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GENERAL BIOLOGY

Variability of the Chromosome 1 HSR of "Asian" Type in the Wild Mouse (*Mus musculus*)

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In chromosomes, homogeneously staining regions (HSRs) are a most interesting cytogenetic phenomenon, which is a consequence of genome instability caused by multiplication (multiple repeats) of genes. Many reports suggest that HSRs are related to tumor cell degeneration and tumor cell resistance to chemical preparations [1]. HSRs are essentially a visual cytological manifestation of tandem repeats, which is similar to the expansion of DNA repeats that are the cause of at least 50 human diseases [2]. These mutations are referred to as the dynamic ones because of rapid and abrupt changes in the size of repeats. Of special interest are the rarest cases of HSRs in the karyotypes of the phenotypically normal animals, rather than HSRs in tissue cultures or tumors. This study describes variation of the HSR-carrying aberrant chromosome 1 in house mice from the natural populations (both synanthropic and wild).

By analyzing abundant natural material, this study has given an insight into the geography, frequency, and morphological variation of aberrant chromosome 1 in different house mouse subspecies, as well as the effect of this aberration on the viability of homo- and heterozygous carriers, and has led to the discovery of a novel rare variant of the aberration. The phenomenon of abnormal chromosome 1 in the house mouse is undoubtedly promising as a model for studying dynamic mutations and human diseases related with them.

In the house mouse, HSRs are a cytogenetic manifestation of DNA amplification, namely, the "high-copy" version of the *Sp 100* gene, which is, evolutionarily, a relatively recent acquisition specific for *M. musculus* [3]. The well-known "European" variant of the aberrant chromosome 1 carries one HSR region. This variant is characteristic of the *M. m. domesticus* subspecies group. It was identified in mice from Switzerland, Germany, Italy, Spain, and Tunis; in Russia, it was found only near Astrakhan. If chromosome 1 contains 60–200 copies of the *Sp 100* gene, this is a normal variant. When the copy number of the *Sp 100* gene exceeds 200, chromosome 1 is regarded as aberrant one [3]. A single HSR insertion may increase the chromosome 1 size by 6–30% compared to the normal homologue [4].

An aberrant chromosome 1 with two HSR insertions is characteristic of the *M. m. musculus* subspecies group (Fig. 1). That is the "Asian" variant, which appeared due to a paracentric inversion in the "European" type aberrant chromosome 1 [4–7]. According to our data, two insertions enlarge chromosome 1 by 30–70%. We described this aberrant variant in mice from Primorskii krai [8], and the same variant was also identified in *M. musculus* in the area from Sweden to East Asia [7–10].

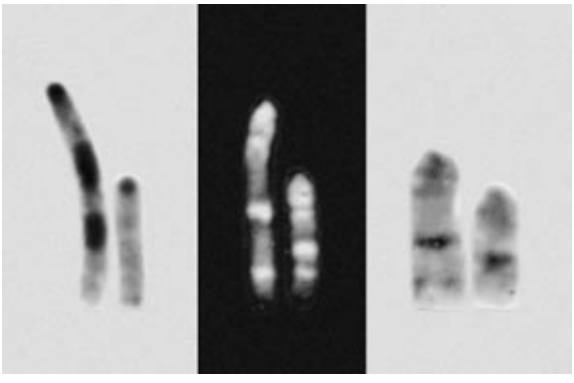

Fig. 1. "Asian" type chromosome 1 (aberrant and normal homologues) in the house mouse as determined using various banding methods: (a) C-banding; (b) Q-H-banding; (c) G-banding.

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The material of this study was at least 700 karyotypes of house mice caught in the area from Moldova to Kamchatka. The aberrant chromosome 1 was identified in 34 animals. With respect to the number of insertions, these were the "Asian" type chromosomes 1 in all mice. At the same time, the "Asian" variant was rather heterogeneous.

The chromosome preparations were analyzed using C-, G-, and fluorescent Q-H-banding. In different years, different techniques were used. The routine of C-, Q-H-, and G-banding patterns are shown in Fig. 1.

We divided all mice into three groups with bright, moderate, and dull intensity of HSR C-banding, respectively. Each HSR region varied also in size (Figs. 1a, 2a). These variations were observed even in mice of the same population. The distal and proximal HSR regions consisted sometimes of one to three adjacent smaller bands ([8] and the latest data). That is presumably the cause of variations of two HSRs in relative size, along with the copy number of the repeats in general. The study [9] yielded further evidence that several HSR variants differing in the size of distal and proximal regions exist. Deletion, duplication, and amplification, as well as unequal crossing-over, were also reported to occur within HSRs [7]. Thus, mutations that lead to arising of independent new aberrant variants seem to appear in the original variants of the aberrant chromosome 1. These rapid changes are typical of dynamic mutations.

Only 4 out of 34 studied HSR carriers were homozygous for the aberrant chromosome. The ratio of homo- to heterozygous HSR carriers in the Southern Urals was similar (5 out of 33) [11]. Among the "European" type HSR carriers ($n = 39$), the ratio of homo- to heterozygous ones was quite different: 28 homozygotes and 11 heterozygotes. Note, in addition, the high frequency of the aberrant chromosome carriers in the sample: 39 out of 44 examined animals [4], i.e., the viability of the carriers of the "European" variant is not decreased compared to the normal animals. Nor does the homozygous state of the "European" aberrant chromosome reduce the viability of the carriers. When compared with our data (34 carriers of the "Asian" aberrant chromosome 1 out of 700 studied animals and as few as 4 homozygotes versus 30 heterozygotes), the above evidence suggests that the "Asian" variant of the aberrant chromosome reduces the carrier's viability, and its homozygous state even more so. This is similar to the well-known anticipation phenomenon in humans (when the disease becomes more severe with increasing repeat length in successive generations) [12].

We identified an unusual variant of the aberrant chromosome 1 in eastern Kazakhstan (the Ayagus River valley; four animals). Note that these mice were caught in an open station and, hence, they are typical, indigenous wild *M. m. wagneri* of Central Asia in both morphology and karyotype [13, 14]. In these aberrant chromosomes 1, two bright C-bands typical of the "Asian" type were identified (Fig. 2a). However, G-banding of these aberrant chromosomes revealed a pattern atypical for HSRs. The regions corresponding to HSRs were much darker, and noticeable banding was observed (Fig. 2b). Comparison of G-banding of these and typical HSRs alone (Fig. 1c) suggests that the aberrant chromosomes of the Ayagus variant do not carry "traditional" HSRs at all.

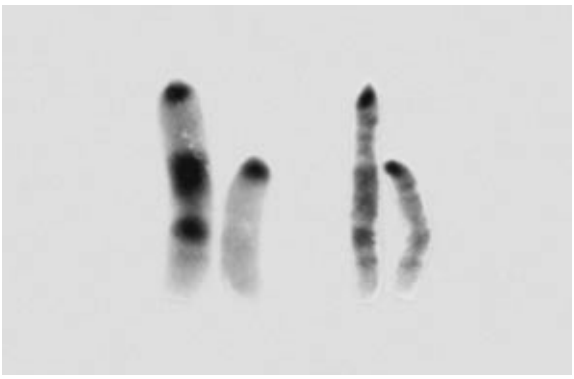

Fig. 2. The rare variant of chromosome 1 (aberrant and normal homologues) in the house mouse from eastern Kazakhstan (the Ayagus River valley): (a) C-banding; (b) G-banding.

In tumor cells and cell strains, HSRs resistant to chemical substances originate from different regions of the mammalian genome [15]. Thus, although rearrangement in the house mouse chromosome 1 is currently assumed to occur only in the *Sp-100* gene, some other genes may also be amplified in those house mouse populations where uncommon variants of HSRs have been identified. The unusual variant of the aberrant chromosome 1 in mice from the Ayagus River valley is undoubtedly interesting for further studies. In addition, this finding disproves the notion of Agulnik et al. [10] that the "Asian" variant is strictly specific for *M. m. musculus* and its hybrids. Note that the mice from the Ayagus population are typical wild *M. m. wagneri* not involved into hybridization. The novel, rare Ayagus variant is likely to have appeared because this locality is close to the Semipalatinsk nuclear test grounds.

We believe that, knowing the geographical distribution of the aberrant chromosome 1 and its variants in natural and synanthropic populations of the house mouse, new materials on this phenomenon can be obtained and used as promising models for studying diseases related to dynamic mutations.

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