

Genomic Instability in the Bank Vole: Population-Ecological Aspects

E. A. Gileva, S. B. Rakitin, and M. I. Cheprakov

*Institute of Plant and Animal Ecology, Ural Division, Russian Academy of Sciences,
ul. Vos'mogo Marta 202, Yekaterinburg, 620144 Russia; e-mail: e.a.gileva@ipae.uran.ru*

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Abstract—Chromosome aberration frequency in relation to population dynamics and demographic parameters was studied for six years in a bank vole population in the Middle Urals. The frequencies of structural chromosome aberrations, chromatid gaps, aneuploidy, and polyploidy in males and females and in animals of different ages did not differ significantly. In the breeding period, the frequencies of structural aberrations and changes in chromosome number increased in the somatic cells of voles. Highly significant differences between the levels of chromosome instability in different years manifested a tendency toward a negative correlation with population size.

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The role of genetic processes in the population cycle, which received much attention in the period from the 1960s to the 1980s, has not been conclusively explained. According to the majority of authors who have analyzed electrophoretic variants of proteins in voles and lemmings, changes in population size are accompanied by fluctuations of allele frequencies, but the existence of a cause-and-effect relationship between these phenomena has not been proved (Tamarin and Krebs, 1969; Gaines and Wittam, 1980; Kuryshv and Chernyavskii, 1988). However, genetic processes in natural populations are by no means limited to variation in allele frequencies. Of considerable interest is the dynamics of chromosome aberration frequency in somatic cells, primarily in the bone marrow, in relation to the population cycle. It is known that somatic mutations are an important mechanism providing for the formation of specific immunity, and the bone marrow of mammals is a major component of the immune system, as it produces stem cells that are progenitors of lymphocytes. In addition, the study of chromosome instability in bone marrow cells provides a basis for characterizing the mutation process in general, as the frequency of mutation events detected under a light microscope in somatic cells closely correlates with the frequency of point mutations and other changes in the genome, including those in the germinative tissue. The cytogenetic approach has not been consistently used in studies on mammals from cyclic populations. The only relevant publication at hand is that by Dmitriev et al. (1997), who assessed the frequency of chromosome aberrations in voles of the genus *Clethrionomys* at different values of relative animal abundance. In 1999, we

initiated research on the dynamics of chromosome instability in bank voles from a population that inhabits the southern taiga subzone and is characterized by considerable fluctuations of abundance. The results obtained in the course of six-year observations are concisely described in this paper.

MATERIAL AND METHODS

Studies were performed with the population of bank voles (*Clethrionomys glareolus* Schreber, 1780) living near the village of Shigaev, Shalinskii raion of Sverdlovsk oblast (57°15' N, 58°44' E). Anthropogenic load on this area is at the background level for the Urals. Animals were captured in the area (approximately 12 ha) located in a mature herbaceous–green moss larch–spruce forest with birch and aspen. The forest is bordered by a small river on one side and adjoins a mixed herb–grass meadow on the other side. No less than 50 live traps installed in line were examined three or four times daily, in the daytime. Animal abundance was estimated from the capture rate per 100 trap–days over the first two days, as the catch was sometimes greater on the second than on the first day. A total of 344 voles were included in the study.

The reproductive status of voles was estimated from the state of reproductive organs. Pregnancy was diagnosed by the presence of yellow bodies in the ovaries and of placental spots and embryos in the uterus. In males, the weight of testes and the filling of epididymides were determined. If testes weight was between 50 and 150 mg, spermatogenesis was additionally evaluated by analyzing smears under a microscope.

Animals classified as reproductive were as follows: pregnant and parous females; males with testes weighing more than 50 mg, well-developed epididymides, and active spermatogenesis; and males with epididymides and testes deflated after breeding. Animal age was determined from the degree of root development in the second upper molar (M^2). We also used the scale of age classes proposed by Olenev (1989), which is based on regular changes in the pattern of M^2 surface concealed in the alveola and in the root index (the ratio of root length to tooth length).

Metaphase chromosome preparations of bone marrow cells were stained with azure–eosin and studied under a microscope to count structural chromosome aberrations, chromatid gaps, and the numbers of aneuploid and polyploid cells. As a rule, 25–100 cells (in some cases, up to 250 cells) per animal were analyzed. True breaks were differentiated from gaps by conventional criteria (in the former, separated parts were displaced relative to the chromatid axis or the distance between them was greater than chromatid width). The results were processed statistically using the Statistica program package, license no. AXXR003A622407FAN8.

RESULTS AND DISCUSSION

The animals were trapped three times per field season (in May, late June, and September) in 1999 and 2000, two times (in July and September) in 2001, and only once a season (in late July) in the following three years, because no seasonal variation in the number of aberrant cells was revealed (Rakitin, 2001). In this study, we consider only summer samples, which are most representative. Table 1 shows the frequencies of three types of chromosome aberrations in voles differing in sex, age, and reproductive status. Our purpose is to analyze probable correlations of the levels of genomic instability with these parameters and with fluctuations of animal abundance. Let us first consider the frequency of chromatid gaps. It is still unclear whether these gaps appear as a result of chromosome breakage, like true structural aberrations of chromosomes. Recent data provide evidence for similarity of mechanisms accounting for true chromosome breaks and gaps (Harvey et al., 1997) and for parallelism of their frequencies revealed by comparisons within and between populations at different levels of anthropogenic pressure (Gileva, 2002). Today, most specialists in cytogenetics consider that chromatid gaps should be included in chromosome aberration analysis (Paz-y-Mino et al., 2002).

As follows from Table 1, the average frequencies of chromosome aberrations in males and females were similar. The absence of sex-related differences in this parameter was confirmed by the χ^2 test. Its values were calculated separately for individual samples corresponding to different combinations of values (grades)

of the aforementioned factors, and the results were summed up. We considered mainly those samples in which the expected values were no less than 4 (Glotov et al., 1982), with only one exception (expected value 3.5). No significant difference between males and females was revealed in any of the pairwise comparisons ($\chi^2 = 0.00$ – 2.34 , $df = 1$, $P = 0.126$ – 1.000) or upon summing up χ^2 values for each of the tree cytogenetic indices ($\chi^2 = 2.08$ – 5.75 , $df = 4$ – 11 , $P = 0.721$ – 0.964), which allowed us to pool the data on males and females for further analysis. It should be noted that, although some authors described sex-related differences by in the frequencies of cytogenetic disturbances in laboratory rodents (e.g., Mavourmin et al., 1990), such differences in wild and synanthropic rodents are usually absent or insignificant (Gileva, 1997). In some instances, however, the frequency of chromosome aberrations in males may be higher (Polyavina, 2002).

The dependence of the level of chromosome instability on animal age was estimated in reproductive voles using three-way log-linear analysis with factors “year,” “age,” and “frequency of cells with chromosome aberrations.” The analysis was performed with pooled data on males and females (overwintered animals and reproductive young of the year) over the period from 1999 to 2003, as no reproductive young of the year were caught in 2004 (Table 1). Nonreproductive animals were not considered, because they were represented by only one age group (young of the year). None of the three indices of chromosome instability showed any significant correlation with age: G -test values were 1.481 for structural aberrations ($df = 5$, $P = 0.915$), 6.289 for aneuploid and polyploid cells ($df = 5$, $P = 0.279$), and 8.064 for chromatid gaps ($df = 5$, $P = 0.153$).

Thus, the bank vole did not exhibit any significant age-dependent increase in the frequency of chromosome aberrations similar to that described in laboratory rodents and man (Uryvaeva et al., 1999; Lezhava, 2001). Such an increase is not always observed for structural aberrations (Bender et al., 1989; Tucker et al., 1999), but the frequency of aneuploid cells usually increases with age (Bocharov and Vilkina, 1966; Xiao et al., 1998). It should be noted, however, that this effect often manifests itself only at an old (senile) age. Such was the case with *Microtus arvalis* voles from our laboratory colony: a statistically significant increase in the level of chromosome instability was revealed only in voles aged 500–600 days (Rakitin, 2002). In this study, most of the overwintered bank voles were less than one year of age, and the effect of aging in this group was manifested weakly, if at all. However, the frequencies of all types of cytogenetic disturbances, especially that of aneuploid and polyploid cells, tended to be higher in overwintered (older) animals than in reproductive young of the year. However, differences between these groups lacked statistical significance, and this formally allowed us to combine them for analyzing the relation-

Table 1. Chromosome aberration frequencies and values of the adrenal index in bank voles differing in sex, age, and reproductive status

Year	Sex	Reproductive status	Age group	Number of animals	Number of cells	Average frequencies of aberrations, %			Adrenal index, $n \times 10^{-3}$
						structural aberrations	aneuploid and polyploid cells	chromatid gaps	
1999	Males	Reproductive	Overwintered	6	300	0.67	1.67	2.00	0.257
		Nonreproductive	Young of the year	24	600	0.50	1.00	1.00	0.214
	Females	Reproductive	Overwintered	6	300	1.67	2.33	1.33	0.434
		Nonreproductive	Young of the year	2	250	1.60	1.20	2.00	0.350
2000	Males	Reproductive	Overwintered	8	325	2.46	1.85	1.23	0.248
		Nonreproductive	Young of the year	10	500	0.80	0.40	2.60	0.193
		Reproductive	Overwintered	3	150	0.67	2.00	2.00	0.530
	Females	Reproductive	Overwintered	3	150	0.67	2.00	2.00	0.530
		Nonreproductive	Young of the year	1	100	1.00	1.00	5.00	0.231
		Reproductive	Overwintered	4	100	3.00	2.00	4.00	0.373
2001	Males	Reproductive	Overwintered	15	400	3.00	1.00	3.00	0.176
		Nonreproductive	Young of the year	34	850	2.47	0.82	3.29	0.202
	Females	Reproductive	Overwintered	4	100	3.00	2.00	4.00	0.373
		Nonreproductive	Young of the year	27	675	2.07	1.48	3.11	0.218
2002	Males	Reproductive	Overwintered	3	225	3.56	1.33	2.67	0.170
		Nonreproductive	Young of the year	10	250	2.40	0.00	3.20	0.239
		Reproductive	Overwintered	5	250	2.40	1.60	3.60	0.359
	Females	Reproductive	Overwintered	5	250	2.40	1.60	3.60	0.359
		Nonreproductive	Young of the year	9	300	2.00	0.33	2.33	0.236
		Reproductive	Overwintered	1	100	3.00	0.00	3.00	0.448
2003	Males	Reproductive	Overwintered	5	250	4.44	1.60	6.40	0.266
		Nonreproductive	Young of the year	9	325	2.77	0.62	3.38	0.227
		Reproductive	Overwintered	1	100	3.00	0.00	3.00	0.448
	Females	Reproductive	Overwintered	1	100	3.00	0.00	3.00	0.448
		Nonreproductive	Young of the year	9	300	1.67	0.67	4.67	0.220
		Reproductive	Overwintered	12	450	1.11	0.44	1.78	0.231
2004	Males	Reproductive	Overwintered	12	450	1.11	0.44	1.78	0.231
		Nonreproductive	Young of the year	23	650	0.77	0.62	1.54	0.244
	Females	Reproductive	Overwintered	12	450	1.56	0.67	2.00	0.353
		Nonreproductive	Young of the year	15	550	0.91	0.73	1.82	0.239

ship between the reproductive status of animals and chromosome instability.

Table 2 shows data on chromosome aberration frequencies averaged with regard to animal sex and age. The results of log-linear analysis with factors “year of capture,” “reproductive status,” and “frequency of cells with chromosome aberrations” are shown in Table 3. It can be seen that, throughout the period of observations, the frequencies of cells with structural chromosome

aberrations were higher in reproductive voles (overwintered animals + reproductive young of the year) than in nonreproductive young of the year by a factor of 1.3–2 (in 1999, by a factor of 4), with these differences being significant at a 5.3% level. A similar tendency was revealed for the frequency of aneuploid and polyploid cells, but its statistical significance did not reach the 5% level, although approached it. The frequencies of cells with chromatid gaps in reproductive and nonreproductive animals were similar.

Table 2. Population parameters and frequencies of chromosome aberrations averaged with respect to animal sex and age in the bank vole population

Year of capture	Relative abundance, ind./100 trap-days	Proportion of reproductive young of the year, %	Number of karyotyped animals*	Number of cells*	Average frequencies of aberrations, %					
					structural aberrations		aneuploid and polyploid cells		chromatid gaps	
					reproductive	nonreproductive	reproductive	nonreproductive	reproductive	nonreproductive
1999	54.0	2.6	14/55	850/1375	1.29	0.36	1.76	0.87	1.76	1.38
2000	12.6	74.6	49/11	1425/600	1.61	0.83	1.05	0.50	2.04	3.00
2001	37.2	1.6	20/61	750/1525	2.93	2.30	1.07	1.11	2.80	3.21
2002	6.8	38.7	20/19	800/550	2.88	2.18	1.25	0.18	2.50	2.73
2003	17.5	33.3	15/18	875/625	3.31	2.24	0.91	0.64	3.89	4.00
2004	69.0	0.0	24/38	900/1200	1.33	0.83	0.56	0.67	1.89	1.67
					$R_S = 0.93; P = 0.008$		$R_S = 0.09; P = 0.872$		$R_S = 0.94; P = 0.005$	

* Values in the numerator and denominator show sample sizes for reproductive and nonreproductive animals, respectively.

Table 3. Results of three-way log-linear analysis of the influence of reproductive status (factor *B*) and year of capture (factor *C*) on chromosome aberration frequency (factor *A*)

Chromosome aberrations	Factor	<i>G</i> test	<i>df</i>	<i>P</i> *
Structural aberrations (<i>A</i>)	Reproductive status (<i>B</i>)	12.46	6	0.053
	Year of capture (<i>C</i>)	49.75	10	0.000001
Aneuploidy and polyploidy (<i>A</i>)	Reproductive status (<i>B</i>)	11.05	6	0.087
	Year of capture (<i>C</i>)	13.13	10	0.216
Chromatid gaps (<i>A</i>)	Reproductive status (<i>B</i>)	2.68	6	0.850
	Year of capture (<i>C</i>)	31.78	10	0.0004

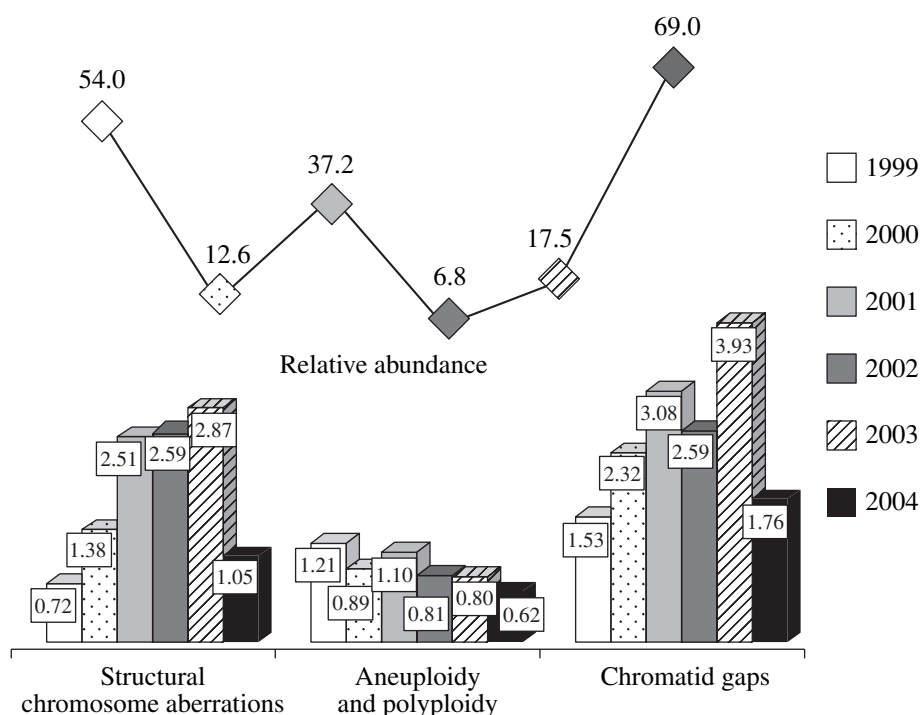
* Significance of relationship.

In the breeding period, chromosome instability in males and females increased, which could be due to increasing hormonal activity. It is known that estrogens induce both chromosomal mutations and disturbances of ploidy (Roy and Liehr, 1999; Liehr, 2000). Moreover, sex steroids (in particular, testosterone and estrogen) act as immunosuppressors (Lokhmiller and Koshkin, 1999), and inhibited activity of the immune system, which is involved in the maintenance of genetic homeostasis, may provide for the growth of genomic instability.

Differences between the frequencies of structural chromosome aberrations in different years were highly significant (Table 3), in contrast to the situation with aneuploid and polyploid cells, with the frequencies of such aberrations and chromatid gaps obviously correlating in both reproductive animals ($R_S = 1.00$, $df = 6$, $P = 0.00$) and nonreproductive animals ($R_S = 0.84$, $df = 6$, $P = 0.04$). This is evidence that chromatid gaps are valuable markers of mutagenesis. The dynamics of cytogenetic parameters by years in the pooled sample (irrespective of sex, age, and reproductive status) is shown in the figure. During the observation period, the

population passed through its complete cycle, including two peaks of animal abundance. Differences between the frequencies of structural chromosome aberrations and chromatid gaps recorded in different years were highly significant and tended to negatively correlate with relative animal abundance, irrespective of reproductive status ($R_S = -0.66$, $P = 0.156$ and $R_S = -0.49$, $P = 0.329$, respectively), in contrast to the frequency of aneuploid and polyploid cells ($R_S = -0.03$, $P = 0.957$) (see Table 3). In the years of population peak (1999 and 2004), the frequency of structural aberrations was three to four times lower than in the years of population decline and growth. The reliability of this tendency needs verification in further studies performed in the same locality over several population cycles.

Let us consider the causes of chronographic variation in the level of genomic instability in bank voles from Shigaevo. We propose three different scenarios which, however, are not mutually exclusive, because the mutation process is controlled by a number of factors.



Average frequency of cells with chromosome aberrations (%) and relative abundance (ind./100 trap-days) of bank voles between 1999 and 2004.

(1) The coefficient of correlation (R_s) between two parameters of chromosome instability (the frequencies of structural aberrations and chromatid gaps) and relative animal abundance has fairly high values, and the fact that their difference from zero lacks statistical significance may be explained by an insufficient period of observations. During this period, animal abundance varied by a factor of no more than 10, although this parameter in the bank vole may vary by factors of 80–100 (Bashenina et al., 1981; Zhigalski and Kshnyasev, 2000). Nevertheless, the statistically significant coefficient of correlation between animal abundance and the proportion of reproductive young of the year ($R_s = -0.89$, $P = 0.019$) indicates that density-dependent control mechanisms operated in the population during the study period. In such situations, hydrocarbon and lipid metabolism in rodents and their endocrine status change significantly, which may be attributed to stress (Evsikov et al., 1999; Chernyavskii et al., 2003). Metabolic variations during the population cycle have a certain influence on the level of genomic instability. In particular, stress hormones in rodents may have a clastogenic effect (Skorova et al., 1986). However, the adrenal index in bank voles (males and nonreproductive females) showed no significant correlation with animal abundance ($R_s = -0.03$, $P = 0.957$) or the frequencies of structural chromosome aberrations and chromatid gaps ($R_s = 0.174$, $df = 6$, $P = 0.742$ and $R_s = -0.030$, $df = 6$, $P = 0.956$, respectively) but negatively correlated with the total frequency of aneuploid and polyploid cells

($R_s = -0.956$, $df = 6$, $P = 0.003$). These data cast doubt on the existence of the relationship between population stress and genomic instability or on the validity of the adrenal index as an indicator of the role of endocrine factors in the population cycle.

(2) It cannot be excluded that the genetic component contributes to variation in the level of genomic instability in bank voles from Shigaevo. Fluctuations of allele frequencies accompanying fluctuations of population size in different species, including *Clethrionomys* (Kuryshv and Chernyavskii, 1988), could affect genes controlling the spontaneous mutation process (Difilipantonio et al., 2000; Morris, 2002) and provide for the accumulation of highly active mutator alleles in the population. It should be emphasized, however, that our data give no reason to regard probable genetic shifts as the cause of change in population size.

(3) It is quite probable that the increase of chromosome instability from year to year was caused by the spread of some infection agents. Such agents (in the first place, viruses) are known to have a distinct mutagenic effect (Buzhievskaya, 1984). This effect is well manifested in the bank vole, and bone marrow cells with numerous chromosome aberrations serve as a marker of persisting viral infections (Gileva et al., 2001). In *C. glareolus* from Shigaevo, such cells were absent in 1999, 2000, and 2004 but occurred with a frequency of 0.07–0.13% between 2001 and 2003, when genomic instability obviously increased.

Thus, the results of our six-year observations on the bank vole population provide a basis for the following conclusions:

(1) The frequencies of structural chromosome aberrations, chromatid gaps, and aneuploid and polyploid cells in male and female bank voles do not differ significantly.

(2) The level of chromosome instability in the natural bank vole population (at least, in its reproductive part) shows no statistically significant correlation with animal age.

(3) In the breeding period, the frequencies of structural aberrations and, probably, aneuploid and polyploid cells in bank voles increase.

(4) Highly significant differences between the levels of chromosomal instability recorded in different years were observed in the cyclic bank vole population throughout the six-year observation period. These differences manifest a tendency toward negative correlation with population size.

The last two conclusions need verification in further studied.

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