Identification of Bangladeshi Domestic Cats with GM1 Gangliosidosis Caused by the c.1448G>C Mutation of the Feline GLB1 Gene: Case Study

Mohammad Mejbah UDDIN1,2), Mohammad Alamgir HOSSAIN1,2), Mohammad Mahbubur RAHMAN1,2), Morshedul Alam CHOWDHURY2), Takeshi TANIMOTO1), Akira YABUKI1), Keijiro MIZUKAMI1), Hye-Sook CHANG1) and Osamu YAMATO1)*

1)Laboratory of Clinical Pathology, Department of Veterinary Medicine, Joint Faculty of Veterinary Medicine, Kagoshima University, 1–21–24 Kohrimoto, Kagoshima 890-0065, Japan
2)Faculty of Veterinary Medicine, Chittagong Veterinary and Animal Sciences University, Chittagong 4202, Bangladesh

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ABSTRACT. GM1 gangliosidosis is a fatal, progressive neurodegenerative lysosomal storage disease caused by mutations in the β-galactosidase (GLB1) gene. In feline GM1 gangliosidosis, a pathogenic mutation (c.1448G>C) in the feline GLB1 gene was identified in Siamese cats in the United States and Japan and in Korat cats in Western countries. The present study found the homozygous c.1448G>C mutation in 2 apparent littermate native kittens in Bangladesh that were exhibiting neurological signs. This is the first identification of GM1 gangliosidosis in native domestic cats in Southeast Asia. This pathogenic mutation seems to have been present in the domestic cat population in the Siamese region and may have been transferred to pure breeds such as Siamese and Korat cats originating in this region.

KEY WORDS: acid β-galactosidase gene, Bangladesh, domestic cat, feline GM1 gangliosidosis, lysosomal storage disease.


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GM1 gangliosidosis, a lysosomal storage disease that affects the brain, is caused by an autosomal recessive deficiency in acid β-galactosidase (EC 3.2.1.23), which is encoded by the GLB1 gene [14]. Lysosomal β-galactosidase is required for the degradation of GM1 ganglioside, other glycolipids and glycoproteins that contain a terminal galactose moiety. Deficiency of this enzyme leads to the storage of massive amounts of GM1 ganglioside and related glycoconjugates in tissues, particularly in the central nervous system, resulting in progressive neurodegeneration and premature death. In domestic animals, naturally occurring GM1 gangliosidosis has been reported in cats, dogs, calves and sheep [13, 14].

Feline GM1 gangliosidosis has been reported in Siamese cats in Japan [7] and the United States [1] and in Korat cats in Italy [6]. The disease has also been reported in non-pure breed domestic cats in the United Kingdom [3–5] and Japan [8, 10]. In general, affected cats manifest neurological signs of progressive motor dysfunctions starting from 4 to 6 months of age and die prematurely by approximately 1 year of age. A pathogenic mutation is a single nucleotide substitution from guanine to cytosine in exon 14 at nucleotide position 1448 (c.1448G>C) in the coding region of the feline GLB1 gene, resulting in the substitution of arginine with proline at amino acid position 483 (p.R483P). This mutation has been found in Siamese cats in the United States [9] and Japan [15] and in Korat cats in the United States, Canada and several European countries [2, 17]. However, to our knowledge, the molecular basis of the disease has yet to be defined for non-pure breed domestic cats.

This case study covers 2 native domestic cats in Bangladesh that were affected by GM1 gangliosidosis caused by the homozygous c.1448G>C mutation. This paper also discusses the meaning of this mutation based on the observations in this study.

In Chittagong, Bangladesh in 2009, 2 stray female short-hair kittens, approximately 6 months old, that appeared to be littermates (animals 1 and 2) exhibiting head and limb tremors and dirty hair coats were brought by a veterinary school student (one of the authors, MAC) to the Veterinary Teaching Hospital, Chittagong Veterinary and Animal Sciences University, Chittagong, Bangladesh. Because the 2 cats were suspected of having an inherited neurodegenerative disorder such as a lysosomal storage disease, DNA from whole blood was transferred to the Laboratory of Clinical Pathology, Kagoshima University, Japan, for genetic tests. Due to the poor predicted prognosis, these cats were taken back to the place where they had been found without any clinical or laboratory examination and were not followed up.

In the Japanese laboratory, molecular diagnostic tests for feline GM1 and GM2 gangliosidoses previously identified and molecularly defined in Japan were carried out using polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) methods [12, 15]. The PCR-RFLP assay for feline GM1 gangliosidosis was slightly modified in the present study. Briefly, a 326-base pair (bp) DNA fragment including position 1448 in exon 14 of the feline GLB1 gene was amplified using forward (5′-AGA GCA ATG TCT TCT CCC GAG TCT G-3′, c.1351–122 to c.1351–101) and reverse
(5′-GAG GAA GTC TTT GTA AAG CCA T-3′, c.1482+51 to c.1482+72) primers designed based on the exonic and intronic sequences of the feline GLB1 gene (GenBank accession nos. AF006749 and ACBE01328632, respectively). To detect c.1448G>C, the amplified product was digested by a restriction endonuclease, HaeIII (New England Biolabs, Ipswich, MA, U. S. A.). Both the unprocessed and digested PCR products were subjected to electrophoresis in 3% agarose (Agarose 21, Nippon Gene, Tokyo, Japan). The presence of the mutation was reflected by the presence of 2 fragments, 218 and 108 bp, due to the restriction site (GG|CC) in the mutant sequence, whereas the absence of the mutation in the control was reflected by a single 326-bp band that remained undigested due to the wild-type sequence (GGC). Direct DNA sequencing was also performed to confirm the homozygous c.1448G>C mutation in the genomic DNA of the 2 affected cats using a general sequencing protocol with the same primer pair as for the PCR-RFLP assay.

The PCR-RFLP assay for feline GM1 gangliosidosis demonstrated that animals 1 and 2 were homozygous for c.1448G>C, but the control cat was not (Fig. 1). The PCR-RFLP assay for feline GM2 gangliosidosis demonstrated that animals 1 and 2 did not have the mutant allele for GM2 gangliosidosis (data not shown). The direct DNA sequencing data confirmed that animals 1 and 2 were homozygous for the c.1448G>C mutation (data not shown).

The molecular diagnostic tests demonstrated that animals 1 and 2, both Bangladeshi domestic shorthair cats, had GM1 gangliosidosis caused by the c.1448G>C mutation. This is the first identification of non-pure breed domestic cats with molecularly defined GM1 gangliosidosis. This is also the first report of feline GM1 gangliosidosis in cats in Southeast Asia around the Siamese region. The results of the present study strongly suggest that the c.1448G>C mutation has existed in the domestic cat population in Bangladesh or the Siamese region.

Cats are thought to have been domesticated in ancient Egypt, where the animal was considered sacred, some time before 1600 BC [16], but recent genetic data point to multiple domestication events in separate locations in the Near East 10,000 years ago [11]. Subsequent gradual human migration then spread domestic cats across the globe. Modern cat pure breeds range from the earliest fancy breeds including Egyptian Mau, Persian, Siamese and Korat, which were established during the late 20th century [11, 16]. The Siamese and Korat breeds originated from Southeast Asian ancestors living around the Siamese region [16]. The c.1448G>C mutation may have been transferred from native domestic cats from the Siamese region to the pure breeds such as Siamese and Korat cats in the process of breed establishment, though the common mutation might have occurred separately in domestic and pure breed cats.

As mentioned above, GM1 gangliosidosis has already been reported in non-pure breed domestic cats in the United Kingdom [3–5] and Japan [8, 10], although molecular diagnoses have yet to be made. The disease in these domestic cats might have been caused by the c.1448G>C mutation. Domestic cats carrying this mutation may exist around the world, especially in Southeast Asia. Further studies are required to clarify these important issues for feline clinical genetics.

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