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A new inbred strain JF1 established from Japanese fancy mouse carrying the classic piebald allele

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Abstract. A new inbred strain JF1 (Japanese Fancy Mouse 1) was established from a strain of fancy mouse. Morphological and genetical analysis indicated that the mouse originated from the Japanese wild mouse, *Mus musculus molossinus*. JF1 has characteristic coat color, black spots on the white coat, with black eyes. The mutation appeared to be linked to an old mutation piebald (*s*). Characterization of the causative gene for piebald, endothelin receptor type B (*ednrb*), demonstrated that the allele in JF1 is same as that of classic piebald allele, suggesting an identical origin of these two mutants. Possibly, classic piebald mutation was introduced from the Japanese tame mouse, which was already reported at the end of the 1700s. We showed that JF1 is a useful strain for mapping of mutant genes on laboratory strains owing to a high level of polymorphisms in microsatellite markers between JF1 and laboratory strains. The clarified genotypes of JF1 for coat color are "*aa BB CC DD ss*".

Introduction

There are many lines of evidence that laboratory mice have been established from the European wild mouse, *M. m. domesticus* (Ferris et al. 1983; Yonekawa et al. 1980). In the course of development of laboratory strains, most of them probably originated from a relatively small number of the fancy mice that had been kept by mouse breeders in Europe and North America (Bonhomme and Guénet, 1996).

Before late 1700s, there were many mouse fanciers in Japan and China. Japanese fanciers were breeding a variety of mutant mice such as albino, agouti, pink-eyed dilution, dwarf, waltzer, and piebald (Figure 1A). Those mice were described in the book titled, "Chingan-sodategusa," published in 1787 (Tokuda 1935; Zeniya 1787). Some of them were then introduced into Europe. The phenotype and the genetics of those fancy mice were reported in the early 1900s (Darbishire 1902a, 1902b, 1903, 1904; Gates 1926; Little and Tyzzer 1915; So and Imai 1920; Tyzzer 1915; Yerkes 1907). Japanese fancy mice were crossed with European and North American mice, and some genetic factors have been introduced into the latter mice (Bonhomme and Guénet 1996; Morse 1981; Silver 1995). Studies of genes on the Y Chromosome (Chr) such as *Zfy2* and *Sry* have shown that the Y Chr of most strains of laboratory mice is derived from Asian mice, probably Japanese wild mouse *M. m. molossinus* (Bishop et al. 1985; Nagamine et al. 1992). Also, the original *p* allele of pink-eyed dilution mutation was reported to be derived from an Asian mouse, most likely *M. m. molossinus* (Brilliant et al. 1994).

Although original Japanese fancy mice were believed to be extinct by the middle of the 1900s, we found pairs of mice in 1987 and established an inbred strain designated JF1. The mouse is phenotypically similar to one of the mice reported in "Chingan-sodategusa" and several other reports in the early 1900s (Gates 1926; So and Imai 1920), which carries a spotting phenotype on the coat resembling an old mutation piebald (Fig. 1B). We will report here the genetical relation of this spotting mutation to piebald and characterizations of the JF1.

Materials and methods

Mice. JF1 and MSM strains were established at the National Institute of Genetics (NIG) in Mishima, Japan. The MSM strain was established from the wild mouse of *M. m. molossinus* captured in Mishima. A detailed description of the inbred strain MSM will be published elsewhere. C57BL/6 was purchased from The Jackson Laboratory (Bar Harbor, Me., USA). All these mice have been maintained at the NIG. DBA/2 was purchased from CLEA Japan (Tokyo, Japan). All inquiries for distribution of these mouse stocks from NIG should be sent to T. Shiroishi.

Establishing JF1. A strain of fancy mouse that had been kept as a Japanese Mouse was purchased at a market in Denmark and introduced into the animal facility of NIG in 1987. Since then, they have been bred as sister-brother matings. The Japanese Mouse was established as inbred strain JF1 (Japanese Fancy Mouse 1) at the 20th generation in 1993. The mouse has been easy to breed since its introduction. We found that the average number of progeny of JF1 per litter is 5.14 (442 progeny in 86 litters), not so different from 5.48 of C57BL/6 (866 progeny in 158 litters) in our animal facility.

Genomic polymorphisms. Polymorphisms of *H2-K* loci were investigated by the method described previously (Sagai et al. 1989). Wild mice and mice maintained at NIG were used for this study. The mice carrying *H2-K*^{f} haplotype were further typed by use of monoclonal antibodies against H2-K classI antigen of B10.MOL-TEN1. A part of the data has been reported before (Sagai et al. 1989).

Restriction fragment length polymorphism (RFLP) of mtDNA obtained from different strains of mice was studied as follows. mtDNA was purified by cleared lysate method (Yonekawa et al. 1981), then dialyzed against 0.1

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The map data reported in this paper have been submitted to the Mouse Genome Database, accession number MGD-JNUM-42684.

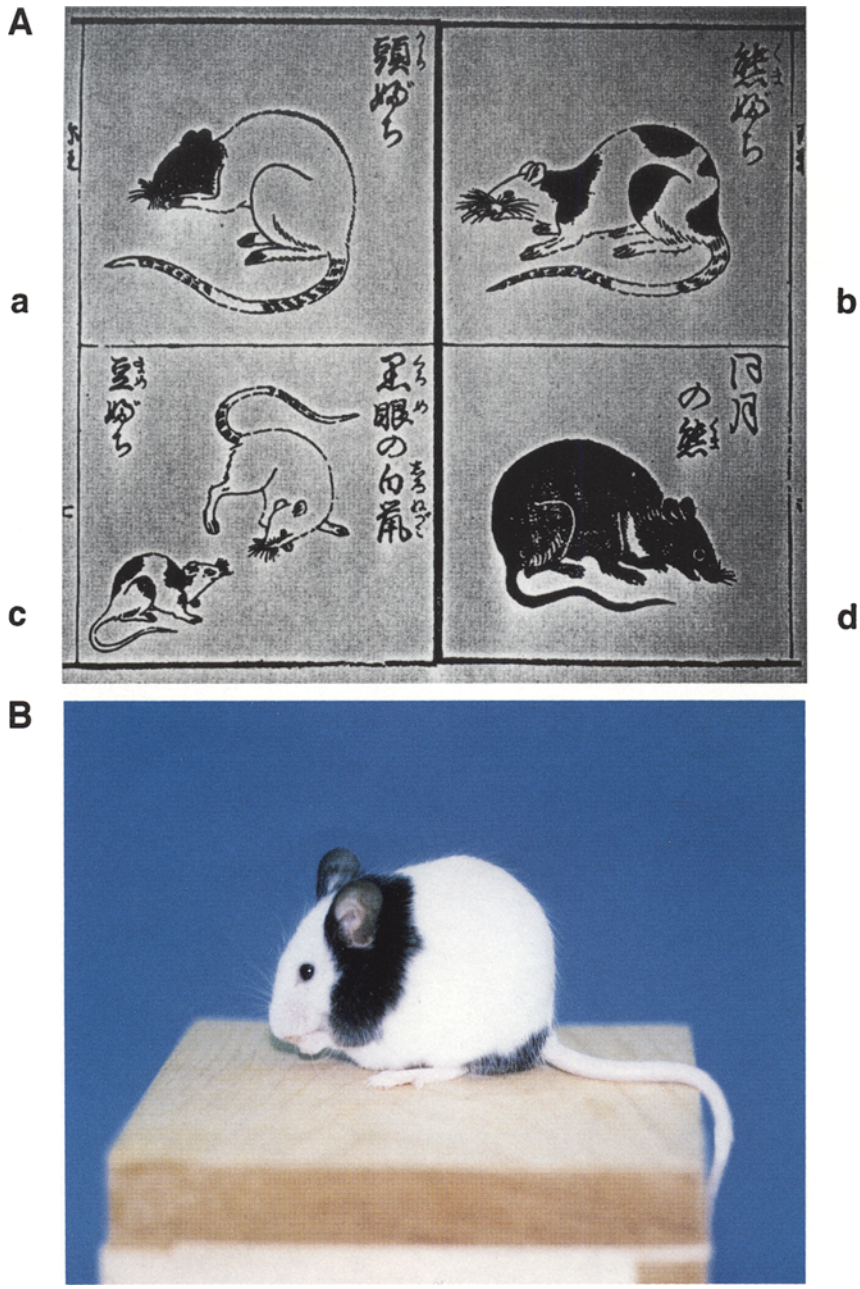

Fig. 1. **(A)** Variety of fancy mice presented in the book titled "Chingan-sodategusa" (published in 1787, publisher unknown). a and b, piebald homozygotes; d, piebald heterozygote; c (left), dwarf with piebald; c (right), black-eyed white. These illustrations have been also reported by Tokuda (1935). **(B)** A standard appearance of JF1.

mM EDTA (pH 7.0). Approximately 0.1 μg of purified mtDNA was digested by *Hin*fI and was post-labeled with ^{32}P α-dATP by polymerase reaction with Klenow fragment (Sambrook et al. 1989). The post-labeled *Hin*fI digests were electrophoresed in a 4% polyacrylamide gel. The gel was transferred on filter paper, then dried on gel dryer and subjected to autoradiography.

Polymorphisms for microsatellite markers were investigated by the simple sequence length polymorphism (SSLP) method. Microsatellite markers purchased from Research Genetics (Huntsville, Ala., USA) were chosen randomly and used for analyzing frequency of polymorphisms. The microsatellite markers that showed reliable band in our analysis were selected for a total of 101 markers and used for the study. Genomic DNA prepared from the liver of four inbred strains, C57BL/6, DBA/2, MSM, and JF1, was PCR amplified with primer sets for the microsatellite markers and analyzed by agarose gel electrophoresis with 4% agarose (3:1 ratio Nusieve:Seakem agarose; FMC Bioproducts, Rockland, Me., USA) in 1XTAE buffer. The visualised band by ethidium staining were analysed for length polymorphism between all the possible pairs in four inbred strains.

Linkage analysis. For the linkage analysis, mice of (C57BL/6J × JF1)F_1 and (JF1 × DBA/2)F_1 were backcrossed to JF1. The numbers of progeny studied in each cross were as follows: (C57BL/6 × JF1)F_1 × JF1, 100; JF1 × (C57BL/6 × JF1)F_1, 50; (JF1 × DBA/2)F_1 × JF1, 54; JF1 × (JF1 × DBA/2)F_1, 43. Coat color phenotype of the backcross progeny was scored, and genotypes of the progeny at microsatellite loci were analyzed by SSLP with genomic DNA. Genomic DNA was prepared from the liver by DNAzol (Life Technologies, Grand Island, N.Y., USA) according to the producer's direction. 1 μl of the DNA solutions was used for each PCR reaction in 20 μl of the reaction volume followed by SSLP analysis. Only markers that show polymorphism between JF1 and both C57BL/6 and DBA/2 were used for linkage analysis.

RT-PCR and sequencing. Total RNA was prepared from the lung tissue of adult mice, C57BL/6, JF1, and MSM, by standard methods (Sambrook et al. 1989). The entire coding region for *ednrb* gene was amplified from 1 μg of total RNA by standard RT-PCR method with two sets of primers,

(EDNRBF: 5′-AGACTGAAAACAGCAGAGCGGCTAC and EDNRB3R: 5′-GACTCCAAGAAGCAACAGCTCGATA; amplifying from nucleotides 152 to 825) and (EDNRB2F: 5′-GTGGGAATCACAGTGCTGAGTCTTT and EDNRBR: 5′-TGTCCACAATGAGGACAGTGAGATTCG; amplifying from nucleotides 756 to 1575). The DNA fragments amplified from three inbred strains, C57BL/6, MSM, and JF1, were subcloned into pT7Blue(R) vector (Novagen, Madison, Wis., USA). The entire coding region was analyzed by sequencing for the duplicated clones with standard primers for the vector sequence and a specific primer for the *ednrb* insert, EDNRB4F (5′-TTCTACTTCTGCTTGCCGCTAGCCA; annealing from nucleotides 1040 to 1065). All the numbers for nucleotides of *ednrb* gene were quoted from the cDNA sequence in the Genbank database submitted by Yanagisawa (accession number:U32329).

Results

External form of JF1. Even though the mouse was called a Japanese mouse, there was no record as to where the mouse originally came from. Japanese wild mouse, *M. m. molossinus,* has characteristic morphology such as small body size and short tail (Foster et al. 1981; Tsuchiya et al. 1994). Measurements for the body length and tail length of JF1, and comparison with that of several subspecies in the species *M. musculus* has shown that the gross morphology of JF1 is similar to the Japanese mouse, *M. m. molossinus* (data not shown).

Genetic analysis of JF1. JF1 was analyzed for genetic profiles to identify the subspecies from which it originated. We have characterized the degree of polymorphisms in microsatellite markers by SSLP analysis. Genomic DNAs prepared from four inbred strains, C57BL/6, DBA/2, JF1, and MSM, established from *M. m. molossinus,* were subjected to PCR analysis with microsatellite markers. Size polymorphisms between four inbred strains, C57BL/6, DBA/2, JF1, and MSM, for 101 microsatellites were analyzed (Table 1). Frequencies of microsatellite markers showing polymorphism in a total of 101 different loci were calculated between all the possible pairs of the strains (Fig. 2). A frequency of polymorphism between JF1 and MSM was 40% and similar to the value obtained between C57BL/6 and DBA/2. The frequency increased to 80% in all the pairs between either JF1 or MSM, and either C57BL/6 or DBA/2. The results indicate that JF1 is diverged from common laboratory strains to the same extent as MSM.

Because it is difficult to distinguish *M. m. molossinus* from mice in some parts of China, we studied polymorphisms in the histocompatibility antigen, H2-K. The *H2-K^f* haplotype is widely distributed in the species *M. musculus.* However, mice with antigens reactive for all the monoclonal antibodies against a subtype of *H2-K^f* haplotype of B10.MOL-TEN1 strain are frequently found in Japan but never found in subspecies *M. m. domesticus* (Sagai et al. 1989). Our analysis of subtype *H2-K^f* haplotype in mice from China and Japan indicated that the *H2-K* haplotype of JF1, which is reactive for all the antibodies tested, is characteristic of *M. m. molossinus* (Table 2).

We looked at polymorphisms in diagnostic biochemical markers used for typing mouse subspecies. All the markers, *Gpd1* (Glucose phosphate dehydrogenase-1), *Pgm1* (Phosphoglucomutase-1), *Hbb* (Hemoglobin beta-chain), and *Thy1* (Thymus antigen-1), appeared to be identical to those of *M. m. molossinus* (data not shown). Furthermore, *Zfy2* on the Y Chr of JF1 has the deletion polymorphism (data not shown) that is specifically observed in Asian mice, as presented by Nagamine and co-workers (1992).

We also investigated the mitochondrial genome to analyze maternally inherited DNA. mtDNAs were prepared from JF1, MSM, and mice captured in China, and subjected to RFLP analysis. Mice from China show a characteristic band that is not observed in *M. m. molossinus* (Fig. 3). In this analysis, a variant band found in mice from China was not detected in the mtDNA of JF1 (Fig. 3).

From all the data of the morphology, polymorphisms in microsatellite markers, biochemical markers, polymorphism in *Zfy-2* on the Y Chr, haplotype of *H2-K* class I, and RFLP polymorphism of mtDNA, we concluded that JF1 originated from *M. m. molossinus.*

Table 1. Polymorphisms of microsatellite markersobserved in SSLP analysis.

Marker	Strain polymorphisms	Marker	Strain polymorphisms
D1Mit3	JF1 > D2 = B6 = MSM	*D10Mit10*	B6 = JF1 > MSM > D2
D1Mit4	D2 = B6 > MSM > JF1	*D10Mit11*	B6 = JF1 = MSM > D2
D1Mit7	D2 = JF1 = MSM > B6	*D10Mit12*	D2 = B6 = JF1 = MSM
D2Mit1	JF1 > MSM > B6 – D2	*D10Mit14*	MSM – JF1 > B6 > D2
D2Mit2	JF1 = MSM > D2 = B6	*D10Mit15*	D2 > B6 > MSM – JF1
D2Mit3	JF1 = MSM > D2 = B6	*D11Mit5*	B6 > D2 = JF1 = MSM
D2Mit8	D2 = B6 = JF1 = MSM	*D11Mit22*	JF1 = MSM > D2 = B6
D2Mit12	B6 = JF1 = MSM > D2	*D11Mit23*	D2 – B6 > JF1 = MSM
D3Mit1	JF1 = MSM > D2 = B6	*D11Mit26*	D2 = B6 > JF1 = MSM
D3Mit3	MSM – JF1 > D2 = B6	*D11Mit28*	B6 > D2 = JF1 > MSM
D3Mit4	D2 = B6 – JF1 = MSM	*D11Mit111*	D2 – B6 > JF1 – MSM
D3Mit7	MSM > D2 = B6 = JF1	*D11Mit113*	JF1 = MSM – D2 – B6
D3Mit14	D2 > B6 > JF1 = MSM	*D12Mit2*	JF1 = MSM > D2 > B6
D3Mit23	MSM = JF1 – D2 – B6	*D12Mit4*	JF1 = MSM > D2 – B6
D4Mit2	D2 = B6 = JF1 = MSM	*D12Mit6*	MSM > JF1 > D2 = B6
D4Mit5	JF1 = MSM – D2 = B6	*D12Mit7*	D2 > B6 = JF1 = MSM
D4Mit7	D2 = B6 = JF1 = MSM	*D13Mit1*	JF1 > D2 = B6 = MSM
D4Mit9	MSM > JF1 – D2 – B6	*D13Mit4*	D2 = B6 = JF1 = MSM
D4Mit11	JF1 – MSM > D2 = B6	*D13Mit5*	JF1 = MSM > D2 = B6
D4Mit15	JF1 – MSM > D2 = B6	*D14Mit1*	B6 > D2 = JF1 = MSM
D4Mit16	JF1 > MSM > D2 > B6	*D14Mit3*	JF1 = MSM > D2 = B6
D4Mit205	JF1 – MSM – D2 = B6	*D14Mit4*	B6 – D2 = JF1 > MSM
D5Mit1	JF1 > MSM > B6 > D2	*D14Mit5*	B6 > D2 > JF1 = MSM
D5Mit3	D2 = B6 > MSM – JF1	*D14Mit8*	D2 = B6 > JF1 = MSM
D5Mit4	JF1 = MSM > D2 = B6	*D14Mit38*	MSM – JF1 > D2 = B6
D5Mit6	D2 = B6 > JF1 – MSM	*D14Mit93*	JF1 = MSM > D2 = B6
D5Mit10	D2 > B6 > JF1 = MSM	*D14Mit94*	JF1 = MSM > B6 > D2
D5Mit12	B6 = JF1 = MSM – D2	*D15Mit5*	JF1 = MSM > D2 > B6
D5Mit51	MSM – JF1 > D2 = B6	*D15Mit17*	D2 = B6 > JF1 = MSM
D6Mit9	MSM – JF1 – B6 > D2	*D15Mit42*	B6 > JF1 = MSM > D2
D6Mit12	D2 = B6 > JF1 = MSM	*D15Mit74*	MSM > D2 = B6 > JF1
D6Mit14	B6 = MSM > D2 = JF1	*D16Mit1*	MSM > JF1 > D2 = B6
D6Mit71	D2 = B6 = JF1 = MSM	*D16Mit2*	JF1 > MSM > D2 = B6
D6Mit74	JF1 = MSM > B6 > D2	*D16Mit3*	MSM > JF1 > B6 – D2
D6Mit91	B6 = JF1 = MSM – D2	*D17Mit3*	B6 – JF1 > D2 > MSM
D6Mit124	MSM > D2 – JF1 > B6	*D17Mit11*	B6 = MSM > D2 = JF1
D7Mit8	D2 = B6 > JF1 = MSM	*D17Mit36*	MSM > JF1 > D2 = B6
D7Mit9	D2 = B6 > JF1 = MSM	*D17Mit38*	B6 = JF1 = MSM > D2
D7Mit10	MSM – JF1 – D2 = B6	*D17Mit41*	D2 = JF1 = MSM > B6
D7Mit12	MSM – JF1 > D2 – B6	*D18Mit1*	MSM > JF1 > D2 = B6
D7Mit16	D2 = B6 > JF1 = MSM	*D18Mit2*	JF1 = MSM > D2 = B6
D7Mit18	D2 = B6 > JF1 = MSM	*D18Mit6*	MSM > JF1 – D2 = B6
D7Nds4	JF1 > MSM > D2 = B6	*D18Mit16*	D2 = B6 > JF1 = MSM
D8Mit3	D2 – B6 > JF1 = MSM	*D19Mit1*	JF1 = MSM > D2 > B6
D8Mit4	D2 > B6 = JF1 = MSM	*D19Mit4*	JF1 = MSM > D2 = B6
D8Mit14	JF1 = MSM > D2 = B6	*D19Mit33*	D2 > B6 = JF1 > MSM
D9Mit10	JF1 > MSM > B6 > D2	*DXMit3*	JF1 > D2 = B6 = MSM
D9Mit22	D2 > MSM – B6 = JF1	*DXMit4*	D2 = B6 > JF1 = MSM
D9Mit23	B6 – D2 = JF1 = MSM	*DXMit5*	D2 = B6 > JF1 = MSM
D10Mit5	D2 = B6 = JF1 = MSM	*DXMit6*	D2 = B6 = JF1 = MSM
D10Mit8	JF1 = MSM > D2 = B6		

Mouse strains used in this study: D2, DBA/2; B6, C57BL/6; JF1; MSM.
Relative size of allele; =, polymorphism is not detected; –, there is a size variation but not much different, and may not be easy to use for typing experiments; >, the strain on the left side of ">" has longer allele than the one on the right side.

P/T %	JF1	MSM	C57BL/6	DBA/2
JF1		41.6	81.2	82.2
MSM	42/101		80.2	84.2
C57BL/6	82/101	81/101		45.5
DBA/2	83/101	85/101	46/101	

Fig. 2. A matrix diagram showing degrees of polymorphism for microsatellite markers between inbred strains. The left lower half of the matrix is indicated by P/T: P = number of microsatellite markers showing polymorphism between two inbred strains; T = total number of microsatellite markers examined. The right upper half represents the calculated frequency of polymorphism.

Table 2. Antigenic determinants for the H2-K^f-specific monoclonal antibodies in Asian mice.

Location of mouse	Sample name or No.	Reactivity with antibody								
		MS60	MS68	MS56	MS61	MS53	MS54	MS55	MS59	MS69
Japan	JF1	+	+	+	+	+	+	+	+	+
	No.1–15	+	+	+	+	+	+	+	+	+
	No.16–20	−	+	−	+	+	+	+	+	+
China	No.21, 22	+	+	+	+	+	+	+	+	+
	No.23	−	+	+	+	+	+	+	+	+
	No.24	+	−	+	+	+	+	+	+	+
	No.25	−	−	+	+	+	+	+	+	+
	No.26	−	−	−	+	+	+	+	+	+
	No.27	−	+	−	+	+	+	+	+	+
	No.28, 29	−	−	−	−	+	+	+	+	+

Localities at which the wild mice of each sample number were collected are as follows. No.1, Teine; 2, Teine; 3, Ashiro; 4, Ashiro; 5, Niigata; 6, Niigata; 7, Niigata; 8, Iiyama; 9, Ohmiya; 10, Mishima; 11, Shizuoka; 12, Shizuoka; 13, Shizuoka; 14, Shizuoka; 15, Kyoto; 16, Ohmiya; 17, Mito; 18, Mito; 19, Mito; 20, Mito; 21, Shanghai; 22, Chungking; 23, Kweilin; 24, Aksu; 25, Tahcheng; 26, Sining; 27, Sining; 28, Chengtu; 29, Chengtu. The data for No.10, 16, 17, and 21 were already reported previously (Sagai et al. 1989).

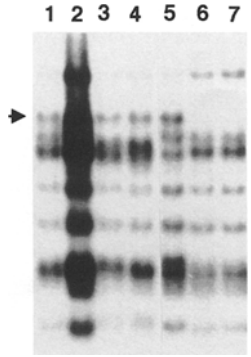

Fig. 3. Polymorphism between Japanese and Chinese mice in the RFLP analysis of mitochondrial DNA. Lanes: 1, Lanchow; 2, Chengtu; 3, Kiayukwan; 4, Shanghai; 5, Changchun; 6, JF1; 7, MSM. The arrowhead indicates the polymorphic band observed between mice from China and Japan.

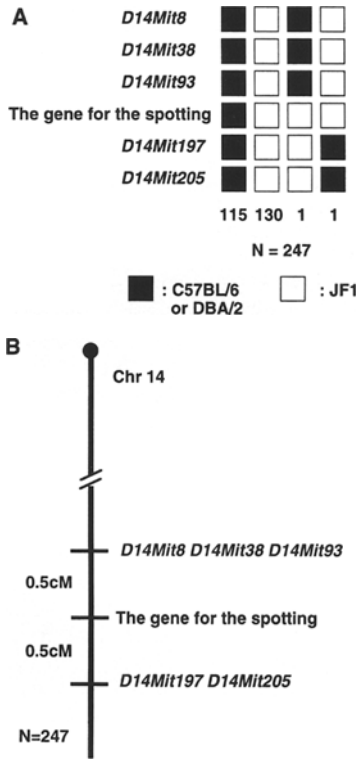

Fig. 4. **(A)** Segregation pattern of the gene for the spotting and microsatellite markers examined in 247 intersubspecific backcross progeny. Each column represents a chromosomal haplotype. The number of the progeny with each haplotype is shown below the column. **(B)** An assigned locus for the gene for the spotting coat color of JF1. Recombination distances between loci shown at the left are given in centiMorgans.

Genetic mapping for the spotting of JF1 mouse. JF1 has characteristic coat color, white coat with black spots. Size and shape of the black spots are irregular, but always dominated by the white coat. The gene for this spotting phenotype is recessive since all the F_1 progeny from the cross of JF1 and either C57BL/6 or DBA/2 have black coat color except for occasional minor and irregular white spotting on their belly. To map the genetic loci for this spotting coat color, we conducted a linkage analysis. The F_1 progeny obtained from the cross between JF1 and either C57BL/6 or DBA/2 were mated with JF1, and a total of 247 backcross progeny were collected. In this experiment, all the crosses were successful and no progeny showed the sterility phenotype. The locus for the spotting coat color was mapped to Chr 14 between a cluster of *D14Mit8, D14Mit38,* and *D14Mit93,* and a cluster of *D14Mit197* and *D14Mit205* (Fig. 4). The genetic distance between the locus for spotting and either cluster of microsatellite markers was 0.5 cM in both cases. This locus was very close to the piebald in SSL/Le strain (Metallinos et al. 1994).

Molecular analysis of the gene for ednrb. Two mutant alleles of *ednrb,* piebald-lethal (s^l) and *s,* have been characterized and reported (Hosoda et al. 1994). The entire *ednrb* gene is deleted in the s^l allele, and the structurally normal mRNA is down-regulated in the *s* allele. It is also reported that the *s* allele in SSL/Le-*s/s* strain carries two silent nucleotide transitions compared with that of the C57BL/6 strain. We analyzed and compared JF1 and C57BL/6 for the entire coding sequences of *ednrb* to identify the mutation in the gene of JF1. We found that the coding sequence for *ednrb* of JF1 was exactly the same as that of the *s* allele and was different from that of C57BL/6 by the two nucleotide substitutions within the entire coding sequences (Table 3). One of the polymorphic substitutions between JF1 and C57BL/6 is also found in the sequence from MSM in nucleotide 1032, even though this strain carries two transitions compared with SSL/Le-*s/s* and JF1 in nucleotides 159 and 560. These data indicate that the *ednrb* alleles in both SSL/Le-*s/s* and JF1 are derived from same mutant mouse.

Discussion

The high level of genetic polymorphisms in microsatellite markers between JF1 and laboratory mice facilitates high-density mapping of any objective gene. In this report, we mapped the locus for spotting coat color to the region linked to piebald. It is also noteworthy that the F_1 progeny of both sexes between JF1 and either C57BL/6 or DBA/2 were completely fertile. In addition to genetic advantages, JF1 is obedient and easy to handle. This will also provide a new experimental system for studying mouse behavior, because JF1 has been highly domesticated and is obedient compared with a genetically related strain MSM, which still maintains the character of the wild mouse and is highly active.

We have shown that JF1 carries piebald as a recessive coat

Table 3. Polymorphisms in DNA sequence for *ednrb* gene.[a]

Mouse (Nucleotide)	159	560	1032
C57BL/6(+/+)	C	C	C
SSL/Le(s/s)[b]	T	C	T
JF1(s/s)	T	C	T
MSM(+/+)	C	T	T

[a] Only polymorphic bases found within the entire coding sequences for *ednrb* in strains C57BL/6, SSL/Le-*s/s*, JF1, and MSM are listed in the table.
All other bases are completely identical in the four strains.
[b] The sequence data are taken from Hosoda et al. (1994).

color mutation. The DNA sequence of the coding region for *ednrb* cloned from JF1 was exactly the same as that of old mutant allele known as the *s* mutant. The level of expression for *ednrb* is markedly more down-regulated in SSL/Le-*s/s* strain than in the normal strain (Hosoda et al. 1994). However, the actual aberration responsible for the down-regulated expression in the *s* allele still needs to be studied. Identification of the mutation of the *s* allele will enable us to compare the primary structures of the *s* allele with that of JF1 in more detail. Our present data suggest that the *s* allele and the mutant gene in JF1 originated from the same mouse. Zeniya reported a variety of mouse mutants in 1787, and one of them is clearly recognized as piebald owing to a spotting pattern and the manner of heredity (Tokuda 1935). It is known that one of those mutant mice, the Japanese waltzing mouse, was introduced into Europe in the late 1800s (Tokuda 1935). This strain was known as a mutant strain carrying piebald mutation as well (Darbishire 1902a; Gates 1926; Weldon 1903; Yerkes 1907). Descendants of this and other Japanese fancy mice were kept in Europe and North America until the middle of the 1900s. It is possible that the classic piebald allele has come from one of those Japanese fancy mice which were developed more than two hundred years ago in Asia, as in the cases of the Y Chr and the pink-eyed dilution gene.

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