

Gm2 Gangliosidosis in European Burmese Cats

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Introduction:

In May, 2005 we were invited to collaborate in the investigation of a neurological disease in a European Burmese* kitten tentatively diagnosed by pathologists at the University of Illinois, College of Veterinary Medicine as a lysosomal storage disease. Based on characteristic pathological changes in brain consistent with a lysosomal disease, we examined tissues and confirmed that the lesions were those of the gangliosidoses. We performed biochemical analyses which identified the storage material as GM2 ganglioside and found a deficiency of the enzyme hexosaminidase. Unfortunately, none of the 3 mutations that we had previously defined for the feline GM2 gangliosidoses matched with these Burmese kitten's DNA. We then searched for a unique error in the Burmese hexosaminidase gene (DNA) and discovered yet another mutation causing feline GM2 gangliosidosis, the 4th to date (see Table 1). Based on our extensive experience with the feline gangliosidoses, we believed that this discovery had substantial significance for the European Burmese breed. Therefore, we tested a few Burmese families, on a limited scale, which confirmed that our molecular test was able to detect carriers. Discovery of the exact mutation responsible for this disease gave us the opportunity to develop a laboratory procedure which could be used to perform molecular screening to detect carriers among Burmese breeders. Results of this initial screening and our recommendations for broad molecular testing to eliminate this inherited disease are discussed below.

The Feline Gangliosidoses

The gangliosidoses are a class of inherited diseases known as "lysosomal storage diseases", so called because they are characterized by the accumulation of unprocessed material in enlarged lysosomes. The gangliosidoses are progressive, fatal neurological diseases of cats, humans and other animals where gangliosides accumulate principally in neuronal lysosomes. Lysosomes are the digestive system of the cell and responsible for breaking down complex chemicals so that they can be recycled. The gangliosides that accumulate are designated according to their chemical structure as G_{M1} or G_{M2} ganglioside. Therefore, the diseases are identified as either G_{M1} or G_{M2} gangliosidosis, depending on which ganglioside metabolic pathway is blocked. These diseases are

* In future text "Burmese" refers to European Burmese caused by inherited defects in the genes encoding lysosomal enzymes which digest gangliosides. G_{M1} gangliosidosis results from a mutation of the β -galactosidase gene (GLB1) with

malfunction of the lysosomal enzyme β -galactosidase (β -gal). G_{M2} gangliosidosis results from a mutation of the hexosaminidase gene (HEXB) and malfunction (no digestive activity for specific chemicals) of the β -hexosaminidase enzyme (β -hex). It is important to understand that while these two diseases involve a common biochemical pathway and induce similar clinical diseases, they are actually two distinct inherited diseases resulting from mutations of completely different genes.

Diagnosis is the First Step Toward Recognition

Diagnosis of affected kittens is the first step and crucial to the recognition that these diseases exist in a family or breed, because they are inherited as recessive traits and “carriers” who are heterozygous for the mutation are completely normal in physical appearance. Therefore, we describe briefly the diagnosis of affected cats, even though the major emphasis of this paper is on detection of the carrier state. Diagnosis of a kitten showing clinical signs can be accomplished by neurological examination, microscopic examination of tissues, ganglioside biochemistry and enzyme activity assays. A breeder will be the first to suspect an inherited disease if several kittens are born with similar symptoms, especially from the same parents. Next, a veterinarian must have a high degree of suspicion and take the proper steps to achieve a correct diagnosis, usually with the assistance of centers having expertise in the pathology and biochemistry needed for a final diagnosis. The earliest signs of the gangliosidoses are fine tremors of the head and hind limbs. People not experienced with these diseases rarely note these early signs or become concerned enough to seek assistance at that point. Signs progress to unsteady gait, wide stance and inappropriate falling. Even at this stage some owners will attribute these well developed signs to a clumsy kitten. Therefore, when presented for diagnosis, affected cats have well developed signs of incoordination. The onset and rate of progression of clinical signs varies with the specific type of mutation. G_{M1} gangliosidosis typically becomes obvious by 2 to 3 months, is less severe and progresses slowly over 12-14 months. G_{M2} gangliosidosis, variants Baker and Korat are apparent by 2 months, are more severe and progresses more rapidly than G_{M1}. G_{M2} Burmese has an earlier onset with signs severe by 3 months. Late signs include complete loss of hind limb use, raspy voice, blindness, exaggerated response to loud noises and epileptic like seizures.

The gangliosidoses are often misdiagnosed as cerebellar hypoplasia caused by fetal infection with the panleukopenia virus. The key distinguishing features are: (a) the age of onset of clinical signs in the gangliosidoses is 2-4 months of age or older, while the incoordination due to cerebellar hypoplasia is present at birth. (b) Clinical neurological signs of the gangliosidoses are progressive, while those of cerebellar hypoplasia remain static or actually improve with age. In European Burmese, hypokalemic myopathy has been suggested as potential confusion with G_{M2} gangliosidosis. Hypokalemia of Burmese has been known since 1984 and is characterized by periodic muscular weakness associated with loss of potassium in the urine. Probably the key differential features are: while hypokalemia may be seen in young kittens, it is often seen in cats 1-2 years of age or older. A Burmese kitten affected with G_{M2} may not survive beyond 6 months. Hypokalemia results in muscle weakness, rather than tremors, uncoordinated gait and hyperactivity that are seen in kittens affected with G_{M2}. Hypokalemia tends to be periodic, with weeks or months of normal appearance. G_{M2} kittens never appear normal after symptoms start and severity is always steadily progressive. Finally, treatment with potassium may reduce the

severity of hypokalemia, but no treatment reduces the progression or severity of Gm2 gangliosidosis.

The second step in defining a possible case of the feline gangliosidosis is microscopic examination of brain, however, this does not confirm that the storage material is a ganglioside, or identify the chemical type (Gm1 or Gm2). Final diagnosis can be made only by chemical identification of accumulated ganglioside in brain and biochemical detection of reduced activity of the appropriate enzyme. These assays are too specialized for most laboratories and should be referred to a qualified diagnostic or research laboratory. Enzyme assays on tissues of affected cats are reliable for diagnosis because enzyme activity is normally high in liver and brain of normal cats, and affected cats have essentially no enzyme activity. It should be noted that enzyme testing is **NOT** reliable for carrier screening because enzymes are not stable and require special handling, and typically, there is an overlap in values between carriers and normals.

Inheritance of the Feline Gangliosidosis

The gangliosidosis is inherited as a simple autosomal recessive trait. That is, three genotypes exist: (1) *Normal*, defined as both genes are normal and the cat is normal in clinical appearance; (2) *Carrier* or heterozygote, where one member of the gene pair is normal and the second is mutant (single dose of the mutation) and the individual is normal in clinical appearance; and (3) *Affected* or recessive, where both members of the gene pair are mutant (double dose of the mutation) and the individual is clinically affected, as described above. European Burmese Gm2 gangliosidosis is inherited as an autosomal recessive trait. The affected genotype is important only in so much as it is an indication that the gangliosidosis exists in the family or breed. For that reason, accurate and timely diagnosis is very important. However, affected cats only represent the tip of a potentially very large iceberg. Carriers are the most important genotype because they give no physical clues to the existence of the disease, but transmit the mutation to half of all their progeny. In addition, the frequency of carriers in a population far exceeds the frequency of affected animals. For example a disease that affects just 1% of the population has an estimated carrier frequency of 18%! Therefore, the carrier state makes recessive diseases the most dangerous of all patterns of inheritance. This is of overwhelming importance in pure breeds. Typically, a recessive trait is not suspected until an individual shows clinical signs and is accurately diagnosed. If a champion tom is heterozygous (carrier) for a disease trait, he will pass this trait to **half** of his progeny and they in turn will pass the trait to **half** of their progeny. The same pattern occurs if the “founder” of the trait is a queen, but the process of dissemination in the breed is slower. Unless two carriers mate and have an affected kitten, the dissemination process proceeds silently, involving an ever expanding number of cats in more and more blood lines. Even if an affected kitten is born, the delay in accomplishing a definitive diagnosis can be very long if the inherited disease is not well known and if specialized laboratory assistance needed to confirm the disease is not readily available. When an accurate diagnosis is made, unless there is a method for detecting the carrier state and this method can be applied readily, no progress can be made in understanding the breadth of the problem or working toward eliminating carriers. For example, the existence of G_{M2} gangliosidosis in Korats was demonstrated 15 years ago. At that time the only diagnostic procedure available was enzyme assay of peripheral blood leukocytes. This procedure was not adaptable to successful carrier screening because enzyme activity is not stable and even when samples were processed properly,

values for normals and carriers overlapped and an unambiguous assignment of genotype could not be made consistently. An attempt was made to eliminate carriers using this method in spite of these limitations, but the effort was narrow in scope and of questionable benefit. It was not until the gangliosidoses mutations were discovered and a molecular testing began in 1999 that an accurate understanding of the Korat problem was revealed and breeders had the necessary tools to begin eliminating these diseases.

Molecular Characterization of Mutations in the Feline Gangliosidoses

Before a mutation can be characterized molecularly, the gene responsible for an inherited disease must be determined and the DNA of the normal gene must be sequenced. Fortunately, the lysosomal enzymes which degrade the gangliosides were characterized for the human diseases in the 1970's. More recently, the genes encoding these enzymes were sequenced for man and mouse, providing some basis for us to sequence the cat genes. Hexosaminidase consists of two subunits, α and β , which join to form different forms of the enzyme: Hex A ($\alpha\beta$) and Hex B ($\beta\beta$). Each subunit of this enzyme is encoded by a different gene. Harmful mutations in the gene encoding the β subunit of hexosaminidase (HEXB) affect both Hex A and Hex B enzymes, producing G_{M2} gangliosidosis variant 0 to indicate loss of both enzymes. In 1978, we described feline G_{M2} gangliosidosis, variant 0 of short haired domestic, non-purebred cats (f G_{M2} Baker). In 1985, Neuwelt, et al described a similar clinical disease in Korat cats (f G_{M2} Korat). A partial sequence for the normal feline hexosaminidase gene (HEXB) was first reported in 1994 which was used to discover the mutation site. Based on this report, we investigated the mutation responsible for f G_{M2} Baker. We sequenced the HEXB cDNA from f G_{M2} Baker mutants to determine if it differed from the Korat mutation. We discovered that the Baker mutation is different from the Korat mutation. In contrast to these two mutations discovered to date in cats, the human G_{M2} gangliosidosis, variant 0 (Sandhoff disease) results from at least 66 different HEXB mutations. G_{M2} Burmese is yet another mutation which results in loss of both enzymes and a severe neurological disease.

In 1971, we described G_{M1} gangliosidosis in Siamese cats and subsequently similar diseases were described in non-purebred cats. In 1998, DeMaria, and colleagues described G_{M1} gangliosidosis in Korats, providing the first evidence of the unexpected occurrence of both gangliosidoses in a single breed. In all cases the activity of β -galactosidase (β -gal) was absent or reduced to less than 10 % of normal and G_{M1} ganglioside was the predominant storage material in brain. Although, the sequence and sites of mutations have been reported for the human structural β -galactosidase gene, this information was lacking for the cat. Therefore, we sequenced the full length feline GLB1(β -galactosidase gene) DNA from normal cat brain, liver and skin fibroblasts. Based on this normal feline GLB1 sequence we amplified GLB1 from tissues of Siamese G_{M1} gangliosidosis mutants and obligate carriers and identified the mutation. This mutation does not correspond to any of the 23 mutations of the GLB1 known to cause human G_{M1} gangliosidosis. In collaboration with DeMaria and colleagues we sequenced the GLB1 gene from tissues of Korats with G_{M1} gangliosidosis and found unexpectedly that this mutation was the same as that responsible for the disease in Siamese. Since a given inherited disease in a pure breed usually results from a genetic "error" in a single individual, commonly called the "Founder Effect", it can be assumed that the mutation would be unique to that breed. Even if the same syndrome is recognized in a second breed, the assumption would be that the

mutations would be different, such as those observed in feline G_{M2} gangliosidosis of American Long Hair, Korats and European Burmese. Finding the identical mutation in both Korats and Siamese might contradict this principle, except that both breeds originated from Siam (Thailand) and use of Siamese breeders was permitted in the early development of the Korat breed in the West. Therefore, it is likely that the mutation of the GLB1 gene originated in Siamese and transmitted to the Korat breed decades ago. Contributions of genes of European Burmese from or to other breeds might result in the same effect.

Molecular Testing Programs for Carriers of the Gangliosidoses

Having accomplished the characterization of the feline HEXB and GLB1 genes and the mutations responsible for the gangliosidoses of Korats, we were able to organize a Korat Gangliosidosis Screening Program. This program offered molecular detection of carriers of both G_{M1} and G_{M2} gangliosidosis. The advantages of a molecularly based test include: (1) unambiguous assignment of genotype, (2) use of a small volume (0.5 ml) of uncoagulated blood sample, (3) no requirement for processing outside of the molecular testing laboratory, (4) stability of DNA which allows for shipping without refrigeration, and long transit times (up to 7-10 days at ambient temperature), and (5) ability to store samples frozen in the laboratory for months to years.

We received the first samples for screening Korats in March 1998 and currently we are processing sample number 454, which translates to 908 separate tests, since each sample is tested for both G_{M1} and G_{M2} gangliosidosis. Samples have been received from 80 Korat breeders in 12 countries including: Australia, Belgium, Canada, Denmark, Finland, Great Britain, Germany, Italy, Norway, Sweden, Thailand and the United States. This high level of participation is really quite remarkable and makes this a truly international program.

Of the 227 Korats tested between 1999 and 2002, we have detected 38 G_{M1} carriers and 14 G_{M2} carriers. Therefore, the total carrier frequency rate for both mutations in Korats is approximately 23 %. As shown in Table 2 there are some variations in the number of carriers detected and the distribution of G_{M1} versus G_{M2} carriers. Only two countries (United Kingdom and Thailand) appear to be unaffected, to date and Australia has no G_{M1} carriers and only one G_{M2} carrier. This low frequency may relate to the strict quarantine of animals entering UK and Australia which restricts entrance of new breeders from other countries. Except for these two island nations, all other countries have G_{M1} carriers. Four European countries and Canada have no G_{M2} carriers. Norway and the United States appear to have a disproportionately high frequency of G_{M2} carriers. The possibility that as many as one in every 5 breeding Korats is a carrier of one of the gangliosidoses (in the early testing period) is staggering! It would not be surprising if the pattern discovered for Korats resembles that of European Burmese.

Keys to a Successful Molecular Screening Program

We believe that the success that we have been able to achieve with Korats and Burmese resulted from the dedicated leadership of a small nucleus of breeders who encouraged others to participate and their effort was greatly facilitated by the international communication made

possible by the internet. This experience provided much information and direction about how this revolutionary approach can be applied to other inherited diseases in other breeds and species, for which a mutation is known. From our data collected so far, we believe that the magnitude of threat from Gm2 gangliosidosis in the European Burmese breed is comparable to Korats. However, if the Burmese breeders are willing, the same success can be achieved in eliminating this threat.

Confidentiality is an irrevocable principle of a successful testing program. Without it, testing will be incomplete and biased toward individuals who want to publish results. Our laboratory will report only to the owner, unless instructed otherwise. Some of the European Burmese breeders involved in the early testing organized a program known as the Burmese Lysosomal Storage Disease (LSD) “**Data Exchange Group**” (DEG). The DEG is open to any European Burmese breeder who has the desire to help eventually eradicate the mutant Gm2 gangliosidosis gene by working together with other breeders who share this goal. This is a group of breeders who have tested their cats and have agreed to share their test results with the group, but not outside of the group. By joining the DEG, breeders agree to share test results, but these results remain confidential within the group and all group members pledge to honor this confidentiality by not sharing the information about the results of cats, other than their own, with anyone outside of the group. Obviously, information about their own cats, such as certificates of testing may be copied for prospective buyers or breeders, or anyone that any individual wishes to share their own results with. Keeping the test results confidential within the DEG will: (1) Encourage more breeders to have their cats tested, join the DEG, and assist the Breed as a whole to conquer this threat. (2) It is critical that the DEG get as many test results as possible to better understand how widespread the problem is and help eliminate this disease as quickly as possible. (3) Members of the DEG enjoy the opportunity to communicate within the Group to facilitate arranging purchases or breeding with cats known to be normal. Having a cat test positive as a carrier does NOT mean that that this cat must be taken out of a breeding program. As explained below, it does mean that a cat who has tested normal must be found and breed with the carrier and all of their kittens must be tested. Since theoretically, half of all kittens from such a mating will be normal, the opportunity to salvage the best characteristics of can be realized. Kittens who test positive as carriers can be neutered and sold as pets. The DEG will help its members work through the details of such arrangements and provide information and mutual support. Anyone who wishes to join the DEG should contact Robin Bryan at chamsey85@aol.com or Ann-Louise Devoe at tdevoe@columbus.rr.com.

Anyone who wants to join this exchange group are welcome. It is win-win, because members get to see all of the results and the group benefits from results of each contributor. However, anyone who does not wish to participate in the data exchange group is allowed to test anonymously.

The most effective way to assure that data is shared is through a certificate of testing. Anyone buying or breeding should require a certificate confirming that that individual cat tested normal. Notice that there is no requirement (or benefit) to disclose carriers if the individual breeder is inhibited to do so. This certificate program can be enforced on an individual basis, assuming all buyers are informed, or by an organization such as a registry. An unexpected result of the success of the Korat screening program has been the voluntary and regulatory restriction on registering Korats that have not been tested for the gangliosidosis. Regulatory restriction must be overseen by the breed organization. That gives credibility and some force to the program. The best interest of the breed must be addressed through the breed organization. If the

organization chooses to solve this important breed problem through a Task Force, then this group should: (1) represent a cross section of the breed, including international representation, (2) assure that the testing program is operating in an ethical, unbiased and effective manner, (3) keep all interested parties informed about the case frequency rate, distribution and current status of testing, (4) create and implement those policies and procedures deemed necessary and desirable for reaching the ultimate goal of eliminating carriers from the breeder pool.

Molecular Screening Procedures

When the Korat Gangliosidosis Screening Program first began, we received whole blood samples from American and Canadian participants and found these samples to be stable at ambient temperature for the usual time in transit. However, DNA extraction prior to shipment was performed on some samples coming from other continents where speed of shipment was a concern. We learned that DNA extraction from cat blood is different from other species and that most laboratories were not uniformly successful in the cat DNA extraction process. As a result we spent much time and effort trying to use some of these samples without success. It is clear now that overnight delivery service provided by most carriers, and relatively easy compliance with United States Department of Agriculture import requirements for cat blood (USDA Guidelines for Importing # 1102, see attached), make it unnecessary to do any processing outside of our laboratory and whole blood can be submitted from any of the participating countries even if transit time is 7-10 days. We continue to use direct genetic sequence analysis for detecting carriers. Although this method is tried and true, it is laborious, time consuming and expensive. Therefore, we are developing other methods that can be more easily adapted to high throughput processing which will reduce processing time and expense. In consultation with several breeders who helped launch this Program, we developed an official certificate which verifies test results (see attached). We continue to report results by email so that owners will have access to this information as soon as possible, but the Certificate is recognized as the formal document for verifying the gangliosidosis status of any Korat. To facilitate processing official certificates of test results, we developed a "Sample Submission Form" to accompany new samples. This form has been accepted readily and substantially aids in record keeping. This sample submission form and instructions for submitting samples to screen for the gangliosidosis are provided at the Scott-Ritchey Research Center web site at <http://www.vetmed.auburn.edu/srrc> and included in this document.

Preserving the Best of the Breed

We anticipated that if the carrier frequency rate was high and we advised neutering carriers, the result in this small breed would be a loss of the best of the breed and ultimately a genetic bottle neck would result from loss of genetic diversity. In the past, the recommendation to not breed carriers was the standard, if not completely satisfying recommendation. It is clear that in breeds with a very high carrier frequency rate coupled with the limited gene pool will not allow simple removal of all carriers from the breeding pool because of the genetic bottleneck that could result. To solve this problem, we suggest that the best of the breed who were found to carry either of these traits should be mated with a normal (tested) and their progeny tested molecularly. Breeders who wish to preserve the best phenotype of champions are offered assistance in developing controlled breeding programs. If an otherwise healthy, superior carrier is selected for

breeding, only normal cats should be selected as mates and all kittens produced should be tested. As many as 50% of kittens from these mating will be normal and available to perpetuate the best characteristics of that family line, while carriers should be neutered and used as pets. The firm restrictions to this strategy include: (1) a known carrier must be mated only to a known normal to assure that no diseased kittens are born, (2) all resulting kittens produced by this breeding must be tested and only normals can be returned to the gene pool as breeders, (3) all carriers must be neutered. This option probably would not be available without the unambiguous determination of genotype that the molecular test provides. This strategy is being adopted by a few breeders and although our experience to date is limited, it appears to be working well. Without molecular testing, this powerful strategy and resulting benefits could not be offered.

Screening Results to Date (June 2006)

While the European Burmese testing program is very new, we have made good progress to date. The first recognition that this might be an inherited disease occurred in May 2005. The necropsy results pointing to a lysosomal disease were reported in August. Biochemical confirmation of GM2 gangliosidosis was completed in September. Discovery of the mutation was made in October and confirmed in November. The first limited testing of a few Burmese families started in January 2006, and expanded in March. As of June 5, 2006, we have tested 145 European Burmese from 26 catteries. These catteries are located in nine US states and 7 catteries are located in 4 other countries. Fifteen catteries (58%) had no carriers, but the remaining 11 catteries (42%) had varying numbers of carriers. The fact that nearly half of the catteries tested had carriers is particularly revealing and significant. There were a total of 21 carriers (15%) detected in the 145 Burmese tested. The total carrier frequency rate for European Burmese is consistent with the Korat carrier frequency rate for individual mutations (17% for Gm1 and 6% for Gm2). When a new inherited disease is reported, the carrier frequency rate seems to approximate 15-20%, which may represent the point at which carriers mate frequently enough to expose a recessive trait by producing an affected kitten and that kitten is diagnosed properly. Because the sample size of US catteries is statistically significant, the carrier frequency found so far might be a fair representation of rate expected in the United States. Of the 6 European catteries tested 3 had no carriers and 3 had as many as 50% carriers. Therefore, an accurate estimate of the rate in Europe must wait for at least 100 cats from 15-20 catteries to be tested. As with Korats, the frequency in Great Britain and Australia will not represent that found elsewhere.

The Future for European Burmese GM2 Screening

What does the future hold? The Korat Gangliosidosis Screening Program was an historical event. Never before 1999, in veterinary medicine had molecular diagnosis been applied successfully, world wide in an attempt to eliminate an inherited disease from a pure breed. If this Program is ultimately successful, it will be the first time that inherited diseases have been systematically controlled or eliminated from a pure breed through an organized testing program. Based on the enthusiastic participation experienced to date and the self imposed or organized restrictions placed on breeding Korats for whom the gangliosidosis status is not known, it is possible to substantially reduce the carrier frequency rate or even eliminate these diseases from the Korat breed entirely! This historic "experiment" now is being repeated in the European

Burmese Gm2 screening program and we predict it will be imitated many times in the decades ahead and may become the standard procedure to control inherited diseases, in much the same way that vaccination is now the standard for controlling infectious diseases.

With pedigree analysis, testing even a relatively small number of Burmese is likely to have a significant impact on identification of carriers and ultimately on elimination of the gangliosidosis from the European Burmese breed. Using molecular test results, pedigree analysis serves as a powerful tool to identify the carrier status of parents, grandparents and siblings. This is particularly applicable to breeds which require detailed pedigrees for all registered cats. As the number of family lines being tested increases, pedigree analysis will become an even more powerful tool for expanding the genotypic data base.

We continue to do the necessary research which will enable us to provide the information needed to streamline the process for large scale testing. To assist us in financing this foundational research we will seek research funding from agencies or individual donors who are dedicated improving the health of cats.

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Table 1. The Feline Gangliosidosis

Disease	Breeds Affected	Enzyme	Gene	Mutation
Gm1 Gangliosidosis	Siamese	β-gal	GLB1	CGT ⇌ CCT
	Korat	Same	Same	Same
Gm2 gangliosidosis V0				
	Korat	β-hex	HEXB	fHEXB Korat cytosine deletion
	DLH	β-hex	HEXB	fHEXB Baker 25 base inversion
	Burmese	β-hex	HEXB	15 base deletion of intron 11, excision of exon12
	Japanese cats	β-hex	HEXB	unknown
Gm2 gangliosidosis A	DSH	Activator Protein	Activator	4 base deletion, premature term

DLH = Domestic long haired, DSH = Domestic short hair, non-pure bred cats

