

# Heterochromatin Dosage Compensation: A Review

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## Abstract

The fact that there is a phenomenon of dosage compensation for the euchromatin part of the genome in eukaryotes has been known for almost a seventy years. This phenomenon is currently being studied under the name epigenetic control of gene expression. Evidence for the existence of dosage compensation at the gene level is obtained from genes localized on the sex chromosomes, the most famous example of which is the X-chromosome inactivation in mammals. As for genes localized on autosomes, there are no convincing data on this score. The question of whether there is a dosage compensation for the heterochromatic part of the genome in eukaryotes remains open. We have data indicating the existence of dosage compensation for the heterochromatin part of the human genome, using the example of chromosomal Q-heterochromatin regions (Q-HRs). It turned out that this phenomenon manifests itself both in sex chromosomes and in autosomes, regardless of gender, age, racial-ethnic origin and climatogeographical characteristics of the place of permanent residence of a human. Moreover, this process is associated with an important part of human life (maintaining temperature homeostasis) and has a phenotypic manifestation, which can be objectively studied. The question is discussed whether the phenomenon of chromosomal heterochromatin dosage compensation should be considered as an example of epigenetics, or it is a different phenomenon, since it does not affect genes?

**Keywords:** Heterochromatin dosage compensation; Gene dosage compensation; chromosomal Q-heterochromatin regions; Epigenetics; X-chromosome inactivation; Cell thermoregulation.

## Introductions

Dosage compensation of genes is an epigenetic mechanism that makes it possible to equalize the level of expression of sex-linked genes in males and females of those species in which sex determination is carried out using sex chromosomes. Epigenetics

studies the processes behind the inheritance of traits that cannot be attributed to changes in the DNA sequence. In mammals, this is done by inactivating one X chromosome in the cells of females, so that in each somatic cell of an individual of either sex, there is only one active X chromosome per diploid set of chromosomes.

It is known that in the nuclei of somatic cells of female mammals, one of the X chromosomes is euchromatic and transcriptionally active and the other is inactive and forms a cytologically dense heterochromatic structure (the Barr body). It is believed that X-chromosome inactivation (XCI) provides dosage compensation in marsupials and placental mammals as a way to align the expression of X-linked genes between individuals with the XX and XY karyotype. XCI mechanisms are the subject of intensive research and significant progress has been made in this direction (see the review in<sup>1</sup>).

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However, we believe that the biological meaning of XCI is to compensate for the dosage of heterochromatin in the genome of females, whose total amount of constitutive heterochromatin is usually less than that of males. The following facts support this assumption:

- Mammalian sex chromosomes are carriers of large chromosomal heterochromatin regions (HRs).
- It is known that the total amount of heterochromatin in the genome of men is significantly greater than in women, due to a large block of constitutive heterochromatin on the Y chromosome.
- There are two groups of observations indicating the existence of compensation for the total dosage of the amount of constitutive heterochromatin in the human genome. The first group refers to the data of the distribution of the number of chromosomal Q-heterochromatin regions (Q-HRs).<sup>2</sup> The second group of data relates to the relationship between the size of the Y chromosome and the number of autosomal Q-HRs.<sup>3</sup> These data were obtained on human populations representing all three racial groups permanently residing in different climatogeographic conditions of Eurasia and Africa. Unfortunately,

such studies cannot be carried out on chromosomal C-heterochromatin regions (C-HRs) due to the fact that after C-staining, most chromosomes in the human karyotype are not identified.

The first group of data shows that at the population level, the total number of chromosomal Q-HRs on the autosomes of women is significantly higher than the Q-HRs on the autosomes of men. In comparative population studies, the following quantitative characteristics of chromosomal Q-HRs are used: (a) the distribution of the number of Q-HRs in the population, i.e. the distribution of individuals with different numbers of Q-HRs in the karyotype, regardless of location (Q-HRs distribution), which also reflects the range of variability of Q-HRs in the population; (b) the mean number of chromosomal Q-HRs per individual, determined by dividing the total number of Q-HRs found in this sample by the number of individuals studied; (c) the size of the Y-chromosome, which is (a) large ( $Y = F$ ), (b) average ( $F > Y > G$ ) and (c) small ( $Y = G$ ).

#### Facts

Table 1 shows the distribution of numbers and the mean number of chromosomal Q-HRs on autosomes in men and women in two age groups of Kazakh nationality.

**Table 1:** Distribution of the numbers and mean number of Q-HRs on autosomes in males and females in newborns and 18-25 years individuals.<sup>2</sup>

Number of Q-HRs	Newborns Boys (n = 207) I	Newborns Girls (n = 182) II	Males 18 - 25 years (n = 49) III	Females 18 - 25 years (n = 190) IV
0	3	1	–	–
1	5	4	9	7
2	39	21	12	24
3	47	38	13	45
4	51	46	11	49
5	37	39	4	40
6	18	20	–	17
7	7	13	–	7
Total number of Q-HRs	770	750	136	745
Mean number of Q-HRs	<b>3.72 ± 0.102</b>	<b>4.12 ± 0.111</b>	<b>2.78 ± 0.176</b>	<b>3.92 ± 0.104</b>
Statistics	t I, II = 2.649; t II, III = 5.775; t III, IV = 5.119; t I, III = 4.137; t II, IV = 1.313;	df = 387; df = 229; df = 237; df = 254; df = 370;	P = 0.008* P = <0.001* P = <0.001* P = <0.001* P = 0.190	

\* - these differences are statistically significant.

As can be seen from this table, in each case, female samples are distinguished by high values of the mean number and wide variability in the distribution of chromosomal Q-HRs compared to men. These differences are statistically significant. The same data were obtained in the study of other racial and ethnic groups (for details see.<sup>3,4</sup>)

The second group of data indicating the existence of dose compensation of constitutive heterochromatin is illustrated by examples of a close relationship between the size of the Y chromosome and the number of autosomal Q-HRs in human populations.<sup>3</sup> It should be emphasized that only autosomal Q-HRs are considered in comparative population cytogenetic studies. The variability of

Q-heterochromatin on the q12 segment of the Y chromosome was usually considered separately from the quantitative variability of autosomal Q-HRs.<sup>5-19</sup>

Our studies of native human populations in Eurasia and Africa have shown that there is a close relationship between the mean number of autosomal Q-HRs and the size of Q-heterochromatin blocks on the Y chromosome (for more details, see).<sup>3,16</sup> Table 2 shows the distribution of numbers and the mean number of chromosomal Q-HRs in males with Y chromosomes of various sizes in newborns in Kazakhstan. The same patterns were found in the study of other racial and ethnic groups.<sup>2,3</sup>

**Table 2:** Distribution of the numbers and mean number of autosomal Q-HRs in males with Y chromosomes of various sizes Kazakh newborns.<sup>2</sup>

Number of Q-HRs	Large Y ≥ F (n = 53) I	Medium F > Y > G (n = 102) II	Small Y ≤ G (n = 32) III
0	3	—	—
1	5	1	—
2	21	12	2
3	11	26	1
4	6	28	10
5	7	22	13
6	—	10	4
7	—	3	2
Total number of Q-HRs	139	406	150
Mean number of Q-HRs	2.62 ± 0.185	3.98 ± 0.129	4.69 ± 0.203
Statistics	t I, II = 6.077; t II, III = 2.748; t I, III = 7.223;	df = 153; df = 132; df = 83;	P = <0.001* P = 0.007* P = <0.001*

\* these differences are statistically significant.

The existence of a close relationship between the number of Q-HRs on autosomes and the size of Q-heterochromatin on the Y chromosome was also shown in adult individuals representing all three racial and ethnic groups permanently residing in Eurasia and Africa.<sup>3</sup> Table 3 shows the distribution of numbers and the average number of Q-HRs per individual in a population of males with different Y chromosome sizes. As can be seen from this table, the decrease in the mean number of Q-HRs in the samples of men with large Y chromosomes is statistically significant. Of independent interest are the facts that in the group of men with large

Y chromosomes, a significant narrowing of the distribution of the number of Q-HRs is visible, as well as an expansion of the range of variability in the distribution of the number of Q-variants in the karyotype of men with Y chromosomes with medium and small sizes. Men with large Y chromosomes were characterized by low values of the mean number of Q-HRs per individual in the population and a low range of variability in the distribution of Q-variants compared to men with medium-sized and especially small Y chromosomes. These differences are statistically significant.

**Table 3:** Distribution of the numbers and mean number of autosomal Q-HRs in males with Y chromosomes of various sizes.<sup>3</sup>

Populations	Number of Q-HR	Y ≥ F (n = 30) I	F > Y > G (n = 261) II	Y ≤ G (n = 36) III
Negroes of Africa (Mozambique, Guinea-Bissau, Zimbabwe, Angola)	0	-	-	-
	1	1	-	-
	2	5	16	-
	3	5	42	7
	4	7	64	7
	5	7	66	6
	6	1	46	8
	7	4	20	5
	8	-	4	2
	9	-	2	1
	10	-	1	-
Total number of Q-HRs	-	123	1 220	187
Mean number of Q-HRs	-	4.10 ± 0.30	4.67 ± 0.09	5.10 ± 0.28
Statistics	-	t I, II = 1.98;	df = 289;	P = <0.049
	-	t II, III = 1.61;	df = 295;	P = <0.108;
	-	t I, III = 2.66;	df = 64;	P = <0.009;
Steppe Mongoloids (Kazakhs, Chinese)	0	2	-	-
	1	7	11	2
	2	4	26	4
	3	4	21	2
	4	2	11	3
	5	1	4	4
	6	-	5	1
Total number of Q-HRs	-	40	220	54
Mean number of Q-HRs	-	<b>2.00 ± 0.31</b>	<b>2.82 ± 0.15</b>	<b>3.38 ± 0.40</b>
Statistics	-	t I, II = 2.39;	df = 30;	P = <0.021;
	-	t II, III = 1.32;	df = 20;	P = <0.194;
	-	t I, III = 2.75;	df = 32;	P = <0.008;
Russians	0	10	23	1
	1	21	53	5
	2	14	103	6
	3	7	65	7
	4	4	25	2
	5	-	9	2
	6	-	2	1
Total number of Q-HRs	-	86	611	62
Mean number of Q-HRs	-	<b>1.53 ± 0.15</b>	<b>2.18 ± 0.07</b>	<b>2.58 ± 0.29</b>
Statistics	-	t I, II = 3.93;	df = 82;	P = <0.000;
	-	t II, III = 1.34;	df = 26;	P = <0.183;
	-	t I, III = 3.14;	df = 37;	P = <0.003;

Populations	Number of Q-HRs	Y ≥ F (n = 16) I	F > Y > G (n = 125) II	Y ≤ G (n = 11) III
Kyrgyz of Pamir and Tien-Shan	0	3	11	–
	1	5	26	3
	2	6	49	4
	3	2	20	3
	4	–	14	1
	5	–	3	–
	6	–	2	–
Total number of Q-HRs	–	23	267	24
Mean number of Q-HRs	–	<b>1.43 ± 0.24</b>	<b>2.13 ± 0.11</b>	<b>2.18 ± 0.29</b>
Statistics	–	t I, II = 2.12;	df = 139;	P = <0.036;
	–	t II, III = 0.13;	df = 134;	P = <0.900;
Northern Mongoloids (Chukchi, Yakuts, Khakass, Nenets, Selkups)	0	10	24	–
	1	22	50	6
	2	12	71	9
	3	6	46	9
	4	6	17	2
	5	–	7	–
	Total number of Q-HRs	–	88	433
Mean number of Q-HRs	–	1.57 ± 0.16	2.01 ± 0.08	2.27 ± 0.18
Statistics	–	t I, II = 2.48;	df = 269;	P = <0.017;
	–	t II, III = 1.29;	df = 38;	P = <0.198;
	–	t I, III = 2.88;	df = 66;	P = <0.005;

It is well known that the size of the Q-heterochromatin segment on the Y chromosome is even larger than the average size of the Q-HRs on any of the seven Q-polymorphic autosomes. The morphological variability of the Y chromosome (large, medium, small) in the population is determined by the size of the block of the Q-heterochromatin on its long arm. Based on the data presented above, we assume that Q-heterochromatin on the Y chromosome, being the largest Q-HRs segment in the human karyotype, somehow "restricts" the total number of Q-HRs on autosomes in men. Apparently, for the same reason, the total number of Q-HRs on autosomes in women significantly increases compared to those in men at the population level (see Table 1).

These data give reason to believe that: 1) the Q-heterochromatin material on the Y chromosome, being the largest in the human genome, somehow "restricts" the total content of Q-HRs on autosomes in men; 2) Q-HRs on human chromosomes seem to have a common nature, regardless of their localization in the karyotype; and 3) human chromosomal Q-HRs may have the same biological

effect regardless of their localization in the karyotype.<sup>3,4,20</sup>

## Discussion

We believe that the increase in the number of chromosomal Q-HRs on autosomes in women at the population level can be explained by the existence of an evolutionarily fixed mechanism that "compensates" for the difference in the "dose" of the amount of Q-heterochromatin in the female genome due to the absence of a chromosome in their karyotype that could carry such a large block of Q-heterochromatin as the Y chromosome. Apparently, there is some mechanism that restricts the "dose" of chromosomal Q-HRs in the human genome to a certain level. Indeed, the human karyotype has only 25 loci (3 cen, 4 cen, 13 p11, 13 p13, 14 p11, 14 p13, 15 p11, 15 p13, 21 p11, 21 p13, 22 p11, 22, p13 and Yq12), where Q-heterochromatin can potentially be. However, so far no one has been able to find a human who would have 25 Q-HRs; usually their number ranges from 0 to 10,<sup>4,9,10,14</sup>

According to Lyon<sup>21</sup>, X-chromosome inactivation (XCI) provides compensation for the dosage of genes linked on the X chromosome, since each cell, male or female, should have only one transcribed X chromosome. We believe that the Lyon's hypothesis, although perfect from the point of view of logic, nevertheless does not fully reflect the essence of XCI. If the problem was only that XCI arose to compensate the doses of X-chromosome-related genes between individuals with karyotype XX and XY, then all the genes associated with the X-chromosome would be inactivated. Moreover, among higher eukaryotes, including homeothermic animals, XCI is found for some reason only in mammals. Chromosome inactivation does not occur in human autosomes even when there is a clear excess dose of genes in his genome. For example, with autosome trisomy, there is no inactivation of an additional chromosome. If the problem was only the inactivation of one "redundant" X chromosome in the female karyotype, then why do women with Turner syndrome suffer from serious developmental abnormalities, including mental ones? While mice with the XO karyotype do not have any serious developmental abnormalities. XCI is not found in the germ cells of females, where both X chromosomes are active in all eggs.

It is known that the mammalian X chromosome is very large and contains more than 1,000 genes in mice and humans. It is believed that a double dose of some of these genes is clearly problematic, since the inability to induce XCI in XX embryos leads to early mortality during development.<sup>22,25</sup> If all the genes are not inactivated on the heterochromatinized X chromosome, then why do mammals need XCI at all? XCI also demonstrates some degree of epigenetic plasticity in pathological contexts such as cancer. For example, in tumors, the Barr body appears to be absent (reviewed in<sup>26</sup>).

The idea that we are trying to convey is that the X-chromosome is not inactivated, but heterochromatinized to compensate for the absence of a large constitutive HRs block in the female karyotype in the interests of cellular thermoregulation (CT). By CT, we mean the elimination of the temperature difference between the nucleus and the cytoplasm when, for one reason or another, the level of thermal energy in the nucleus becomes higher than in the cytoplasm (for more details, see:<sup>4,27,28</sup>

The hypothesis of CT has experimental confirmation at the level of the human body. In particular, it has been shown that individuals in the population differ from each other in the level

of body heat conductivity (BHC), and its level depends on the number of chromosomal Q-HRs in the human genome.<sup>29</sup> Our studies have shown that: (a) individuals in the population differ from each other on the levels of BHC; (b) on average, BHC in men is statistically significantly higher than in women; (c) individuals from different age groups significantly differ in their level of BHC, on average, the level of BHC in humans steadily decreases with age; (d) natives of low-mountain areas and low geographical latitudes differ on average in a higher level of BHC than permanent residents of highlands and high latitudes.<sup>4,29-31,42-44</sup>

Thus, it would be more correct to talk about the compensation of the dosage of heterochromatin, and not about the dosage of (double) genes. The fact that CT is associated with the inactivation of one of the X chromosomes is evidenced by the statistically significantly low level of BHC in women compared to men.<sup>39,31</sup> This is probably due to the fact that condensed chromatin (CC) in the cells of women does not have the same density as in men. As we believe, excess heat from the nucleus is removed outside of it with the help of the CC layer, which is the densest and, accordingly, the most heat-conducting structure in the interphase cell.<sup>27-</sup><sup>29</sup> Apparently, the facultative heterochromatin of the inactivated X chromosome is still inferior to the constitutive heterochromatin on the Y chromosome in the ability to compact CC layer around the interphase nucleus.

There are not many facts in favor of this point of view. However, even they deserve attention.

- From a morphological point of view, constitutive and facultative heterochromatin do not differ significantly.
- The inactivated X chromosome in the interphase cell is found in close connection with the nuclear membrane<sup>32-34</sup> and/or on the periphery of the nucleolus.<sup>35,36</sup>
- The inactivated X chromosome is often found in the nucleolus<sup>35</sup>, where chromosomal C-HRs of autosomes<sup>1,9,16</sup>, Q-HRs acrocentrics<sup>13-15,21,22</sup> and Y chromosomes are collected<sup>37</sup>, which we consider as CT components involved in the dissipation of excess heat from the cell nucleus.<sup>38,39</sup>
- In embryogenesis, XCI begins at the blastocyst stage, that is, at the multicellular stage, when the problem of removing excess heat from the nucleus begins.<sup>27,40</sup>

Therefore, we believe that the cause of XCI is the compensation of the dosage of heterochromatin, and



not genes, in the genome of female mammals due to the absence in their karyotype of a chromosome with a large block of constitutive heterochromatin, like the Y chromosome in males. Apparently, for the same reason, facultative heterochromatin (heterochromatinized euchromatin) occurs on one of the X chromosomes in women. The biological meaning of heterochromatinization of the X-chromosome euchromatin may be to strengthen the CC density around the interphase nucleus in order to compensate for the missing dosage of constitutive heterochromatin in the genome of female mammals, since the CC density depends on the number of chromosomal HRs. The consequence of this process is the inactivation of genes that have appeared in the heterochromatinized zones of the euchromatin regions of the X chromosome.

And finally, how to consider the heterochromatin dosage compensation in the human genome? Should this phenomenon be considered as an epigenetic process? The following facts testify against this point of view: (a) under normal conditions, chromosomal HRs does not affect the function of genes, despite their wide variability in the population; (b) in humans, the phenomenon of heterochromatin dosage compensation concerns both autosomes and sex chromosomes; (c) chromosomal HRs have a phenotypic manifestation different from genes, namely, instead of producing proteins, enzymes or RNA, they participate in the dissipation of excess metabolic heat from the interphase nucleus through CT mechanisms, the manifestation of which are different levels of heat conductivity of the human body in the population.<sup>4, 27-29</sup>

## Conclusion

A phenomenon of dosage compensation for the euchromatin part of the genome in eukaryotes has been known for almost a seventy years and is currently being studied under the name epigenetic control of gene expression. The most famous example of which is the X-chromosome inactivation in mammals. The question of whether there is a dosage compensation for the heterochromatic part of the genome in eukaryotes remains open. We have data indicating the existence of dosage compensation for the heterochromatin part of the human genome, using the example of chromosomal Q-heterochromatin regions (Q-HRs). It turned out that this phenomenon manifests itself both in sex chromosomes and in autosomes, regardless of gender, age, racial-ethnic origin and climatogeographical characteristics of the

place of permanent residence of a human. The question is discussed whether the phenomenon of chromosomal heterochromatin dosage compensation should be considered as an example of epigenetics, or it is a different phenomenon, since it does not affect genes?

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