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GENERAL GENETICS

Factors of Maintaining Chromosome Polymorphism in Common Vole *Microtus arvalis* Pallas, 1779: Reduced Fertility and Meiotic Drive

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Abstract—The common vole *Microtus arvalis* (the form *obscurus*) exhibits polymorphism of a pericentric inversion in chromosome pair 5 throughout the species range. In the Urals populations, the frequency of an acrocentric variant of the heteromorphic chromosome is very low (on average 3.2%) and virtually does not change annually. The factors of maintaining stable chromosomal polymorphism in the common vole were studied under conditions of a laboratory colony. Heterozygous and homozygous for the acrocentric chromosome females showed a significant reduction of the reproductive output irrespective of the male karyotype. This effect was manifested mostly in litter size at birth. A number of cytogenetic and exophenotypic characteristics, as well as parent–offspring transmission of this chromosome in crosses of various types, were examined. We have found meiotic drive in favor of the acrocentric, as a result of which the frequency of the acrocentric (without taking into account the postnatal mortality) totaled over all cross variants (0.48) was significantly higher than that expected with random segregation (0.42). It is likely that meiotic drive of the acrocentric largely compensates for the reduced fertility of its carriers, being among the factors of maintaining it in natural populations.

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INTRODUCTION

Chromosomal polymorphism, detected by means of light microscopy, is a form of interspecific variability of chromosome material. Explanation of its long-term existence in populations (including the case with constant frequencies of karyomorphs) encounters the same difficulties as in the case of polymorphism of nucleotide sequences of different lengths and functional significance [1]. The conclusions of Lewontin, made more than three decades ago (cited in [2]), are still valid. In each particular case of stable polymorphism, the possible roles of both random and selective factors should be taken into account.

The role of selection in maintaining inversion polymorphism in *Drosophila* was shown in classical works by Dobzhansky and Dubinin [3, 4]. Individual components of fitness of structural homo- and heterozygotes, primarily fertility, were examined in a number of mammals that exhibit stable intrapopulation polymorphism. In carriers of a less frequent variant of the heteromorphic chromosome, it was often reduced. This was documented for some insectivores [5], rodents [6], and ungulates [7, 8]. However, in other members of the same orders, no association between chromosome polymorphism and fertility has been found [9–12]). An unclear situation is observed also in the case of growth and development parameters [13, 14]. This multiple variants of phenotypic response for polymorphism seems to be related to diversity of functions of the genetic material involved in chromosome rearrangements in different species. Apparently, depending on the phenotypic effect of the rearrangement of genetic material, random (in particular, connected to population dynamics) or selective factors of maintaining chromosome polymorphism prevail. A special place in this series is occupied by meiotic drive. This term is often used in a broad sense, denoting any deviation from Mendelian segregation. Meiotic drive can compensate for fitness differences in carriers of different variants of polymorphic chromosomes.

We have examined the problem of maintenance of chromosome polymorphism, using as a model the common vole *Microtus arvalis* Pallas, 1779, which exhibits heteromorphism of one of the autosomes. The present work is devoted to analysis of the association of this phenomenon with several of reproductive, cytogenetic, and exophenotypic traits, as well as segregation of a polymorphic autosome under conditions of a laboratory colony.

MATERIALS AND METHODS

The laboratory colony of the common vole (the form *obscurus*, $2n = 46$, $NF_A = 68$) was founded by four males and ten females, seven of which were captured pregnant and gave birth to nine pups, which later participated in reproduction. The animals were collected on the territory of the Biological Station of Urals State

University (near the town of Dvurechensk, Sverdlovsk oblast, 56°37′ N, 61°08′ E).

In forming the pairs, we tried to maximally decrease the degree of inbreeding. A high number of founders allowed us to avoid negative consequences of high inbreeding. In total, more than 1700 animals were obtained for the laboratory colony. To study reproductive traits, 230 litters from 86 pairs were used. The effect of season and the ordinal litter number on reproduction parameters, reported for many rodent species [15], proved to be statistically nonsignificant in common voles from our laboratory colony [16]. Consequently, we pooled all litters for analysis of reproductive traits. The reproducing animals were sacrificed for karyotyping, usually after two or three litters. Segregation of the chromosome pair 5 was examined in 159 litters, obtained from crosses of four types.

Genome instability was studied in 80- to 100-day voles. The metaphase chromosome preparations were made of bone marrow of the animals, stained with azure–eosin. From each animal, 50 cells were examined, scoring structural chromosome aberrations, gaps, aneuploidy, and polyploidy. True breaks were distinguished from gaps, using standard criteria (shift in relation to the chromatid axis and (or) the presence of a gap exceeding the chromatid width).

In all, 3500 cells of 70 voles were examined. In all animals, standard exophenotypic characteristics were studied. Statistic analysis was conducted using the software package Statistica, license number AXXR003A622407FAN8.

RESULTS AND DISCUSSION

Heteromorphism of the chromosome pair 5 in *M. arvalis* (the form *obscurus*) has appeared because of a pericentric inversion and, possibly, a subsequent increase in the heterochromatin amount in the region of the inversion [17]. Thus, this pair is represented by an acrocentric (designated A in the tables) and a subtelocentric (designated St in the tables), with a clear prevalence of the subtelocentric variant throughout the species range. The acrocentric chromosome was recorded in many populations in various parts of the range at a relatively low frequency, although in some regions (for example, in Armenia and the Volga region) it reached 30–40% [17–19]. In the Middle and Southern Urals, we have recorded heteromorphism of the fifth chromosome pair in eight out of nineteen localities examined (Table 1). These data are analyzed in detail in [20]. In all cases, the acrocentric frequency was low (on average 3.2%) and did not show significant among-population or annual differences ($\chi^2 = 3.72$, *d.f.* = 15, $P = 0.999$; Bartlett test for low frequencies [21]). In five localities, the observations were conducted for several years, showing that the acrocentric frequency did not significantly change over this period. Thus, the common vole from the Urals showed stable chromosomal polymorphism with an extremely low frequency of the minor variant. It is hardly conceivable that this type of polymorphism could exist for a long time in many populations, being maintained only by random processes. Rather, it is likely to result from a balance of opposite forces, including selective ones. In this connection, reproductive characteristics of carriers of different morphological variants of chromosome 5 should be primarily compared. These characteristics are presented in Table 2.

As an integral measure of reproductive output of the parental vole pair was taken the mean monthly number of pups survived to an age of 20 days (R). This parameter scores the number of pups in a litter, time intervals between the litters, and pup death in postnatal ontogeny before their transition to the independent life mode, which occurs at an age of 20 days. Estimates for different cross types were significantly different, and this difference was mainly accounted for by the female karyotype. Statistical significance of this effect was demonstrated using two-way ANOVA (cross scheme with one empty cell, factors of female karyotype and male karyotype). The results of the ANOVA are presented in Table 2. Using the contrast method, we have shown that in crosses of females with the same pair 5, R does not depend on the karyotype of the male ($P = 0.141$–0.684), whereas the differences between the R values of the females with different karyotypes were highly significant ($P = 0.010$–5×10^{-5}). The integral female reproductive output decreased with an increase of the number of acrocentrics in pair 5. However, one should make sure that this decrease is not caused by inbreeding depression, since the inbreeding level inevitably increases in each generation in any population derived from a limited number of founders. A two-way ANOVA with female karyotype and male karyotype factors did not show a relationship between R and the generation number ($F = 1.37$; *d.f.* = 2/77; $P = 0.261$). This result is probably explained by the fact that the bulk of the material in all cross variants was obtained as early as in generations 3–5, when the inbreeding level was too low.

The scheme of analysis of the integral parameter was used for estimating significance of differences of two of its component traits: litter size and time interval between litters. For litter size, the situation is essentially the same as in the case of R, that is, litter size does not depend on the male karyotype (contrast method: $P = 0.115$–0.664), but depends on the female karyotype (contrast method: $P = 0.005$–1×10^{-7}). The exception was cross ♀StA × ♂AA, in which the mean litter size was lower than in variants ♀StA × ♂StSt и ♀StA × ♂StA ($P = 0.008$). A significant effect of the male karyotype was found only for the time interval between litters, characterizing intensity of reproduction. Analysis of contrasts showed that only the differences between cross ♀AA × ♂StA and the remaining variants are significant ($P = 1 \times 10^{-6}$).

Table 1. Frequencies of the acrocentric variant of chromosome 5 in the common vole populations from the Urals

Sampling locality		Year	Number of animals examined	Frequency*
Perm oblast, Predural'e Natural Reserve,	Sylva River, right shore	1998	6	0.08 (1)
57°20′ N, 57°09′ E	Sylva River, right shore	2000	31	0.02 (1)
	Sylva River, left shore		31	0.02 (1)
	Sylva River, right shore	2001	36	0.04 (3)
	Sylva River, left shore		56	0.07 (8)
Sverdlovskaya oblast, village of Shigaevo, 57°15′ N, 58°44′ E		1999	28	0.02 (1)
Yekaterinburg, Yugozapadnyi district, 56°48′ N, 60°40′ E		2003	16	0.03 (1)
Sverdlovskaya oblast, village of Bainy, 56°42′ N, 62°08′ E		2000	14	0.04 (1)
		2001	74	0.01 (1)
		2004	20	
Sverdlovskaya oblast, Urals Sate University, Biological station, 56°37′ N, 61°08′ E		1995	13	0.04 (1)
		1997	12	0.04 (1)
		2002	14	0.04 (1)
Sverdlovskaya oblast, village of Starikovo, 56°10′ N, 61°25′ E		2003	23	0.04 (2)
		2004	14	
Chelyabinsk oblast, Eastern Urals Natural Reserve, 55°47′–55°50′ N, 60°55′–61°00′ E		1994	23	0.02 (1)
Chelyabinsk oblast, Arkaim Natural Reserve, 52°37′ N, 59°33′ E		1996	5	0.10 (1)
		2002	17	0.03 (1)
Total			433	0.03 (26)

* The number of heterozygotes at chromosome pair 5 is given in parentheses.

Although prenatal and postnatal pup mortality was expressed in proportions, it was analyzed using the same scheme without transformation, according to Quinn and Keough [22]. Analysis of the integral parameter of reproductive output did not show significant differences in mortality between all cross variants. This suggests that differences in integral fertility parameter between carriers of different variants of the heteromorphic chromosome mostly depend on litter size at birth. To explain this phenomenon, we compared the number of corpora lutea at pregnancy (i.e., ovulation intensity) and embryonic death in females of different types (Table 2). Neither parameter showed significant differences, but the question remains open in the case of embryonic death, because it was markedly higher in homozygotes for the acrocentric, but the number of females examined was too small to make definite conclusions. Yet, the decrease of litter size in females heterozygous and homozygous for the acrocentric clearly was not caused by a decrease in the number of ovulating egg cells.

Thus, carriers of the rare acrocentric variant of chromosome 5 (primarily females) showed markedly reduced reproductive ability, which must have led to elimination of this variant from populations of the common vole. Since, as shown above, acrocentric 5 occurs in many regions and its frequency, at least in the Urals, remains stable, there are probably factors that compensate for low fitness of its carriers. To find these factors, we examined some phenotypic traits of voles differing in chromosome 5 morphology. These traits included pup weight in first days after birth; body weight, body length, foot index in 3-month animals; and the frequency of chromosomal mutations in the bone marrow of 80- to 100-day voles. The foot index, characterizing growth intensity, is the proportion of foot length to body length.

Studies of the association between exophenotypic traits and the karyotype should account for a possible effect of sex and birth season on these parameters, reported for many rodents from laboratory colonies [15]. ANOVA with sex, birth seasons and karyotype as factors demonstrated highly statistically significant effect of the former two factors, but these results will be considered in detail in a forthcoming paper. Here, we present only the data combined according to sex and birth season and the F values for the karyotype effect (Table 3). It can bee seen from Table 3 that, irrespective of age, carriers of different chromosome 5 variants were similar in weight and body length, but had differ-

Table 2. Reproductive characteristics of the common voles homozygous and heterozygous for autosome 5 (at the bottom of the table, the results of ANOVA: factor A, female karyotype; factor B, male karyotype)

Parental karyotypes	Number of parental pairs	Mean reproductive output per pair	Mean time interval between litters, days	Mean litter size at birth (number of litters)	Death by age of 20 days, %*	Mean number of corpora lutea (number of females)	Embryonic death, %*
♀StSt × ♂StSt	23	1.87	56.5	4.14 (70)	25.52	4.69 (16)	10.7
♀StSt × ♂StA	12	2.17	54.7	4.44 (25)	20.72	4.67 (9)	21.4
♀StSt × ♂AA	3	2.70	50.4	5.13 (8)	19.51	4.40 (5)	9.1
♀StA × ♂StSt	19	1.71	67.5	3.40 (52)	14.12	4.60 (10)	30.4
♀StA × ♂StA	19	1.68	56.1	3.34 (53)	10.73	5.14 (7)	13.0
♀StA × ♂AA	4	1.10	47.3	2.18 (11)	25.00	5.40 (5)	18.5
♀AA × ♂StSt	4	0.50	79.8	1.75 (8)	28.57	5.33 (3)	50.0
♀AA × ♂StA	2	0.18	184.0	1.33 (3)	50.00	6.00 (1)	50.0
F_A (*d.f.*, *P*)		7.89 (1/77, 0.006)	0.10 (1/77, 0.755)	37.11 (1/222, 4×10^{-9})	0.10 (1/222, 0.769)	0.61 (1/48, 0.439)	0.83 (1/48, 0.366)
F_B (*d.f.*, *P*)		0.01 (1/77, 0.915)	6.51 (1/77, 0.013)	0.03 (1/222, 0.861)	6×10^{-5} (1/222, 0.994)	0.21 (1/48, 0.650)	0.08 (1/48, 0.776)

* The number of litters and the number of females for each cross variant are the same as in the previous column.

Table 3. Mean values of exophenotypic characteristics of common voles homozygous and heterozygous for chromosome pair 5

Characteristic		Karyotype (*n*)			*F* (*d.f.*; *P*)*
		StSt	StA	AA	
Body weight at age 3 days, g		3.2 (106)	3.1 (84)	3.0 (23)	0.66 (2/201; 0.516)
3-Month voles (age 89–95 days)	body weight, g	24.6 (215)	25.0 (144)	25.3 (31)	0.88 (2/378; 0.417)
	body length, mm	100.7 (215)	100.5 (144)	100.6 (31)	0.94 (2/378; 0.391)
	foot index	0.148 (215)	0.150 (144)	0.149 (31)	3.06 (2/378; 0.048)

* Values for the karyotype factor.

ent foot indices (at the 5% significance level). Note that body weight is closely associated with viability, particularly in the first days after birth: death risk is higher for low-weight pups (see, e.g., [23]). Absence of weight differences in 3-day pups with different karyotypes is in agreement with the fact that mortality of progeny of all crosses was similar in the early postnatal development. A small increase in foot index in heterozygotes and homozygotes for the acrocentric indicates that carriers of the acrocentric chromosome 5 tend to have slower growth, but a definite conclusion seems premature. Postnatal development in carriers of the minor variant of the polymorphic chromosome seems to proceed without apparent disturbances.

Table 4 lists the frequencies of chromosome aberrations in somatic cells of 80- to 100-day voles. The values of the three parameters studies were lower in heterozygous animals than in both heterozygotes. Only intergroup differences in gaps were highly significant. However, recently the evidence on the same nature of gaps and structural chromosome aberrations has been accumulating. It is very likely that both of these lesions are caused by two-strand DNA breaks, and thus they can be measured by a single index (see, e.g., [24, 25]). By this index, calculated from on the data given in Table 4, heterozygous and homozygous animals show a highly significant difference ($\chi^2 = 10.50$; *d.f.* = 2; $P = 0.005$). In other words, the common voles heterozygous for autosome 5 are characterized by higher stability of the genome, which may contribute to their selective advantage and promote maintenance of the inversion polymorphism. However, it is unlikely that this contribution is of primary importance for compensation for substantially reduced fertility, observed in carriers of acrocentric chromosome 5. Meiotic drive in favor of the acrocentric seems to be a more significant factor.

Segregation of the chromosome pair 5 was studied in 159 litters from crosses of four types (Table 5). In some litters (designated in the table a incomplete), some pups died by the time of karyotyping. We pooled the data on complete and incomplete litters, because the differences between them in frequencies of different karyotypes were statistically nonsignificant in all types of crosses. Table 5 shows that in the progeny of these

Table 4. Frequencies of chromosome aberrations in 80- to 100-day common voles homozygous and heterozygous for autosome 5

Karyotype	Number of animals	Number of cells	Mean number of cells, %		
			with aberrations	aneuploid and polyploid	with gaps
StSt	35	1750	1.31	0.34	2.00
StA	20	1000	0.70	0.10	0.60
AA	15	750	1.20	0.27	1.20
χ^2			2.24	1.47	9.21
P			0.326	0.480	0.010

Table 5. Segregation of polymorphic chromosome 5 in the common vole

Cross type	Litter type	Number of litters	Number of pups with karyotypes*			χ^2 (*d.f.*; *P*)**	χ^2 (*d.f.*; *P*)***
			StSt	StA	AA		
♀StA × ♂StA	Complete	20	11 (16)	33 (32)	20 (16)	5.80	1.20
	Incomplete	38	16 (14.5)	34 (29)	8 (14.5)	(2; 0.055)	(2; 0.549)
♀StSt × ♂StA	Complete	6	6 (9.5)	13 (9.5)	–	2.06	0.56
	Incomplete	21	23 (22.5)	22 (22.5)	–	(1; 0.151)	(1; 0.454)
♀StA × ♂StSt	Complete	17	18 (23)	28 (23)	–	1.23	11.67
	Incomplete	41	17 (29.5)	42 (29.5)	–	(1; 0.267)	(1; 0.0006)
♀StA × ♂AA	Complete	6	–	8 (8)	8 (8)	2.61	1.09
	Incomplete	10	–	1 (3.5)	6 (3.5)	(1; 0.106)	(1;0.296)
						Σ	14.52 (4; 0.006)

* The expected values are in parentheses.

** Test for homogeneity of complete and incomplete litters in homo- and heterokaryotype frequencies.

*** Test for correspondence of the expected and the observed frequencies of pups with different karyotypes.

crosses, the numbers of homozygotes and heterozygotes for the acrocentric mostly exceed the expected values, while the total χ^2 value indicates statistical significance of the effect. As a result, the total (summed over all variants) proportion of the acrocentric in the examined animals from the laboratory colony (0.42) exceeds the value expected with random segregation (0.38), particularly in complete litters (0.48 and 0.42, respectively). However, there may be doubts as to whether this effect is partly connected to the use of incomplete litters, in which selective elimination of the subtelocentric carriers could take place. This particularly concerns cross ♀StA × ♂StA, in which homogeneity of the distribution of homo- and heterokaryotypes in complete and incomplete litters is open to question ($P = 0.055$). However, in this case using exclusively complete litters would only increase significance of the total effect, i.e., nonrandom segregation of the subtelocentric and acrocentric variants of chromosome 5.

Deviation form Mendelian inheritance of heteromorphic homologs may result from a number of phenomena, occurring both at the prezygotic and the postsygotic stages of development [26, 27]. Apparently, in the common vole from our laboratory colony, two possible postzygotic mechanisms (selective embryonic and early postnatal death) did not affect transmission of the heteromorphic chromosome variants. Male prezygotic mechanisms include, for instance, selective mortality or, conversely, preferential participation in fertilization of gametes of a particular class. Such prezygotic selection of male gametes was reported for a number of rodents [28, 29]. However, in mammals meiotic drive in the narrow sense is most common. This mechanism is primarily associated with oogenesis in heterozygotes, when the element under drive with higher probability enters the egg cell than a polar body [30]. Very likely that this is exactly the case in the common vole: the most marked and highly significant drive of the acrocentric was observed when heterozygous females were crossed with male homozygous for the subtelocentric (Table 5). It may well be that in mammalian females, nonrandom segregation in meiosis I, associated with different numbers of centromeres in paired chromosome segments, is observed not only in Robertsonian heterozygotes [31], but also with heteromorphism for other chromosome rearrangements, involving the cen-

tromere, as is in the case of chromosome 5 in the common vole.

Thus, analysis of the material, obtained in the laboratory colony of the common vole, conforms to the assumption on balanced polymorphism for a pericentric inversion of chromosome 5. Two opposite forces are likely to contribute to the maintenance of this polymorphism in natural populations. Meiotic drive favoring the acrocentric chromosome variant (the first factor) must substantially compensate for reduced fertility of its carriers (the second factor) and promote the inversion polymorphism in populations of the common vole. Probably, there are other compensating factors in these populations. These may include, for instance, better physiological homeostasis in the heterozygotes, which is evidenced by the fact that these homozygotes exhibit a lower frequency of chromosome mutations in somatic cells, than both homozygotes. However, we have failed to reveal an association between growth parameters and karyotypes in the common vole.

It seems that the contribution of meiotic drive to the formation of intraspecies and intrapopulation genetic diversity is underestimated. In the common vole, precisely this mechanism may underlie interpopulation differences in the frequency of the acrocentric chromosome 5. As mentioned above, in some populations of the common vole, the acrocentric frequencies are by an order of magnitude higher than in the Urals populations [18, 19]. Since chromosome segregation in meiosis I is controlled by many loci [32], it cannot be excluded that under certain conditions (for instance, under isolation, as in highland Transcaucasia [18]), the concentration of segregation distorter alleles, promoting drive in favor of the acrocentric, is increased. These alleles are very common in the common vole populations, as evidenced by high frequencies of X-chromosome monosomy in females, previously recorded in Central Europe [33] and also observed in the Urals populations [34]. Apparently, meiotic drive in favor of chromosome mutations, reducing fitness of their carriers, is a powerful evolutionary force, making possible chromosome speciation based on structural transformations of the karyotype.

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