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GENERAL GENETICS

Genetic Analysis of the Predisposition to Audiogenic Seizure Fits in Krushinsky–Molodkina Rat Strain

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Abstract—The expression of audiogenic seizure fits has been studied in F_1 hybrids between audiogenic seizure–prone Krushinsky–Molodkina rat strain and Wistar rats not prone to audiogenic seizures, as well as in two backcross generations. Only 10% of F_1 hybrids exhibit audiogenic seizure fits, whereas the frequency of this character in two generations of their backcrosses with Krushinsky–Molodkina rats is about 50%. A digenic model with incomplete penetrance has been put forward to explain the control of audiogenic seizure fits. This model fits the data obtained: the theoretically expected distributions of the character in offsprings of different crosses do not differ significantly from those observed in experiments. The model explains why the distribution of the character is the same in the first and second backcross offsprings.

INTRODUCTION

Audiogenic seizure fits develop in response to a loud sound. A fit consists of the phases of motor excitation, clonic seizures of the extremities and the body, and tonic extension of the entire body musculature. This type of seizure fits is classified as reflex epilepsy and is observed almost exclusively in rodents [1], including laboratory animals (mice and rats).

No special selection for audiogenic seizures has ever been performed in laboratory mice. Nevertheless, there are strains highly prone to audiogenic seizure fits [1, 2]. Strain DBA/2 is the best known among them. Experiments with the use of a set of 23 recombinant inbred strains obtained from parental strains DBA/2J and C57BL/6J have demonstrated that three genes control audiogenic seizure fits [3]. One of them, *Asp-1* (*audiogenic seizure prone*), is located between loci *Ah* and *D12Nyul* in chromosome 12; another one, *Asp-2*, no farther than 8 cM distal to locus *brown* (*b*) in chromosome 4. The third gene, *Asp-3*, is linked to locus *Mtv-1* in chromosome 7. These genes account for the largest part of the genetic variation of the character. In addition, it has been found that genomic imprinting affects the genetic predisposition to audiogenic seizure fits in these mice. This complicates genetic analysis, because the expression of the character strongly depends on both nonallelic interactions and the origin of the allele (maternal or paternal).

Audiogenic seizures have also been observed in rats. They are expressed most strongly in adult rats, in contrast to DBA/2J mice, where the seizures only occur within a narrow age range (between the 16th and 40th days of life). In rats, no genes responsible for this character have been mapped. It is unknown whether mice and rats differ from each other in the genetic control of audiogenic seizure fits.

Rats are a better object for studying this character than mice. First, their brain is larger, which makes it possible, e.g., to analyze the order of the involvement of different cerebral structures into a seizure fit [4–7]. Second, rats, in contrast to mice, have been selected for the predisposition to audiogenic seizure fits, and several seizure-prone strains have been obtained [8–10]. These are, for instance, genetic epilepsy prone strains *GEPR3* and *GEPR9* obtained from the outbred strain Sprague-Dowley [9] in the University of Arizona (United States) in the late 1950s, strains WAR and KM (Krushinsky–Molodkina) selected from outbred Wistar rats [10, 11], and the well-known outbred strain Long–Evans [12].

We did not find any published data on the mode of inheritance of the predisposition to audiogenic seizure fits in GEPR3 or GEPR9 rats; however, the existence of these strain, with GEPR9 being characterized by more intense seizures than GEPR-3, indicates that the genetic control of this character is complicated [13].

The breeding of WAR rats [14] was accompanied by rapid changes in the character in response to selection. Between generations 3 and 17 of selection, the mean intensity of seizure fits (on an arbitrary point scale) increased from 37.13 to 83.06 s, and their initial latent period decreased from 22.82 to 7.84 s. This indicated an additive control of the character and a weak contribution of gene interaction.

Audiogenic seizures in KM rats have also been studied in detail. Krushinsky and coworkers began selection aimed at creating this strain as early as in 1947 [11]. In the 1980s, the strain was transferred into the inbred state [8]. At present, almost all KM rats respond to

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sound by intense seizure fits, and this strain is used as a model for studying seizures.

Physiological characteristics of the brain of KM rats have been studied, and some morphological and physiological specificities have been found [8, 15, 16].

The analysis of the inheritance of audiogenic seizure fits in KM rats yielded contradictory results. According to Krushinsky [11], the predisposition to seizures is inherited as an incompletely dominant character, whereas the results obtained by Elkin [17] suggest a monogenic recessive inheritance. The study by Romanova [18, 19] was one of the few special works on the inheritance of the predisposition to audiogenic seizure traits in KM rats. According to the results of these experiments, the increased sensitivity to sound is controlled by a polygenic system the genes of which have an additive effect. The results of diallelic crosses have shown that these gene are recessive. Note that the possible difference in penetrance between the genetic elements responsible for audiogenic seizure fits has never been touched on, although this difference may play a substantial role in the phenotypic expression of this character due to its polygenic inheritance.

We performed the genetic analysis of the sensitivity to sound in the offspring of crosses between two contrasting strains, KM and Wistar. Our data allowed us to put forward a hypothesis on the mode of inheritance of this complex physiological character. In contrast to previous studies, inbred KM rats and sound-insensitive Wistar rats were used for crossing.

MATERIALS AND METHODS

Strains. We used two rat strains. Strain KM, with a background of 40 generations of inbred selection, is highly inbred and, probably, homozygous for all genes predisposing to seizures. Almost all KM rats exhibit audiogenic fits of the maximum intensity (tonic seizures with a short latent period). Strain Wistar is outbred. Only 25–30% of Wistar rats are prone to weak audiogenic fits (usually, either motor excitation or clonic seizures) [20].

Estimation of the predisposition to audiogenic seizure fits. To estimate the predisposition to audiogenic motor excitation and seizures, we placed the animals into a special chamber and exposed to 100-dB sound for 1.5 min according to the standard method [11].

To estimate the predisposition to audiogenic seizures, we used a scale of intensity that somewhat differed from the traditional scale [11]. The points of this scale corresponded to the following intensities of seizures:

0, no signs of audiogenic motor excitation or seizures;

1, motor excitation (one or two excitation waves without seizures);

2, clonic seizures; and

3, tonic seizures.

Types of crosses. We obtained offsprings of the following types of reciprocal crosses.

(1) Wistar × KM. A random sample of Wistar rats was obtained from the Stolbovaya animal farm. From this sample, we selected animals that did not respond to the audiogenic stimulus (point 0 response) upon three exposures. From strain KM, we selected animals with the strongest predisposition to audiogenic fits (point 3 on our scale of intensity). Eleven crosses yielded 97 F_1 hybrids (44 males and 53 females).

(2) We selected sound-insensitive F_1 hybrids and crossed them with highly sensitive KM rats. A total of 28 crosses yielded 235 B_1 offspring (112 males and 123 females).

(3) We selected sound-insensitive B_1 rats and crossed them with highly sensitive KM rats. A total of 19 crosses yielded 118 B_2 offspring (54 males and 64 females).

Statistical treatment. The model was tested by comparing the empirical distribution of the offsprings of crosses with theoretically expected distributions with the use of the χ^2 test. The penetrances of different genotypes were estimated using the maximum likelihood method. The significance of differences in the segregation of the offsprings of different crosses was estimated using Fisher's *F* test.

RESULTS AND DISCUSSION

We estimated the intensity of seizure fits by a point scale. However, the points were not a quantitative measure of the physiological response; they are used to designate qualitatively different responses. Therefore, the predisposition to audiogenic seizure fits estimated by the intensity of seizures was a qualitative character. Extreme expressions of this character are the absence of response (point 0 on the intensity scale) and tonic seizure fits (point 3). The motor response is considered to result from the spread of a seizure neuronal discharge onto the cerebral regions responsible for locomotor reactions of running [21]; hence, intermediate phenotypes (intensity points 1 and 2) may be combined into a single phenotype. Thus, in the subsequent genetic analysis, we used a character with three phenotypic gradations: rats without a detectable response to sound (point 0) were taken to have phenotype I; rats that exhibited motor excitation or clonic seizures (point 1 or point 2), phenotype II; and rats that exhibited tonic seizure fits (point 3), phenotype III. Note that the classification of audiogenic seizure fits used in our study differed from that used by other authors [8].

Table 1 shows the numbers of three phenotypes in the offsprings of different crosses.

As seen from these data, the proportion of rats resistant to sound among F_1 hybrids was significantly higher than their proportion among backcrosses ($F = 45.7$, $F = 39.3$, $P < 0.01$). In addition, the proportions of rats with

Table 1. The numbers of animals with different phenotypes in the F_1 generation and two backcross generations (B_1 and B_2)

Type of cross	Intensity of fits, points	Number of animals	Percentage	Phenotype	Percentage
F_1	0	44	45.36	I	45.36
	1	6	6.19	II	44.33
	2	37	38.14		
	3	10	10.31	III	10.31
Total		97	100		100
B_1	0	25	10.6	I	10.6**
	1	8	3.4	II	42.6
	2	92	39.2		
	3	110	46.8	III	46.8**
Total		235	100		100
B_2	0	11	9.3	I	9.3**
	1	1	0.85	II	34.74
	2	40	33.89		
	3	66	55.96	III	55.96**
Total		118	100		100

** Significant difference from F_1 ($P < 0.01$).

the strongest response to sound (tonic seizure fits) in the first and second backcross generations also significantly differed from this proportion in F_1 ($F = 50.07$, $F = 53.2$, $P < 0.01$). There was no significant differences between the two backcross generations. This phenotypic segregation of the offsprings of different crosses cannot be approximated by a model where the character is controlled by alleles of a single locus. Therefore, we assumed digenic control of the character as a working model.

Digenic Model

Let us assume that the resistance and sensitivity to sound depend on two genes (*A* and *T*). Let recessive alleles control sensitivity to the auditory signal and dominant alleles, resistance to it. The genotype entirely consisting of recessive alleles (*aatt*) determines the highest sensitivity to seizures (phenotype III), and that entirely consisting of dominant alleles (*AATT*), the highest resistance (phenotype I).

Let each dominant allele decrease the predisposition to fits. Then, the phenotype of an individual is determined by the numbers of dominant and recessive alleles of both genes. In the most general case, when we do not predetermine the dominance of on allele over the other, each genotype may yield any of the three phenotypes at a certain probability. To describe this model, we should introduce 18 parameters of penetrance (two parameters for each of the nine digenic phenotypes) whose estimation would require too many empirical data. To simplify the model, we introduced the following restrictions:

the genotypes with the largest and the smallest numbers of dominant alleles have a complete penetrance, i.e., all *AATT* rats have phenotype I, and all *aatt* rats, phenotype III;

the remaining genotypes may be expressed as one of two "adjacent" phenotypes (I–II or II–III) rather than any phenotype; and

the effects of genes *A* and *T* are approximately equal to each other, so that the genotypes symmetrical with respect to these genes (e.g., *AATt* and *AaTT*) have the same penetrance.

Table 2 shows the list of possible phenotypes and their probabilities expressed by parameters ω describing the penetrances of different genotypes.

As evident from Table 2, under the aforementioned assumptions, the phenotypic expression of genotypes may be described by four parameters of penetrance: ω_1, ω_2, ω_3, and ω_4.

Table 2. Phenotypes expected in rats with different genotypes and their frequencies

Genotype	Probabilities of the expression of different phenotypes		
	I	II	III
AATT	1	0	0
AaTT	$1 - \omega_1$	ω_1	0
AATt	$1 - \omega_1$	ω_1	0
AaTt	$1 - \omega_2$	ω_2	0
aaTT	0	$1 - \omega_3$	ω_3
AAtt	0	$1 - \omega_3$	ω_3
aaTt	0	$1 - \omega_4$	ω_4
Aatt	0	$1 - \omega_4$	ω_4
aatt	0	0	1

In the framework of our model, its seems reasonable to assume that the highly inbred, highly sensitive rat strain KM has genotype *aatt.* The outbred strain Wistar may contain all genotypes. However, only Wistar rats with phenotype I, rather than all Wistar rats from the random sample, were used for crossing in our study. According to the model, only rats with genotypes *AATT, AaTT, AATt*, and *AaTt* may have had this genotype. Table 3 shows all possible genotypes of parents and offspring in different crosses, as well as the expected frequencies of offspring with different phenotypes.

As can be seen from Table 3, all F_1 offspring resistant to the loud sound provoking seizures had the same genotype, *AaTt.* These rats served as "resistant" parents of B_1 offspring. The B_1 offspring that had phenotype I were also double heterozygotes *AaTt.* Therefore, the genotypes of the parents of B_1 and B_2 were identical to each other. This explains the results of the experiment demonstrating the identical phenotypic segregation of the B_1 and B_2 offspring.

Note that, if our model is adequate, the offsprings of all crosses analyzed here had only four out of the nine possible genotypes (*AaTt, Aatt, aaTt*, and *aatt*), the penetrances of these genotypes being described by two out of four parameters of penetrance (ω_2 and ω_4).

To estimate the parameters of the digenic model, we used the maximum likelihood method (see Appendix for more details). We obtained the following estimates: the frequencies of both allele *A* and allele *T* were 0.87, the penetrances of genotypes *Aatt* and *aaTt* were 0.50, and the penetrance of genotype *AaTt* was 0.48. These estimates allowed us to predict the numbers of offspring with different phenotypes in different crosses. Table 4 shows the observed and expected numbers of different phenotypic classes in F_1 and in the pooled backcross group (B_1 and B_2). Their comparison using the χ^2 test did not show significant differences. This indicates that the digenic model that we propose here is a good approximation of empirical data. Another evidence for the adequacy of the model is that it predicts a frequency of phenotypes II and III in Wistar rats about 0.1–0.2. This corresponds to the empirical frequencies [20].

Thus, the proposed digenic model with incomplete penetrance of genotypes adequately describes the genetic determination of seizure fits. Penetrance is usually incomplete if the expression of the given character is affected not only by the major gene, but also by other genes and environmental factors. The sensitivity of audiogenic seizure fits to environmental conditions was noticed earlier when analyzing the results of diallelic crossing [18]: the mean sensitivity of rats with all genotypes was found to be increased the replicate of crossing (made in triplicate) that was performed during the extremely hot summer of 1972.

As noted above, three genes affecting the variation of the character studied have been found and mapped in the house mouse. Our data suggest that, in rats, a significant effect of two genes is a plausible explanation. Probably, there are species differences in the mechanisms of the brain response to a loud sound. However, it cannot be excluded that the mechanisms are similar to one another. In experiments with mice, recombinant inbred strains were used and gene mapping was performed, whereas we used only segregation analysis in experiments with rats. Analysis of the genome of hybrid rats may yield more accurate data and reveal weaker effects of other genes.

Physiological data allow us to make the following assumptions on the candidate genes of this character. These may be genes controlling the function of membrane-bound monoamine oxidases, which is found to be disturbed in KM rats [15], as well as the genetic elements that affect the number of neurons using a certain neurotransmitter (namely, GABA-ergic neurons) in brainstem structures, which has been demonstrated in GEPR rats [22].

Thus, we have demonstrated that only 10% of the F_1 hybrids between KM rats (highly sensitive to sound) and outbred Wistar rats (insensitive to sound) develop audiogenic seizure fits, whereas the frequency of seizure-prone rats in two generations of backcrosses with KM rats is about 50%.

We have put forward a digenic model with incomplete penetrance to describe the genetic control of audiogenic seizure fits in rats. This model agrees with factual data: the expected distributions of the character in the offsprings of different crosses do not differ significantly from those observed experimentally. The model explains why these distributions in the first and second backcross generations coincide with each other.

Table 3. The genotypes of parents with the "resistant" phenotype, genotypes of offsprings of different types of crosses, and probabilities of the expression of different phenotypes in the offspring

Type of cross	Genotype of the "resistant" parent	Offspring genotypes	Phenotype probabilities in the offspring		
			I	II	III
F_1	*AATT*	*AaTt*	$(1 - \omega_2)$	ω_1	0
	AaTT	*AaTt* *aaTt*	$1/2(1 - \omega_2)$	$1/2\omega_2 + 1/2(1 - \omega_4)$	$1/2\omega_4$
	AATt	*AaTt* *Aatt*	$1/2(1 - \omega_2)$	$1/2\omega_2 + 1/2(1 - \omega_4)$	$1/2\omega_4$
	AaTt	*AaTt* *aaTt* *Aatt* *aatt*	$1/4(1 - \omega_2)$	$1/4\omega_2 + 1/2(1 - \omega_4)$	$1/4 + 1/2\omega_4$
B_1	*AaTt*	*AaTt* *aaTt* *Aatt* *aatt*	$1/4(1 - \omega_2)$	$1/4\omega_2 + 1/2(1 - \omega_4)$	$1/4 + 1/2\omega_4$
B_2	*AaTt*	*AaTt* *aaTt* *Aatt* *aatt*	$1/4(1 - \omega_2)$	$1/4\omega_2 + 1/2(1 - \omega_4)$	$1/4 + 1/2\omega_4$

Table 4. Comparison of the observed and expected sizes of different phenotypic classes

Sizes of phenotypic classes	F_1			Backcrosses		
	I	II	III	I	II	III
Observed	44	43	10	36	141	176
Expected	38.8	48.5	9.7	44.1	135.9	173
χ^2	0.70	0.62	0.01	1.50	0.19	0.05
Summary χ^2	1.33			1.74		

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APPENDIX

MAXIMUM LIKELIHOOD ESTIMATION OF THE MODEL PARAMETERS

The likelihood function of the sample obtained in several independent experiments has the form

$$L = \sum_i \sum_j N_{ij} \ln Pr(j|i), \qquad \text{(A1)}$$

where the index i designates the experiment and the index j, the qualitative character; N_{ij} is the number of individuals with phenotype j obtained in the ith experiment; and $Pr(j|i)$ is the frequency of phenotype j in the ith experiment expected if the model used is adequate.

We analyzed the results of three independent experiments, namely, offsprings F_1, B_1, and B_2 described by three qualitatively different phenotypes (I, II, and III). Table 1 shows the numbers of individuals with different phenotypes obtained in each experiment. Table 3 shows the probabilities of different phenotypes of offsprings in the last two experiments expressed as the model parameters ω_2 and ω_4. To obtain these probabilities for the first experiment, the probabilities of offspring phenotypes shown in Table 3, weighted with respect to the genotype frequencies in the "resistant" parent, should be summed.

The frequencies of genotypes determining phenotype I in the outbred strain Wistar are determined as follows. Let us denote the frequency of allele *A* in Wistar rats by p_1 and the frequency of allele *T* by p_2. Then, taking into account that the breeding of this strain was not accompanied by selection for audiogenic seizure fits, the frequencies of genotypes *AA, Aa,* and *aa* are p_1^2, $2p_1(1-p_1)$, and $(1-p_1)^2$, respectively, and the frequencies of genotypes *TT*, *Tt*, and *tt* are p_2^2, $2p_2(1-p_2)$, and $(1-p_2)^2$, respectively. If genes *A* and *T* are not linked, the frequencies of digenic genotypes are equal to the products of these frequencies. According to our model, phenotype I may be expressed only in animals with genotypes *AATT*, *AaTT*, *AATt*, and *AaTt*. the frequencies of these genotypes are $p_1^2p_2^2$, $2p_1(1-p_1)p_2^2$, $2p_2(1-p_2)p_1^2$, and $4p_1(1-p_1)p_2(1-p_2)$, respectively. Table 2 shows the probabilities of the expression of phenotype I in rats with these genotypes. According to these data, the expected frequency of phenotype I in Wistar rats is

$$PP = p_1^2p_2^2 + 2(1-\omega_1)[p_1(1-p_1)p_2^2 + p_2(1-p_2)p_1^2] + 4(1-\omega_2)p_1(1-p_1)p_2(1-p_2),$$

and the frequencies of different genotypes in "resistant" rats are calculated as

$$P_1 = p_1^2p_2^2/PP \quad \text{for} \quad AATT,$$

$$P_2 = 2(1-\omega_1)p_1(1-p_1)p_2^2/PP \quad \text{for} \quad AaTT,$$

$$P_3 = 2(1-\omega_1)p_2(1-p_2)p_1^2/PP \quad \text{for} \quad AATt,$$

$$P_4 = 4(1-\omega_2)p_1(1-p_1)p_2(1-p_2)/PP \quad \text{for} \quad AaTt.$$

Therefore, the expected frequencies of F_1 offspring with different phenotypes obtained in F_1 are

$$Pr(I|F_1) = (1-\omega_2)[P_1 + 1/2(P_2+P_3) + 1/4P_4],$$

$$Pr(II|F_1) = \omega_2[P_1 + 1/2(P_2+P_3) + 1/4P_4] + 1/2(1-\omega_4)(P_2+P_3+P_4),$$

$$Pr(III|F_1) = 1/2\omega_4(P_2+P_3+P_4) + 1/4P_4.$$

Substituting the phenotype frequencies in F_1 indicated above, their frequencies in B_1 and B_2 shown in Table 3, and the sizes of different phenotypic classes shown in Table 1 into Eq. (A1), we obtain the likelihood function of the sample studied in terms of the model parameters. The estimates of these parameters are the values at which the likelihood function is the maximum.

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