomes, namely they tend to be lower in all the autosomes, depending on the  $\bar{x}$  value, with the exception of autosomes 4 containing the lowest amount of Q-HRs in the human population genome and vice versa. Of interest is the fact that this difference was most pronounced in autosomes 3 and 13 containing more than half of the Q-HRs of the human population genome. At the same time, all the samples studied did not differ significantly from each other in the portion of Q-HRs in the polymorphic loci of seven Q-polymorphic autosomes, in keeping with our previous observations [16-19,21,29].

Number of Q-HRs	Alcoholics	Drug addicts	Ethnic composition of drug addicts
	(n=105)	(n=100)	
	I	II	
0	17 (16.2)		1. Kyrgyz-34
1	40 (38.1)		2. Russians-32
2	34 (32.4)	12 (12.0)	3. Uighurs-14
3	12 (11.4)	13 (13.0)	4. Koreans-18
4	2 (1.9)	36 (36.0)	5. Germans-2
5		30 (30.0)	
6		9 (9.0)	
Total number of Q-HRs	152	411	
	$\chi^2_{21, II} = 114.23$		
	df=1		
	P<0.001		
Mean number of Q-HRs	1.45 ± 0.094	4.1 ± 0.113	
	t <sub>I, II</sub> = 18.17		
	df=203		
	P<0.000		

**Table 2:** Distribution and mean number of Q-HRs per individual in alcoholics and drug addicts.

## Discussion

It is found that non-genic part of human genome makes about 98% of cell nucleus DNA. Approximately 15-20% of this non-coding part of human DNA is constitutive heterochromatin. There are two types of constitutive heterochromatin: C- and Q-heterochromatin. C-heterochromatin regions (C-HRs) are found in the genome of all higher eukaryotes, while Q-heterochromatin regions (Q-HRs) are only in the genome of three higher primates (*Homo sapiens*, *Pan troglodytes* and *Gorilla gorilla*). Human chromosomes possess both types of constitutive heterochromatin. However, there is a fundamental difference between them: quantitative variability of chromosomal Q-HRs in the genome exists only in human populations. In man C-heterochromatin is present in all his chromosomes, varying mainly in size, while Q-heterochromatin can only be detected on seven autosomes and the Y-chromosome. In this case individuals in a population differ from each other on the number of chromosomal Q-HRs.

However, the question of possible biological role of chromosomal heterochromatin regions in human life remains open. Since human chromosomal C- and Q-HRs have no structural genes, the traditional "genotype → phenotype" approach is unacceptable in this case. To search a way out of the situation, we came back to the hypothesis of cell thermoregulation (CT) [30,31]. CT is the process of equalization of temperature difference between cytoplasm and nucleus and finally inside of the whole cell. Structural basis of CT is peripheral layer of condensed chromatin (CC) which is chromosomal C- and Q-HRs. We assume that thermal energy transfer between the cytoplasm and the nucleus is carried out through this dense layer of peripheral CC, located inside of the nuclear envelope.

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. These researches showed that individuals in population truly differ from each other in body heat conductivity (BHC) and its level depends on the amount of chromosomal Q-HRs in human genome. In other words, there are some parallels in the distribution of the amount of chromosomal Q-HRs and variability of BHC at the level of human populations [32].

In the available literature we were unable to find biological or genetic markers confirmed by independent studies, indicating predisposition to alcoholism or drug addiction in man. But there are facts that were repeatedly confirmed, at least on the territory of the ex-USSR: 1) there is gradient of consumption of strong alcoholic beverages from the south to the north in the scale of a country, individual republics, territories and regions 2) strong alcoholic beverages are significantly more frequently consumed by residents of northern latitudes and high-altitude regions, regardless of their nationality, ethnic or religious affiliation [33]. As far as we know, an almost similar picture is observed in countries of Europe and North America [34,35].

Taking into account the above mentioned data we believe that there may be certain relationship between the amount of Q-HRs in the genome, development of alcoholism and drug addiction, especially its relation to the level of human BHC.

The point is that: a) quantitative chromosomal Q-HRs variability only exists in human populations, though this type of heterochromatin is present in the genome of chimpanzee (*Pan troglodytes*) and gorilla (*Gorilla gorilla*); b) the problem of alcohol abuse and drug addicts is exclusively human; c) notorious propensity to addiction of southerners to drug addicts and northerners and mountaineers to alcoholism still needs further research.

Actually, life and climate in the Far North or at high altitude predisposes, in a certain sense, to drink alcoholic beverages just in order to get a feeling of thermal comfort. But, as we suppose, one and same dose of alcohol in people with different amounts of chromosomal Q-HRs in their genome can lead to different consequences. Thus, people with low BHC, among other factors, to get a sense of thermal comfort are forced to take a relatively large amount of alcohol, and it eventually leads to more severe intoxication with hangover syndrome, than in individuals with normal or great number of chromosomal Q-HRs. In other words, for warming of the body of individuals with low BHC requires more alcohol and time than ones with normal or high BHC, even if they have similar physical characteristics.

Drug addicts, i.e., individuals with a high BHC also become accustomed to use drugs because of their wish to get a feeling of thermal comfort, but in this case this “pleasure” is actually due to “narcotic cooling”, with consequent emotional or other feelings in drug addicts. Perhaps drug addicts intuitively feel that more pleasure can be received by “cooling” of their body through the drugs than “heating” them with alcohol, since their body having high thermal conductivity liable to rapid heating and cooling.

From the data obtained by us, of interest are the following results: 1) alcoholics have the lowest number of Q-HRs in their genome, and they do not differ from each other in all the quantitative characteristics of chromosomal Q-HRs variability despite their different ethnic affiliation (Table 1); 2) in the genome of drug addicts the number of Q-HRs is significantly greater than in controls, especially in subjects abusing in strong alcoholic beverages (Tables 1 and 2); 3) however, all the samples studied do not differ in the relative content (portion) of Q-HRs in seven Q-polymorphic autosomes, i.e., in no group there was preferential Q-HR localization on seven potentially Q-polymorphic chromosomes (Table 3), and this is again suggesting that Q-heterochromatin is not locus-specific material in the genome [17-19,36].

Location of Q-HRs	Drug addicts	Controls		Alcoholics
	(n=100)	Kyrgyz (n=202)	Russians (n=556)	(n=105)
	I	II	III	IV
3	134 (0.670)*	141 (0.349)*	445 (0.400)*	64 (0.305)*
	(32.6)**	(30.7)**	(37.3)**	(45.1)**
4	10 (0.050)*	27 (0.067)*	14 (0.013)*	2 (0.010)*
	(2.6)**	(5.9)**	(1.17)**	(1.4)**
13	145 (0.725)*	160 (0.396)*	399 (0.359)*	42 (0.200)*
	(35.3)**	(34.9)**	(33.5)**	(29.6)**
14	23 (0.005)*	26 (0.064)*	76 (0.068)*	11 (0.052)*
	(5.6)**	(5.7)**	(6.4)**	(7.7)**
15	34 (0.170)*	34 (0.084)*	94 (0.084)*	5 (0.024)*
	(8.3)**	(7.4)**	(7.9)**	(3.5)**
21	40 (0.200)*	43 (0.106)*	97 (0.087)*	14 (0.067)*
	(9.7)**	(9.4)**	(8.1)**	(9.9)**
22	25 (0.125)*	28 (0.069)*	68 (0.061)*	4 (0.019)*
	(6.1)**	(6.1)**	(5.7)**	(2.8)**
Total number of Q-HRs	411	459	1193	152
Mean number of Q-HRs	4.1 ± 0.113	2.27 ± 0.094	2.15 ± 0.510	1.45 ± 0.094

\*-Q-HR frequency from the number of chromosomes analyzed;  
 \*\*-Q-HR frequency as percentage of the overall number of chromosomal Q-HR.

**Table 3:** Q-HRs frequencies in seven Q-polymorphic autosomes in alcoholics, drug addicts and controls.

Here we just draw attention to the fact that in the vulnerability of man to alcoholism and drug addiction is also of significance, in addition to other things, the amount of chromosomal Q-HRs in his genome. We believe that in such a complicated problem as alcoholism and drug addiction in the contemporary world theoretical constructions are not very important. Even when there are the slightest suspicions as to certain biological factors, if they really point to possible predisposition to alcohol and drug abuse, deserve verification by independent investigations, no matter by whom and where such investigations were carried out.

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