Inheritance of Chediak-Higashi Syndrome in Japanese Black Cattle

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ABSTRACT. Fifty-six Japanese black cattle affected with Chediak-Higashi syndrome (C-HS) have been referred to Miyazaki University Veterinary Teaching Hospital during the past 12 years, and 44 pedigree records were collected. In pedigree analysis, the parents had no clinical sign, the affected dams had clinically normal calves, and approximately equal numbers of males and females were affected, we therefore considered this syndrome to be an autosomal recessive trait. Quantitative genetic analyses were then made in a restricted area. Segregation analysis by the *a priori* method in 8 families showed that C-HS was a simple autosomal recessive trait. Furthermore, 36 dams and their 257 offspring (including 8 C-HS affected cattle) were analyzed using population genetics in the same area. The result was the same as in the former analysis. — KEY WORDS: bleeding disorder, cattle, Chediak-Higashi syndrome, inheritance.

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Chediak-Higashi syndrome (C-HS) is found in a wide variety of mammalian species including man, cattle, mink, cats, mice, rats [10], foxes and a killer whale [1]. The syndrome in humans is a rare, genetically determined disease characterized by partial oculocutaneous albinism [2, 3, 14, 15, 18, 21], abnormally large granules in all granule-containing cells [2, 3, 11, 14, 15, 18, 21], frequent pyogenic infections [2, 3, 14, 15, 18, 21], and bleeding tendency [3, 10, 14, 18, 19]. Bovine C-HS possesses similar characteristics which have been described in Hereford [14], Japanese black [20], and Brangus cattle [1]. Between 1982 and 1993, we found 56 Japanese black cattle with C-HS characterized by hemorrhagic disorders, partial albinism, abnormal leukocytic granules in both peripheral blood and bone marrow cells, and low platelet aggregation levels.

The autosomal recessive nature of the condition in human C-HS patients has been proved by pedigrees and statistical analyses [3, 14]; in C-HS Hereford cattle [14], mink [13, 14], rats [10] and mice [17] it has been ascertained by test matings; and in C-HS cats it is suggested by pedigree analysis and test matings [5]. In C-HS Hereford cattle, a simple autosomal recessive condition was documented in an experimental herd by Padgett [14]. This report is concerned with genetic studies performed on C-HS Japanese black and related cattle in the field. The pedigree data on 44 naturally occurring cases were collected and analyzed and population genetic analyses in a specific area were also performed to ascertain its inheritance mode in Japanese black cattle.

MATERIALS AND METHODS

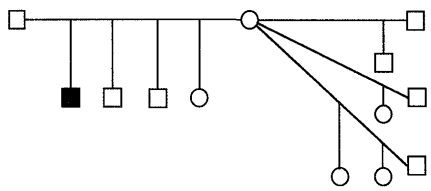
Animals: Over a 12 year period, more than 200 sick Japanese black cattle with bleeding tendency were referred to Miyazaki University by local veterinarians around Miyazaki and Kagoshima prefectures. Fifty-six of those cattle (27 males, 26 females, and 3 unknown sex) were diagnosed as C-HS based on two prominent abnormalities, large granules in eosinophils in either peripheral blood or bone marrow and low collagen-induced platelet aggregation levels. Other abnormalities of C-HS, such as reduced pigmentation of hair and/or retina, and C-HS clinical characteristics, are described in other published papers [12]. The remaining cattle were diagnosed as hemophilia-like disease, factor XIII deficiency, etc.

Pedigree analysis: We assembled the affected cattle's pedigree records issued by the Japanese black cattle register society, and information about their relatives was collected when we took their histories. Of the 56 C-HS cattle, we were able to collect 44 pedigree records.

Genetic analyses: We chose an isolated animal husbandry area (H area) in Miyazaki with a special breeding program for our population genetic investigation. Segregation analysis and the gene frequency analysis were used in the quantitative analyses. For statistical investigation, we randomly collected the breeding records of 36 dams in 36 farms, which included the mother of 8 C-HS affected cattle (6 males and 2 females). The families of these 8 were used for segregation analysis. In all, 257 offspring of 36 dams × 29 sires were used for gene frequency analysis. The analysis was based on the Hardy-Weinberg law [7].

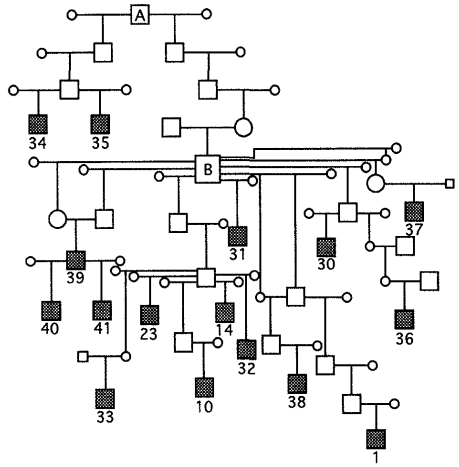
RESULTS

Pedigree analyses: Examining the 56 medical records of C-HS affected animals, we found that the parents had neither bleeding problem during their life time nor abnormality detected by examinations. The pedigree (Fig. 1) of case T-



○ Female
□ Male ■ Chediak-Higashi syndrome affected animal

Fig. 1. Pedigree of a case of Chediak-Higashi syndrome (T-157) in Japanese black cattle showing that the affected animal had clinically normal parents, full sibs, and half sibs.



○ Female ■ Sires who have ever had affected offspring

Fig. 2. Pedigree network demonstrating the common ancestry of all sires of Chediak-Higashi syndrome affected Japanese black cattle. The sire labeled A is the common ancestor and B is A's progeny, the sire or grandsire of most disease-related sires.

Table 1. Numbers of Japanese black cattle in H area used for inheritance mode analyses of the Chediak-Higashi syndrome

Cow no.	No. full sib	No. affected	No. half sib	Sibling no. each cow
1	1	1	11	12
2	1	1	13	14
3	1	1	3	4
4	1	1	0	1
5	2	1	2	4
6	3	1	2	5
7	3	1	13	16
8	4	1	4	8
Total	16	8	48	64

157 demonstrated that the affected animal had normal parents, full sibs, and half sibs. Two C-HS cows (cases T-67 and T-76) that mated with sires, which had never had affected offspring, produced normal calves. On the basis of the facts presented above, dominance of the trait could be excluded. The affected numbers of male and female were approximately equal (27:26), so probable autosomal inheritance was considered. The family tree (Fig. 2) of all the sires who produced affected offspring showed that they had a common ancestor A.

Genetic analyses

Segregation analysis: The data of the affected cattle's fraternities in H area were obtained (Table 1). The *a priori* method of segregation analysis was used to test for specific agreement between the data and the simple autosomal recessive Mendelian mode of inheritance. The expected number of affected cattle obtained was 9.2002 (S.E.=1.0337, d.f.=1, $p>0.5$). This result supported the hypothesis of simple autosomal recessive inheritance.

Gene frequency analysis: As there was no selection in C-HS cattle, this isolated population was thought to be in Hardy-Weinburg equilibrium [7]. Assuming the trait to be inherited as an autosomal recessive, the gene frequency could be calculated from the incidence rate (q^2=8/257) in the region. Therefore, the gene frequency q was 0.1764. Table 2 shows the 29 sires used in H area with numbers of the total and affected offspring of each sire. Only the sire no. 1 produced affected calves in this area. Except no. 1, sires number 10, 14 and 23 had at least one affected calf in areas other than H. If a sire is heterozygous and dam population has a gene frequency of 0.1764, the sire would rise at least one affected offspring in about 33 offspring at $p<0.05$. Thus, the assumptive heterozygous sire with 17 offspring could have one affected calf at $p<0.20$. The probability of 0.20 has been applied to determine the genotype of the parent in rats and mice with small litter-size. Therefore, we selected the sires who had produced more than 17 offspring for population genetic analysis. The population was consisted of 7 sires in which the sire no. 1 alone could be heterozygous. In dam's population, 36 dams were used for the analysis. Among them, each of the 8 cows produced an affected calf, suggesting they were heterozygous. The carrier cows produced 8 affected out of 64 offspring (Table 3). Assuming affected animals would not be included in the parents and Hardy-Weinberg's equilibrium would be established in both sexes at the gene frequency of 0.1764, we could calculate the expected incidence for carriers in the population as 0.300. If the partner of the carriers has equilibrated gene frequency of 0.1764, the incidence of the affected calves in the carrier descendants was calculated as 0.088. Observed and expected values of carriers and affected calves of the carrier descendants fitted well to the hypothetic condition due to a single autosomal recessive trait (Table 3).

DISCUSSION

According to the history of the improvement of Japanese black cattle which has been traced back to the Meiji dynasty, Simmental, Brown Swiss, Shorthorn, Devon, Ayrshire and Holstein cattle have been temporally introduced to improve the Japanese black cattle's performance [4]. None of these

Table 2. Numbers of Japanese black cattle sires and their offspring in H area used in the study of Chediak-Higashi syndrome

Sires	Total offspring	No. affected
1[a)]	56	8
2	35	0
3	33	0
4	21	0
5	18	0
6	17	0
7	17	0
8	9	0
9	7	0
10[a)]	7	0
11	6	0
12	4	0
13	4	0
14[a)]	3	0
15	3	0
16	2	0
17	2	0
18	2	0
19	1	0
20	1	0
21	1	0
22	1	0
23[a)]	1	0
24	1	0
25	1	0
26	1	0
27	1	0
28	1	0
29	1	0

a) The sires who had produced affected offspring in the Southern Kyushu which included H area.

Table 3. Fitness of the simple autosomal recessive genetic hypothesis for inheritance of Chediak-Higashi syndrome in Japanese black cattle

	Carriers	Non-carriers[a)]	Total	X^2	P
No. of sires	1 (2.10[b)])	6 (4.90)	7	0.752	>0.30
No. of dams	8 (10.80)	28 (25.20)	36	1.037	>0.30
	Affected	Non-affected	Total	X^2	P
No. of carrier sires's offspring	8 (4.939)	48 (51.061)	56	2.0806	>0.10
No. of carrier dams' offspring	8 (5.64)	56 (58.36)	64	1.0830	>0.20

a) The animals who did not produce any affected offspring.
b) Expected number (in parentheses).

breeds is related to Hereford and Brangus, in which C-HS has been reported [1, 14, 15], so C-HS in Japanese black cattle seems not to be transmitted from these two breeds. The same disease has not necessarily the same mode of inheritance such as central retinal atrophy in dogs [16]. Therefore, genetic analyses were necessary to confirm the inheritance mode for C-HS Japanese black cattle.

Since the biochemical deficiency involved in C-HS is not fully understood, simple autosomal recessive inheritance of C-HS in affected mammals can be demonstrated in two ways. One is by pedigree examination and statistical analyses as carried out in humans [8, 14], and the other is test mating as performed in Hereford cattle [14], mink [13, 14], rats [10] and mice [17]. In this research, controlled mating was not possible due to space limitation and economic reasons. From the definitely documented mode of C-HS inheritance in humans, Hereford cattle, mink, rats, and mice, we can perhaps extrapolate that C-HS in Japanese black cattle is also inherited by a simple autosomal recessive mode [8]. We used a method similar to that used in the human studies in our investigation. On the basis of the data presented above, good agreement was obtained between the

observed and expected numbers. The hypothesis of simple autosomal recessive inheritance was fitted to the observed inheritance of C-HS in Japanese black cattle.

Present genetic analysis distinguished the possible genotypes of some cattle. Four bulls (no. 1, 10, 14 and 23) and 8 cows (no. 1 to 8) could be regarded as heterozygotes for C-HS. Two sires (no. 2 and 3) could be assumed to be free from the responsible gene for C-HS. If carriers can be detected in autosomal recessive diseases, then the diseases can be controlled in similar ways to those used for mannosidosis in Aberdeen-Angus cattle [9] or bovine leukocyte adhesion deficiency (BLAD) in Holstein-Friesian [6]. For the time being, there is no biochemical and genetic means of carrier detection; so, C-HS carrier can be detected only by pedigree analysis and test matings. Those means are very inefficient and impractical. So, effective means for the carrier detection are expected to be developed.

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REFERENCES

1. Ayers, J. R., Leipold, H. W., and Padgett, G. A. 1988. Lesion in Brangus cattle with Chediak-Higashi syndrome. *Vet. Pathol.* 25: 432–436.
2. Barak, Y. and Nir, E. 1987. Chediak-Higashi syndrome. *Am. J. Pediatr. Hematol. Oncol.* 9: 42–55.
3. Blume, R. S. and Wolff, S. M. 1972. The Chediak-Higashi syndrome: studies in four patients and a review of the literature. *Medicine* 51: 247–280.
4. Fukuhara, R. and Harada, H. 1995. Personal communication.
5. Kramer, J. W., Davis, W. C., and Prieur, D. J. 1977. The Chediak-Higashi syndrome of cats. *Lab. Invest.* 36: 554–562.
6. Nagahata, H. 1994. Pathobiology of bovine leukocyte adhesion deficiency in cattle. *J. Jpn. Vet. Med. Assoc.* 47: 79–85.
7. Nicholas, F. W. 1987. Single gene in populations. pp. 153–194. *In*: Veterinary Genetics (Nicholas, F. W. ed.), Clarendon Press, Oxford.
8. Nicholas, F. W. 1987. Is it inherited? pp. 217-231. *In*: Veterinary Genetics (Nicholas, F. W. ed.), Clarendon Press, Oxford.
9. Nicholas, F. W. 1987. Genetic and environmental control of inherited disease. pp. 311–339. *In*: Veterinary Genetics (Nicholas, F. W. ed.), Clarendon Press, Oxford.
10. Nishimura, N., Inoue, M., Nakano, T., Nishikawa, T., Miyamoto, M., Kobayashi, T., and Kitamura, Y. 1989. Beige rat: a new animal model of Chediak-Higashi syndrome. *Blood* 74: 270–273.
11. Novak, E. K., McGarry, M.P., and Swank, R. T. 1985. Correction of symptoms of platelets storage pool deficiency in animal models for Chediak-Higashi syndrome and Hermansky-Pudlak syndrome. *Blood* 66: 1196–1201.
12. Ogawa, H., Kagamizono, H., Soki, K., Inoue, Y., Kanemaru, K., Shimada, S., Akatsuka, H., Nagata, S., Makimura, S., and Otsuka, H.1989. Hemorrhagic disease of cattle — with special reference to Chediak-Higashi syndrome. *J. Vet. Clin. (Jpn.)* 318: 19–25.
13. Padgett, G. A., Leader, R. W., Gorham, J. R., and O'Mary, C. C. 1964. The familial occurrence of the Chediak-Higashi syndrome in mink and cattle. *Genetics* 49: 505–512.
14. Padgett, G. A. 1968. The Chediak-Higashi syndrome. *Adv. Vet. Sci. Comp. Med.* 12: 239–284.
15. Page, G. A., Berendes, H., Wamer, J., and Good, R. A. 1962. The Chediak-Higashi syndrome. *Blood* 20: 330–343.
16. Pidduck, H. 1985. Is this disease inherited? A discussion paper with some guidelines for canine conditions. *J. Small Anim. Pract.* 26: 279–291.
17. Pierro, L. J. and Chase, H. B. 1963. Slate- a new coat color mutant in the mouse. *J. Heredity* 54: 47–50.
18. Prieur, D. J., and Collier, L. L. 1978. Animal model of human disease—Chediak-Higashi syndrome. *Am. J. Pathol.* 90: 533–536.
19. Prieur, D. J., Collier, L. L., Bryan, G.M., and Meyer, K. M. 1979. The diagnosis of feline Chediak-Higashi syndrome. *Feline Practice* 9: 26–32.
20. Umemura, T., Katsuta, O., Goryo, M., Hayashi, T., and Itakura, C. 1983. Pathological findings in a young black cattle affected with Chediak-Higashi syndrome. *Jpn. J. Vet. Sci.* 45: 241–246.
21. Wolff, S. M., Dale, D. C., Clark, R. A., Root, R. K., and Kimball, H. R. 1972. The Chediak-Higashi syndrome: studies of host defenses. *Ann. Intern. Med.* 76: 293–306.