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ANIMAL GENETICS

Effects of the Mutant Gene *wellhaarig* in the Chimeric Mice

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Abstract—The mutant gene *wellhaarig* (*we*) controls the formation of the waved coat in mice, which is most pronounced in homozygotes at 10 to 21 days of postnatal development. Abnormal hair growth and structure in the *we*/*we* mutant mice results from defective cell differentiation in the inner root sheath of a hair follicle. To localize the site of the *we* gene action, we obtained ten chimeric mice by aggregation of the early C57BL/6-2*we*/*we* and BALB/c embryos. The chimera coat was waved, shaggy, or almost normal depending on the percentage of the mutant component. In the *we*/*we* ⟷ +/+ chimeric animals of the first generation (G1) aged 21 days, both mutant and normal hair phenotypes were observed, which was especially discernible in zigzag hair. Note that none of the chimeras exhibited the alternating patterns of transversely oriented stripes or patches of either mutant or normal hair; i.e., they had a mixed parental hair phenotype. We also did not observe the animals with an intermediate phenotype, which suggests a discontinuous hair formation in chimeras according to the "all or nothing" principle. The data obtained indicate that the dermal papilla cells of a hair follicle are the sites for the *we* gene action. During the embryonic development, dermal cells are strongly mixed, which accounts for the lack of the clear-cut transverse stripes of either mutant or normal hair. The mutant gene *we* is probably responsible for a disrupted induction signal from the dermal papilla towards ectodermal cells of a hair follicle.

INTRODUCTION

In mice, about 100 mutant genes are known that are responsible for abnormal skin and hair development; many of these genes are localized to definite chromosomes [1, 2]. Some mutant genes, such as *Re*, Re^{wc}, Re^{den}, $Tgfa^{wa1}$ (*waved 1*), $Egfr^{wa2}$ (*waved 2*), and *wal*, controls the formation of waved coat. However, the sites of these gene action in various cells systems remain unknown, which prevents understanding the mechanisms of genetic control of hair formation.

In 1936, P. Hertwig received from A. Blum a maintained waved-coat inbred mouse line. Hertwig described this line as a new recessive mutation *wellhaarig* ("waved-haired," designated *we*). This author determined the linkage group of the mutant gene, described the appearance of the mutant animals, and noted that the phenotypic effect of the *we* gene, the waved coat, was the most pronounced in mice at the age of ten days to three weeks, i.e., this trait was characteristic of the first hair generation [3].

B.V. Konyukhov and S.D. Kupriyanov [4] showed that like in normal animals, in mice homozygous for the *wellhaarig* gene, the first generation hair (G1) are represented by the four types: guard, awl, auchene, and zigzag. In homozygotes *we*/*we*, zigzag hair consists of three rather than four segments as in normal animals. In addition, hairs of all types are shorter than normal, wavy, and their basal segments are deformed. Examining the body dorsal hair follicles in 8-, 12-, and 16-day-old mice showed that in the *we*/*we* animals, the Huxley-layer cells of the inner root sheath (IRS) were hypertrophied in the apical part of a hair follicle, whereas their cytoplasm did not stain with alkaline dyes and exhibited no double refraction. Cytoplasm of the Henle-layer IRS cells also showed no affinity to the alkaline dyes, which was indicative of the disturbed keratinizaiton of the IRS cells in homozygotes for the *wellhaarig* gene. In the mutant hair, the stem cell structure did nod differ from that of the normal animals. These data suggest that disturbed differentiation of the IRS cells accounts for the G1 hair abnormalities in the *we*/*we* mice.

In the 12-day-old *we*/*we* mice, electron microscopy of the guard follicles in the body dorsal area revealed abnormal differentiation of the IRS cells. In the Huxley-layer IRS cells, at the stage of trichohyaline granules (TG), the number and size of the latter were reduced, cisterns of the endoplasmic reticulum hypertrophied, the enlarged mitochondria had abnormal structure and lacked crists, the cytoplasm was vacuolized, and keratin filament were irregularly oriented to form a shaggy gel. In the Henle-layer and cuticle cells of the IRS, the filament orientation was less disturbed than in the Huxley-layer IRS cells of the *we*/*we* mice. In cells of the outer root sheath (ORS), cytoplasm vacuolization and a loss of mitochondrial crists were also observed [5, 6].

Although the site of the *wellhaarig* gene expression was established (ectodermal cells of a hair follicle), it remains unclear whether the gene effect was realized directly at that site or it was mediated by another cell

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system, that of the dermal papilla. To localize the site of the gene effect, the chimeric animals carrying at least two genotypically different components are commonly used [7]. Tissues of the chimeric animals obtained by aggregation of the mutant and normal early embryos exhibit cellular mosaicism represented by cells of the two parental genotypes, mutant and normal. By studying the mutant gene effects in various cell systems of a chimeric organism it can be established whether the gene effect is local (restricted to a definite cell system, in which it is phenotypically expressed) or mediated by some other cell system. In this work we determined the site of the *wellhaarig* gene effect by using chimeric analysis of the coat formation in mice *we*/*we* ⟷ +/+.

MATERIALS AND METHODS

A mutant C57BL/6-*we*/*we* line (genotype *we*/*we*, *C*/*C*, *a*/*a*, *Gpi-1*^{bb}) and a BALB/c mouse line (genotype +/+, *c*/*c*, *A*/*A*, *Gpi-1*^{aa}), which differed in pigmentation and isozymes of glucosophosphate isomerase, were used to obtain aggregation chimeras. The C57BL/6-*we*/*we* mice are characterized by black coat and the electrophoretically rapid variant of glucosophosphate isomerase GPI-1B, whereas albino BALB/c mice, by its electrophoretically slow variant, GPI-1A.

The eight-cell C57BL/6-*we*/*we* and BALB/c embryos were aggregated by the Mintz method [8] at the ratio 1 : 1 in 0.01% solution of phytohemagglutinin-P [9] after removal of zonae pellucidae in 0.5% solution of pronase-E (Serva, 8 DMC-U/mg) in phosphate-salt Dulbecco buffer.

The aggregated C57BL/6-*we*/*we* ⟷ BALB/c morulas (hereafter designated *we*/*we* ⟷ +/+) were cultivated until the blastocyst stage for 1.5 days in the drops of Whitten's modified medium [10, 11] under paraffin oil (Fluka) in the atmosphere containing 5% O_2, 5% CO_2, and 90% N_2 at 37°C. The chimeric blastocysts were transplanted into the uteruses of the falsely pregnant females on the third day of the false pregnancy (the day when a copulative plug was detected was taken as the first day of pregnancy).

Chimerism of the newborn mice was determined from a mosaic coat coloration and from different variants of the glucosophosphate isomerase in the kidney, liver, and brain. In both the chimeric mice and the one-component mice of the *we*/*we* and +/+ genotype (BALB/c), which served as control, the coat was visually examined at the age of 21 days. The first-generation (G1) completely formed hairs were pulled out from the anterior, median, and posterior mid-dorsum of the 3-week-old mice with dormant hair follicles. Hairs were examined under a binocular microscope in a layer of glycerol to classify them into the following four types: guard, awl, auchene, and zigzag [12]. The hair samples were examined to calculate the number of the normal and mutant zigzag hairs and to record in the reflected light their color variants: agouti, black, and nonpigmented (white). In the *we*/*we* homozygotes, zigzag hairs consisted of the three segments instead of the four normally observed ones, whereas the remaining hair types lacked this qualitative marker and, therefore, were not analyzed.

Chimeric mice were killed by dislocation of cervical vertebras and the percentage of the mutant component C57BL/6-*we*/*we* was determined in their kidney, liver, and brain using electrophoresis of the glucosophosphate isomerase isozymes. Electrophoresis was conducted on the acetate-cellulose plates [13]. After electrophoresis, electrophoregrams were stained, dried, and scanned in a densitometric analyzer of a Gilford spectrophotometer at 560 nm in a quartz cuvette filled with the mineral oil [14]. The densitograms were used to determine the percentage of the GPI-1B isozyme in the samples, which corresponded to the amount of the *we*/*we* mutant component.

The quantitative data were processed statistically using STATISTICA for Windows 5.1 (StatSoft, 1996).

RESULTS

Twenty mice were obtained after aggregation of 68 pairs of the eight-cell morulas C57BL/6-*we*/*we* ⟷ BALB/c, which was followed by cultivation of the aggregates until the blastocyst stage and their transfer into the uterus of the false pregnant females. Ten of these mice were the *we*/*we* ⟷ +/+ chimeras and the other ten were the one-component animals: four *we*/*we* ⟷ and six BALB/c (+/+).

In the chimeras obtained, the pigmented coat regions (a marker for melanoblasts C57BL/6-*we*/*we*) were transverse stripes and patches comprising from 30 to 80% of the coat. Beginning from the age of 10 days, the coat of all chimeras was waved or almost normal, which depended on the percentage of the mutant component GPI-1B in the chimeric organism. Note that no alternating transverse stripes or patches constituted by only straight or waved hair were clearly discernible on the coat. The latter was waved or shaggy irrespective of pigmentation (Fig. 1).

In two out of ten chimeric animals *we*/*we* ⟷ +/+ (animals 1 and 2), the pigmented regions comprised 30 and 40% of the coat, respectively. The main color of these animals was white, and in their appearance, the chimeras 1 and 2 were similar to the BALB/c mice, but unlike the latter, their coat had pigmented regions and was shaggy rather than smooth (Fig. 1). The chimera pigmented regions were relatively clear-cut stripes and patches of black and agouti hair on the body dorsal part. These animals had straight vibrissae and slightly pigmented eyes.

In chimeras 3, 4, 5, 6, 7, and 8, the pigmented regions of the coat occupied from 40 to 60% of their bodies. The main coat color in these animals was dark-gray. The nonpigmented regions looked like stripes and patches on both dorsal and ventral body sides. Individ-

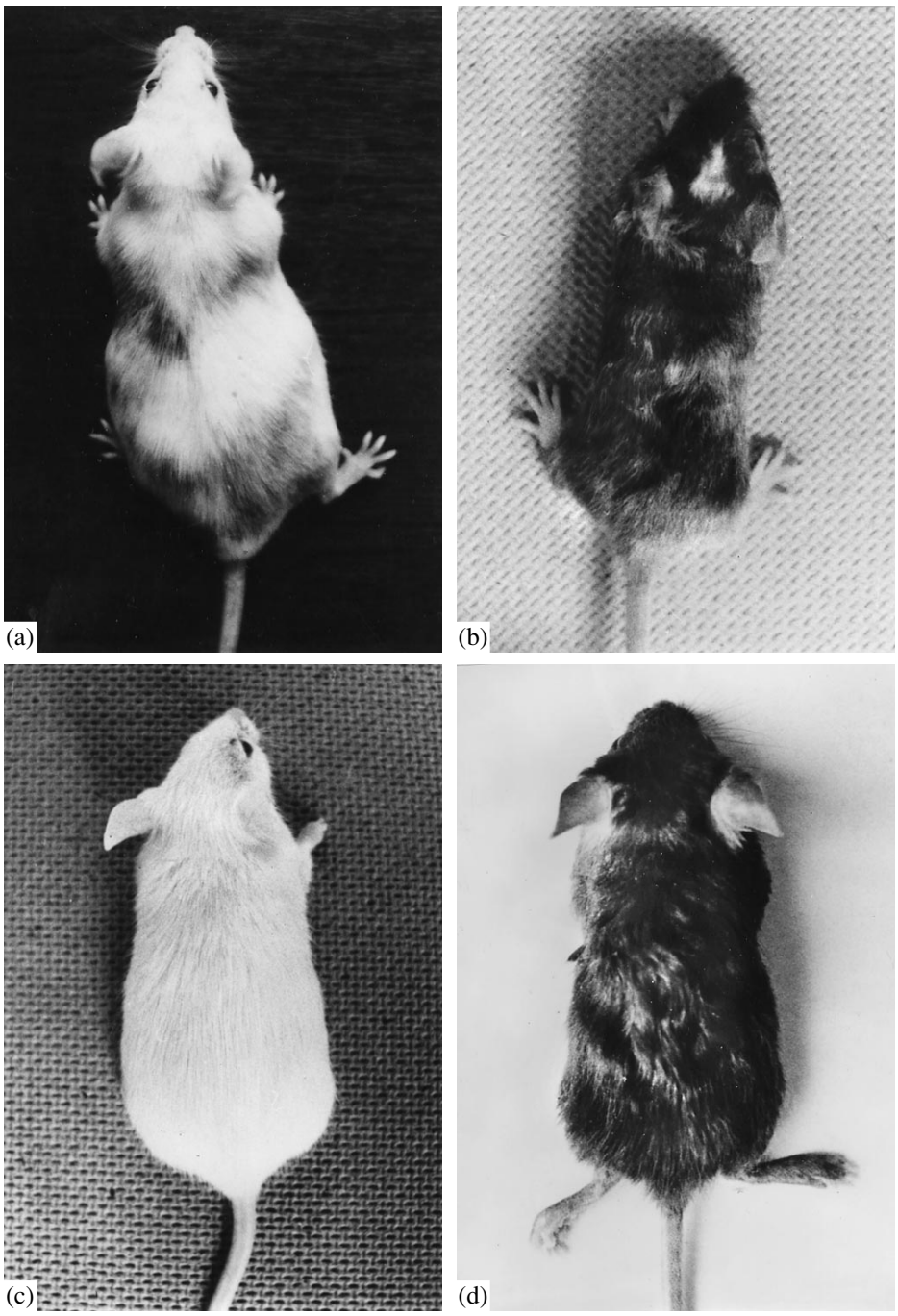

Fig. 1. The coat of the *we*/*we* ⟷ +/+ chimeric mice with different percentage of zigzag hair of the mutant phenotype. (a) 37% of the *we*/*we* phenotype hair, chimera 1; (b) 86% of the *we*/*we* phenotype hair, chimera 9. Mouse lines used to obtain chimeras: (c) mouse of the BALB/c (+/+) line; (d) a homozygote for the *wellhaarig* gene (*we*/*we*).

ual pigmented hair were always on the nonpigmented regions and, vise versa, nonpigmented (white) stripes were on the pigmented regions. In these six chimeras (animals 3, 4, 5, 6, 7, and 8), the waved coat was more pronounced the less the percentage of the nonpigmented regions. All of these animals had pigmented eyes and waved vibrissa.

The chimeric animals 9 and 10 were similar to the *we*/*we* homozygotes in their phenotype, because the main color of their coat was black though somewhat lighter due to the presence of nonpigmented hair. In these animals, the pigmented regions occupied about 85% of their bodies. The nonpigmented patches and stripes were on their heads as well as on the right and

Table 1. Percentage of the mutant component (GPI-1B) in the viscera and percentage of zigzag hair of the *we*/*we* phenotype in the *we*/*we* ⟷ +/+ chimeras

Chimera no.	GPI-1B content in			Zigzag hair of *we*/*we* phenotype
	kidney	liver	brain	
1	24	36	27	37
2	39	40	37	42
3	38	48	54	50
4	53	62	45	63
5	55	53	56	56
6	52	53	63	63
7	65	67	56	60
8	60	65	67	54
9	85	71	67	86
10	76	74	77	86

Table 2. Percentage of zigzag hair of phenotypes *we*/*we* and +/+ differing in color in 21-day-old chimeras *we*/*we* ⟷ +/+

Chimera no.	Number of hair examined	Hair of phenotype *we*/*we*			Hair of phenotype +/+		
		agouti	black	white	agouti	black	white
1	519	9	4	24	11	1	51
2	493	4	6	32	6	3	49
3	522	4	34	12	3	11	36
4	332	2	58	3	4	15	18
5	429	3	44	9	5	12	27
6	465	4	27	32	5	4	28
7	525	3	36	21	4	7	29
8	396	2	46	6	3	9	34
9	513	1	83	2	2	8	4
10	590	–	81	5	1	4	9

Note: Chimera 1 had minimum and chimera 10, maximum percentage of the mutant component GPI-1B and zigzag hair of the *we*/*we* phenotype.

left body sides (chimeras 10 and 9, respectively). The waved coat in these chimeras was similar to that of the *we*/*we* homozygotes of the same age (Fig. 1). The pigmented regions were constituted by black and agouti hair. Both chimeras 9 and 10 had pigmented eyes and waved vibrissae.

Electrophoretic analysis of glucosophosphate isomerase isozymes revealed the *we*/*we* (GPI-1B) component in the kidney, liver, and brain of all chimeras (Table 1). It was found that the percentage of the mutant component in the kidney, liver, and brain of the chimeric animals was directly proportional to the percentage of zigzag hair of the *we*/*we* phenotype in them.

The percentage of the mutant component (GPI-1B) in the kidney, liver, and brain was shown to be strictly and positively correlated: $r_{\text{kidney–liver}} = 0.94$ at $P = 0.000$; $r_{\text{kidney–brain}} = 0.83$ at $P = 0.003$; $r_{\text{brain–liver}} = 0.83$ at $P = 0.003$. A high correlation was also revealed between the content of the mutant component in the viscera and percentage of zigzag hair of the *we*/*we* phenotype in the coat: $r_{\text{hair–kidney}} = 0.92$ at $P = 0.000$; $r_{\text{hair–liver}} = 0.87$ at $P = 0.001$; $r_{\text{hair–brain}} = 0.80$ at $P = 0.005$. These data suggest that the C57BL/6-*we*/*we* and BALB/c (+/+) cell clones were uniformly distributed in a chimeric organism.

Examination of hair samples of the 3-week-old chimeras showed that as in normal animals and the *we*/*we* homozygotes, the first generation hair (G1) were represented in chimeras by the four types: guard, awl, auchene, and zigzag. All samples contained hairs of both normal and mutant phenotypes, which was especially marked with the zigzag hairs consisting of either four (+/+) or three *we*/*we* segments. No zigzag hair of an intermediate phenotype were found. In all chimeric animals, zigzag hair of both normal and mutant phenotypes exhibited three color types: agouti, black, and nonpigmented. The percentage of black *we*/*we* zigzag hair was shown to increase with the increasing content of the GPI-1B mutant component in a chimeric organism, whereas the agouti and nonpigmented (white) *we*/*we* zigzag hair decreased with increasing GPI-1B mutant component. The same was characteristic of the normal hair phenotype (Table 2). These data suggest that the percentage of black hair (genotype *a*/*a*) was directly dependent on the percentage of the mutant component in a chimeric organism; whereas the percentage of the agouti hair (genotype *A*/*A*) depended on the amount of normal component. The percentage of the nonpigmented hair (white, genotype *c*/*c*) decreased with the increasing mutant component.

DISCUSSION

The hair follicles consist of two major components: epidermal and mesenchymal ones. The latter is dermal papilla, which is far smaller in size than the epidermal component but plays an important informative role in hair growth and development [15–18]. In mice, hair follicle formation from the epidermal cells is induced by mesenchymal cells of the developing derma on the 14th days of embryonic growth. Mutations of the genes responsible for hair growth and development may lead to either a lack of normal induction factor produced by the dermal papilla cells or to abnormal perception of the induction signal by cells of the hair follicle epidermal component. This may result in disturbed hair growth and development.

Chimeric analysis with the use of a genotypic marker, whose site of action is already known, makes it

possible to determine the site of the mutant gene action. The agouti hair color, controlled by alleles of the locus *agouti* (*a*), characterized by a clear-cut phenotypic expression can serve as such marker. Many authors showed that most alleles of the *a* locus (in particular, the *A* and *a* alleles) are expressed in the dermal papilla cells [19]. McLaren and Bowman [20] used chimeras between the wavy-coated black mice ($Egfr^{wa2}/Egfr^{wa2}$ *a*/*a*) and the straight-haired agouti (+/+ *A*/*A*) to determine the site of action of the mutant gene *waved 2* ($Egfr^{wa2}$). If both characters are expressed in the same cell system, then the nonagouti (black) hair should be waved, whereas the agouti hair, straight. However, the coat of chimeras contained all possible combinations of the characters and the percentage of the nonagouti hair was inversely correlated with that of the waved hair [21]. Later, it was established that the *Egfr* gene encoding the receptor for the epidermal growth factor is expressed in the cells of outer root sheath of a hair follicle [22].

In mammalian embryogenesis, the cell clones of the developing epidermis do not mix. Hence, in the chimeric mice, clear-cut alternation of the transverse stripes of original parental genotypes is observed in the epidermis [23]. We have revealed pronounced alternation of the transverse stripes of the waved and normal coat in the *wal*/*wal* +/+ chimeric mice, which indicates the site of the gene *wal* action in the epidermal cells of a hair follicle [24]. In mice, chimeric analysis of the effect of the mutant gene *angora-Y* ($Fgf5^{go\text{-}Y}$, the former symbol is go^{Y}) showed that this gene responsible for increased length of all the four hair types in homozygotes acts in the epidermal cells of the hair follicles. In the chimeric mice, the alternation of the transverse stripes consisting of short and long hair was observed [25]. Using the method of aggregation chimeras, Mintz obtained evidence indicating that the mutant gene *fuzzy* (*fz*) responsible for waved coat in the *fz*/*fz* mice is expressed in cells of the hair follicle dermal papilla [26]. In the present study, we did not observe stripes or patches of the coat consisting of either only waved or straight hairs in ten chimeras *we*/*we* ⟷ +/+ obtained. Thus, the lack of a clear-cut pattern of the mutant and normal hair distribution in the *we*/*we* ⟷ +/+ chimeras indicates that the *wellhaarig* gene is inactive in the epidermal cells of a hair follicle.

In the BALB/c (genotype +/+ *c*/*c A*/*A*) mice, which were used in our analysis to confer the normal component (+/+) on the chimeric mice *we*/*we* ⟷ +/+, the expression of the agouti (*A*) gene was epistatically masked by a lack of the pigmentation (genotype *c*/*c*). Hence, the agouti coloration of the normal hair phenotype observed in the chimeras *we*/*we C*/*C a*/*a* ⟷ +/+ *c*/*c A*/*A* in our study was determined by the presence of cells of the BALB/c component in the dermal papilla and by the melanocytes of the *C*/*C* genotype (Table 3). In the chimera coat, the normal black and mutant agouti hair were observed along with other hair phenotypes listed in Table 3. However, the amount of these zigzag hair was low (Table 2). These rare hair phenotypes could appear at a definite ratio of mutant (*we*/*we C*/*C a*/*a*) to normal +/+ *c*/*c A*/*A* components in a dermal papilla.

Table 3. Intercellular interactions leading to development of a particular hair phenotype in the *we*/*we* ⟷ +/+ chimeras

Genotype of dermal papilla cells	Genotype of follicle melanocytes	Hair phenotype
we/*we a*/*a*	*c*/*c*	Mutant white
	C/*C*	Mutant black
+/+ *A*/*A*	*c*/*c*	Normal white
	C/*C*	Normal agouti

If the *wellhaarig* gene is expressed in the dermal papilla, the inverse relationship must exist between agouti color and waved coat, because the presence of a sufficient number of the BALB/c cells in a dermal papilla leads to the development of normal hair. We have determined that the coefficient of correlation between the percentage of the *we*/*we* and agouti hair phenotypes in the samples was $r = -0.80$ ($P = 0.005$). This indicates that genes of both the *agouti* and *wellhaarig* loci are expressed in cells of the dermal papilla (Fig. 2).

Apart from the lack of a clear-cut pattern of the mutant and normal hair distribution in the chimeric mice (the absence of distinct transverse stripes of the waved and straight hair in their coat), we have not revealed zigzag hair of the intermediate phenotype. The induction signal from a dermal papilla seems to follow the "all or nothing" principle, i.e., the signal intensity of a definite threshold value leads to development of either mutant or normal hair phenotype.

Our results indicate that the dermal papilla cells rather than the epidermal component of a hair follicle represent the site for the *wellhaarig* gene action.

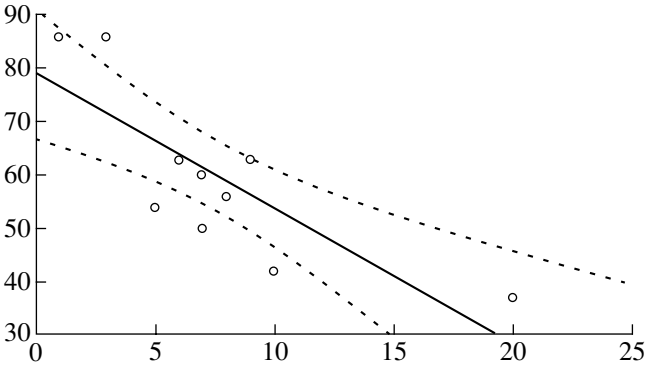

Fig. 2. Inverse correlation between the waved coat and agouti coloration in the chimeras *we*/*we* ⟷ +/+. Y axis, % of the agouti zigzag hair; X axis, % of zigzag hair of the *we*/*we* phenotype. Confidence interval 95%.

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