RECIPROCAL VARIATION OF THE Q-HETEROCHROMATIN CONTENT IN THE HUMAN GENOME

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The writer previously found a high frequency of phenotypically normal men in a population of Western Siberia with morphologically identical subtotal deletion of the brightly fluroescent heterochromatin segment of the Y chromosome [3]. Since the heterochromatin block of the Y chromosome has a complex structural organization and it contains different types of satellite DNA [4], it was interesting to assess the effect of loss of a considerable part of this material on the Q-heterochromatin content in the human genome. The aim of this investigation was to study this problem.

METHODS

Q-band frequency was studied in the centromere regions of the 3rd and 4th chromosomes and also in proximal regions of the short arms (p11) and satellites (p13) of all acrocentric chromosomes in 57 persons with subtotal deletion of heterochromatin of the Y chromosome (main group) and in 224 men from the same ethnic group with a normal Y chromosome (control group). The mean ag- of the subjects was 23.7 ± 2.2 and 23.8 ± 1 year. Chromosome preparations were obtained by the standard method by culture of peripheral blood lymphocytes for 72 h. A 0.005% solution of propylquinacrine mustard in Soerensen's phosphate buffer (pH 6.0) was used as the stain. No fewer than 10 metaphase plates from each individual, with good scatter and moderate coiling of the chromosomes were studied under the fluorescence microscope. Brightly fluorescent bands, found in more than 50% of the metaphases examined, were taken as Q variants. The results were subjects to statistical analysis by the chi-square and Student's tests.

RESULTS

Comparative analysis of the frequency of Q-heterochromatin bands in individuals with subtotal deletion of heterochromatin of the Y chromosome and in subjects of the control group showed no statistically significant differences between them as regards the majority of Q bands, located in 12 regions of seven autosomes (Table 1). With regard to the mean number of Q-variants per individual, the groups of subjects likewise were indistinguishable ($t = 0.4$, $P > 0.50$), despite some increase in the value of this parameter in subjects with a marker Y chromosome. However, in subjects who had lost a considerable part of the brightly fluorescent heterochromatin block of the Y chromosome a significant increase (by about 1.5 times) was observed in the frequency of this brightly fluorescent material in the centromere region of the 3rd chromosome ($\chi^2 = 10.72$, $P < 0.01$).

Analysis of the distribution of frequencies of homo- and heterozygous carriers of Q bands of the 3rd chromosome in the main and control groups revealed deviation of the observed frequencies from those expected theoretically on the basis of Hardy–Weinberg ratios in subjects with a marker Y chromosome (Table 2). This deviation was due mainly to an excess of heterozygotes. With regard to the remaining Q segments, agreement was noted between the observed and theoretically expected frequencies in both the main and control groups.

An increase in Q-band frequency in the 3rd chromosome of persons with subtotal deletion of heterochromatin of the Y chromosome may evidently be nonrandom in character. This result is probably evidence that reciprocal variation in the content of certain heterochromatin

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TABLE 1. Comparative Analysis of Q-Band Frequency in Men with Subtotal Deletion of Heterochromatin of Y Chromosome and in Controls

No. of chromosome and band	Frequency of Q bands in persons with undermentioned karyotype		χ^2	P
	46, XY (n=224)	46, X, del (Y) (q12) (n=57)		
3 cen	0,350	0,518	10,72	<0,01
4 cen	0,022	0	—	—
13p11	0,596	0,544	1,02	>0,30
13p13	0,078	0,132	3,20	>0,05
14p11	0,013	0,009	—	—
14p13	0,091	0,070	0,52	>0,40
15p11	0,022	0,035	0,61	>0,40
15p13	0,232	0,202	0,48	>0,40
21p11	0,009	0,018	—	—
21p13	0,187	0,123	2,64	>0,10
22p11	0,013	0,018	—	—
22p13	0,136	0,132	0,02	>0,80
Mean number of Q band per individual	3,50±0,11	3,60±0,24	—	>0,50

Legend. Q-band frequency calculated per chromosome.

TABLE 2. Distribution of Frequencies of Homozygotes (+/+ and −/−) and Heterozygotes (+/−) for Q-Bands of 3rd Chromosome in Individuals with Subtotal Deletion of Heterochromatin of Y Chromosome and in Controls

Karyotype	Number of homo- and heterozygotes			χ^2	P
	+/+	+/−	−/−		
46, X, del (Y)(q12)	10 (15,27)	39 (28,46)	8 (13,27)	7,82	<0,05
46, XY	24 (27,51)	109 (101,98)	91 (94,51)	1,06	>0,30

Legend. Expected frequencies based on Hardy–Weinberg theorem given between parenthesis.

fractions may take place, as a result of which their level in the human genome is maintained within certain optimal limits. A similar phenomenon, corresponding formally to the phenomenon of compensation of some lost DNA sequences, has been described in *Drosophila* also [2]. In this connection it must be pointed out that in Japanese, who have a longer Y chromosome than other ethnic groups, supposedly on account of partial duplication of heterochromatin of the long arm [11], the Q-band frequency in the 3rd chromosome is appreciably reduced [10] to 26.6% compared with 40.9-59% in members of other ethnic groups [1]. Evidence of the existence of genetic control of the distribution of highly replicating DNA in the human genome also is given by the negative correlation found between the total content of constitutive heterochromatin in the 1st, 9th, and 16th chromosomes and the size of the heterochromatin block of the Y chromosome [5].

Satellite DNA fractions, similar or identical in base composition and degree of reiteration, are evidently involved in the variation described above. According to some investigators [7], brightly fluorescent regions of the 3rd and Y chromosomes, rich in A-T base pairs, contain the largest concentration of type I satellite DNA, and also regions of lateral asymmetry and uncoiling, induced by certain agents [9], evidence of similarity of the heterochromatin regions of these chromosomes at the molecular level. The change in the number of repeating sequences may perhaps be based on their differential replication. The possibility likewise cannot be ruled out that loss of certain fractions of heterochromatin in some chromosomes predisposes to nonrandom segregation in meiosis of other chromosomes, carrying certain heterochromatin variants. As the result of this nonrandom segregation, Hardy–Weinberg equilibrium may be disturbed for these chromosomes. Nonrandom segregation of chromosomes or

myotic drive, owing its origin to certain regions of heterochromatin in the genome, was described long ago in *Drosophila* and *Zea mays*. It has also been shown that deficiency of sex chromosome heterochromatin in *Drosophila* may affect the nonrandom character of segregation not only of the sex chromosomes, but also of autosomes [6, 8]. The possibility that an analogous phenomenon may be found in other organisms cannot be ruled out.

The results thus show that reciprocal variation of the content of Q heterochromatin is possible in human chromosomes. One result of this process is evidently maintenance of the stability of the genome with regard to the heterochromatin content and the balance between its components.

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EXPRESSION OF eyeless MUTANT GENES IN PRIMORDIAL MOUSE RETINA

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Autorecessive genes eyeless-1 (ey-1) and eyeless-2 (ey-2), in the homozygous state, determine a severe disturbance of morphogenesis of the eye in mice, leading to anophthalmia or microphthalmia [2, 3]. In mice of the LRDCT-AN line, with ey-1/ey-1 ey-2/ey-2 genotype, bilateral anophthalmia is observed in about 70% of cases and microphthalmia in the rest [4, 6]. Disturbance of eye development in LRDCT-AN mice takes place as early as at the optic vesicle stage. In 10-day-old mutant embryos the anlagen of the lenses are smaller than normally and, as a rule, they are located outside the cavity of the optic cup, which is abnormal in shape and orientation. In the majority of ZRDCT-AN mouse embryos the anlaga of the lens and the optic cup undergo resorption. Several hypotheses have been put forward regarding the primary mechanism of disturbance of eye development in ZRDCT-AN mice, and in particular: depression of growth of the optic vesicle, blocking out the process of lens induction by mesenchymal cells, or inability of the lenticular ectoderm to respond to inductive influences from the optic vesicle [1, 3, 4, 6, 7]. Salaün [5] reported that her data indicate expression of eyeless genes in cellular systems not involved in eye formation.

The aim of this investigation was to determine the site of action of eyeless mutant genes in mice.

METHODS

Mouse embryos, aged 10 days, of the mutant genotype ey-1/ey-1 and ey-2/ey-2 (line LRDCT-AN) were used for the experiments, and embryos of the same age, of normal genotype (line CC57BR)

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