Glycogen Storage Disease IV (GSD IV): the disease

Genetic inheritance and own observations

Glycogen Storage Disease IV is an autosomal recessive disorder, the responsible mutated allele is noted GBE 1 (for Glycogen Branching Enzyme 1) and only homozygous mutated kittens express the disease. Heterozygous cats are theoretically not ill. There are also 3 different possibilities in a mating.

(1) Both parents are healthy (homozygous for the normal GBE allele) and all their children will be healthy.
(2) If only one parent carries the mutation (heterozygous for the GBE1 allele), you should statistically get 50% of carriers and 50% of healthy babies. When an unidentified carrier is always mated with healthy cats, there isn't any sign that he carries the mutation, which has disastrous consequences if such a cat has numerous descendants.
(3) When two carriers are mated together, we statistically get 25% of affected cats, 50% of carriers and 25% of healthy cats.

Inherited alleles (**mother / father**)	**m**	**N**
m	**mm (=ill)**	**Nm (=carrier)**
N	**Nm (=carrier)**	**NN (=healthy)**

NB: m (recessive) represents the mutated allele (GBE 1); N (dominant) represents the normal allele (GBE).

Affected cats lineages have been created by John Fyfe (1992-1996) from a NFO carrier ancestor for an experimental study of this disease. This work confirmed the genetic recessive determinism and enabled to estimate the different clinical forms prevalence: 80% of the homozygous mutated kittens are still-born and the remaining 20% develop the juvenile form disease. Interestingly the Glycogen Branching Enzyme (GBE) activity was measured and estimated fewer than 10% (of the normal activity) in the homozygous GBE 1 kittens whereas it was between 17 and 75% for the heterozygous cats.
Thanks to my own observations in **natural** GSD IV lineages, I note that many kittens (50% or more in the litter) from only a carrier parent are weaker, unhealthy and sometimes: several vegetate and die in the first weeks or a little later with a supposed FIP (Feline Infectious Peritonitis) diagnosis.

Even though I observed or heard this special sensitivity in several catteries from different countries, it was always only in some affected lineages, not in all. That's why I wonder if these observations could be related with the variable GBE activity in carrier cats (from 17% which are likely to be sensitive to 75% which are clinically healthy).
We are anyway to closely involved with this "new" disease and this assumption isn't currently proved and only a personal speculation. Nevertheless you should be aware and careful with carrier kittens. For this reason, I personally believe that it's advisable not to keep carrier cats in a selection program for a too long time. On the contrary if the carrier frequency is high, do not neuter all carriers, it would be a disaster for the breed.

NB: this frequency is **estimated** between 10-12% in France and adjacent countries (may 2007-april 2008, Antagene and Genindexe data) and around 9% in Laboklin laboratory (may 2007-october 2007). The carrier frequency was around 15% before beginning to test in the United States.

Population	{Nm} frequency	{NN} frequency	{mm} frequency	GBE normal allele frequency	GBE1 allele frequency
United States (1996)	15%	84,3%	0,7%	91,8%	8,2%
France (2007)	12%	87,6%	0,4%	93,6%	6,4%
Germany (2007)	9%	90,8%	0,2%	95,3%	4,7%

NB: Estimated frequencies in different NFO populations. The carrier frequency obviously decreased as soon as measures were taken for the carriers.

The GBE 1 mutation is sublethal and affected cats die generally before being sexually mature what implies that this mutation is under a natural negative selection pressure. With a simple genetic model, it's supposed that the mutation frequency should decrease about 0,4% for each following generations.
However this model is only reliable in natural population, not in NFO European population because breeding imposes a human selective pressure according to the phenotype and pedigree. A few well-known European cats are/were carriers and unfortunately contributed to increase the mutation frequency because they fathered lots of kittens whose many are in current selection plans.

GSD IV clinical course and pathogenic way

GSD IV corresponds to a deficiency in the α 1-6 glycosyl-transferase protein, also called Glycogen Branching Enzyme (GBE). Consequently to the mutation, the glycogen molecule has fewer glycosyl structural ramifications which damages the glycogen solubility, is responsible for an abnormal systemic glycogen stocking (intestinal, neuronal, immune, pulmonary, muscular cells …) and causes especially disorders in muscular cells.
Thus the GBE 1 mutation prevents the organism to use the glycogen metabolic way and to stock energy from glucose. As a consequence the GSD IV clinical course is dominated by neuromuscular signs, due to a chronic hypoglycaemia getting gradually worse and to muscular cells lesions.

- Most of affected kitten (80%) are still-born or die quickly after birth: this rapid death is presumably related to a strong hypoglycaemia causing cardiac or respiratory failure indeed a neurogenic coma.
- The juvenile clinical form is scarcer (20%) but more specific too. In this case hypoglycaemia is not systematic, possibly because the cat organism is able to use other energy forms for producing glucose (from lipids and proteins). These affected kittens grow more or less until 5 months old but suddenly stop their development and become weaker and weaker with the following clinical signs:
    - High hyperthermia (over 40 degree Celsius) likely due to a strong inflammatory response consequently to the abnormal glycogen systemic accumulation. Corticosteroids are completely ineffective against this hyperthermia.
    - Intermittent generalized body tremors getting permanent (due to hypoglycaemia and/or muscular cells lesions)
    - Intermittent listlessness and "bunny hopping".
    - Muscle weakness then muscle atrophy, fibrotic contractures of selected joints leading to difficulties for moving itself and eating, what involves nursing for the owner.

- Tetraplegia and convulsions.
- The disease is inevitably lethal, often around 10 to 14 months old. Such young adults die of hearth attack sometimes after neurogenic coma because of hypoglycaemia when the cat organism consumed and finished all his energy stocks. The owner often decides to euthanatize his pet because of the lethal prognosis and the cat suffering.

GSD IV diagnosis

It's relatively easy when you know the disease. Although the disease is well-known since 1992 in the United States, just a fewer persons though that it existed in NFO European population too. Consequently the first GSD IV cases are likely to have been undiagnosed until the last year.

You must think about GSD IV when you are confronted with a young Norwegian Cat (4-5 months old) with an unexplained hyperthermia showing muscular and then neuromuscular clinical signs. The pedigree of the cat is obviously another very important point in the diagnosis.
On the contrary the still-born kittens form is difficult to diagnose, simply because lots of other neonatal mortality causes exist. In such a case, the GSD IV hypothesis is not the first to look for, except if the pedigree is risky or if the mating was already led several times with the same neonatal mortality. Anyway there is statically only 25% of still-born kittens and such a low percentage do not generally worry any breeder.

NB1: Differential diagnosis of the neonatal lethal form: traumatisms (dystocy), congenital abnormalities, foetal erythrolysis, viral or bacterial infections, maternal negligence …

NB2: Differential diagnosis of the juvenile neuromuscular form: Feline Infectious Peritonitis, Toxoplasmosis, nervous system lymphoma (FeLV) or infections, other neuromuscular hereditary diseases …

Complementary analyses

Different biochemical and blood analyses can be undertaken. The only relevant variations concern the increased creatinine kinase (CK) level (related to muscular lesions) with sometimes an increased ALT hepatic enzyme level and a decreased fructosamine level (related to a possible chronic hypoglycaemia).
Veterinarians often reported abnormalities in the electrocardiography and ultrasound cardiography scan in the juvenile form with ventricular cardiac hypertrophy which is not to confuse with hereditary hypertrophy cardiomyopathy (HCM).
Needle electromyography or electroencephalography can also be informative without giving the final diagnosis.

Definitive diagnosis just needs a reliable genetic test. Several laboratories currently propose this test in the world: Genindexe and Antagene in France, Lakoblin and Biofocus in Germany, PennGen in the United States. Address, phone numbers and e-mail are available on this link (http://www.pawpeds.com/healthprogrammes/gsdivtest.html).

NB: the GBE1 mutation is a complex structural rearrangement which explains why laboratories develop their own genetic test, different from the first American test, marketed from 1996. European laboratories only proposed it since the last year.

Necropsy analyses

Autopsy does not show any characteristic lesions. Nevertheless it's observed cachexia, muscular atrophy and fibrosis, joint contractures and unspecific cardiac abnormalities.
In the past they used histopathology and special colorations which showed the abnormal glycogen systemic accumulation or measured the Glycogen Branching Enzyme activity.

Treatment and prevention

There isn't any curative treatment except nursing and palliative measures when the cat becomes disabled. The best decision for him is to euthanatize before he goes into a coma or die from heart failure because of the lethal prognosis and his suffering.

On the contrary we are able and must do something for preventing such tragedies.

- All cats used for breeding must be tested once in life or have homozygous normal parents.
    - Homozygous mutated cats die or get ill before becoming sexually mature. They consequently pose no problem for selection because they cannot transmit the mutation.
    - Heterozygous or carrier cats have to be closely watched.

- Carrier should be neutered and his breeding descendants must all be tested.

- However if the carrier is very important for breeding, you can mate him, **but only with homozygous normal cats**. In this case all breeding kittens must be tested and the carriers reserved as pets. Before being sold such kittens should be chipped and neutered.

- Be careful, because even carrier kittens seem weaker in many GSD IV lineages and die before 2 years old in a polymorphic and misunderstood affection. In this case carriers must be neutered as quickly as possible.

- If you introduce a new cat in your selection plans, be careful about his GSD IV status. If he is not tested, do it even though it's just a covering with your dames. Otherwise you must test all kittens.

- In all cases inform all concerned breeders about your GSD IV results, even and especially for the carriers. In Germany, France and Switzerland we succeeded in identifying several concerned lineages and we should be able to go further with testing in North-Europe.

Olympia Edle von Rada clinical course

Anamnesis

Olympia is born in April 2006. The first clinical signs appeared when she was only 4 months old. Firstly there were just hyperthermia (over 40°Celsius), tremors and apathy.
From August 2006 her growth stopped then tremors and ataxia in all limbs (but more important in hind limbs) got gradually worse. Until 7 months old she had normal appetite. Her owner reported nervous fits everyday which lasted a few minutes: after having tumbled, she licked furiously her back and bit furiously all objects she found.

Olympia was seen by different veterinarians and finally followed by the National Veterinary School in Nantes (ENVN, France) when she was 7 months old.
Different analyses were done between August and October: her complete hemogram was normal, usual biochemical analyses were done and were twice normal (urea, creatinine, ALT, PAL, inorganic phosphate, calcemia); just her glycaemia was a little too low. Creatinine kinase was extremely high (1048U/L).

Clinical checking

When the owner consulted in ENVN, the only clinical signs were high hyperthermia, deficient development, and muscle atrophy. The neurological examination revealed just intermittent generalized body tremors.

- Conscious proprioception was normal in all limbs; other postural reaction responses were considered normal.
- The cranial nerve examination was normal.
- All reflexes were normal.

Differential diagnosis

At this stage five hypotheses were firstly viewed.

- Feline Infectious Peritonitis (FIP),
- Toxoplasmosis,
- Hepatic shunt,
- Spinal lymphoma (associated to feline leukaemia, FeLV)
- and after many researches Glycogen Storage Disease IV.

Complementary analyses

- Test for Feline Leukaemia (FeLV) and Feline Immunodeficiency (FIV): negative

- Biochemical analyses

	Results	Usual values
Urea (g/l)	0.38	0.2-0.6
Creatinine (mg/l)	14.1	< 16
Phosphatases alcalines (PAL) (U/l)	37	< 200
Alanine aminotransferase (ALT) (U/l)	**107**	**< 80**
Blood proteins (g/l)	**80**	**65-75**
Glycaemia (g/l)	**0.72**	**0.6-1.1**
Calcemia (mg/l)	108	90-115
Sodium, Na^+ (mEq/l)	150	147-156
Potassium, K^+ (mEq/l)	4.5	3.5-4.5

- A protein electrophoresis was done (protein=84, 5g/l): electrophoresis picture was normal (no gamma globulin peak) and the quotient albumin/globulin too. This result was not in favour with a FIP.
- Hemogram: normal
- Fructosamin measure showed that Olympia was in chronic hypoglycaemia.
- Other hepatic analyses excluded the hepatic shunt hypothesis:
  - liverish acid (before and after meal) and ammonia were in usual values.
  - abdominal ultrasound scan was normal.
- A brain scan which did not show any abnormality.
- A Feline Coronavirus PCR was done on LCR and was negative which excluded FIP once more. Moreover there were just 0,40g/l of protein and a few cells in the LCR, not in favour with an inflammatory process.
- Toxoplasmosis and herpesvirus PCR from the LCR were both negative.

A metabolic affection was privileged afterwards and Olympia was tested for GSD IV in USA (PennGen) thanks to French breeders who heard about a similar case in Germany two years ago. Olympia was homozygous for the GBE 1 allele.

Evolution

Olympia got corticosteroid (anti-inflammatory dose) but there was no amelioration. She was gradually worse and had difficulty in taking and swallowing food. Then she wasn't able anymore to move herself because of ataxia. Generalized body tremors became permanent excepting when she slept.
Her owner decided to euthanatize her in the end of January (10 months old), because Olympia seemed to suffer a lot. Thanks to female we are currently aware that GSD IV exists in Europe and her story enabled to test almost breeding cats in France and hopefully soon in the remaining European countries too.

Glycogen Storage Disease IV (GSD IV): Story and genealogy

GSD IV history

It has been described for the first time in the United States in 1992 and was characterized by strange deaths after neuromuscular troubles concerning only related young Norwegian Forest Cats. Professor John Fyfe succeeded in proving that there was a genetic cause because of the narrow inbreeding for starting American NFO lineages.
The mutation has been sequenced afterwards by John Fyfe, a genetic test has been developed and has been available since 96 in PennGen.

Though the first cases have only been officially reported two years ago in Germany, the mutation is likely well present in Europe because the ancestors of American NFO stayed and fathered other kittens in Europe contributing to widespread the mutation in the NFO European population. As nobody (breeders and veterinarians) really knew about this problem and because almost affected kittens are "just" still-born, the situation was completely ignored in Europe until the last year. In France and adjacent countries, GDS IV testing enables us to keep veterinarians informed of this disease.

GSD IV in the United States in 1992

At this time the affected cats were all very related with the first novices. GSD IV affected lineages studies are obviously difficult since we don't know anything about novices geographical and genealogical origins.

John Fyfe had once identified two lineages of GSD IV in American NFO, by name D* Jarl av Trollsfjord and N* Nano ur Skogi.
Nano ur Skogi is born on the 8th July 1981 in Norway (her brother Prince Charles ur Skogi was also likely to be carrier but he was not officially tested); Jarl av Trollsfjord is born on the 6th september 1984 in Germany and is apparently not related to Nano's pedigree. Only Jarl and his descendants are mentioned in the winterfyre first GSD IV database.

These first observations strongly imply that there are at least (and maybe more) two novices which were carriers and widespread the mutation in the NFO European population. Unfortunately nobody has been able until now to inform me about a possible relation between Nano's and Jarl's ancestors.

N* Pans Tøffen (15/06/77)	N* Pans Silver (25/07/74)	N* Pans Truls (May 73)	N* King
			N* Lucy (14/09/72)
		N* Pans Trulte (05/07/73)	N* Peter Pan
			N* Nusse
	N* Elin von Plysch (10/05/76)	N* Pjewiks Forest Troll (17/04/74)	N* Pans Truls (May 73)
			N* Pippa Frøken Skogpus (01/09/72)
		N* Skrekken (Juni 74)	Foundation
			Foundation
N* Mjavos Satie (22/06/78)	N* Colosseum´s Anton Prikken (18/12/76)	N* Pans Silver (25/07/74)	N* Pans Truls (May 73)
			N* Pans Trulte (05/07/73)
		N* Josefine (01/12/74)	Foundation
			Foundation
	N* Mjavos Scirpus (25/03/77)	N* Pans Tussen (02/04/76)	N* Pjewiks Forest Nisse (17/04/74)
			N* Pans Trulte (05/07/73)
		N* Saga (Juni 75)	Foundation
			Foundation

Nano ur Skogi pedigree

D* Cri-Cri von Oslo (02/10/81)	D* Percy von Oslo (04/02/80)	D* Peter (01/01/77)	Foundation
			Foundation
		D* Fee	Foundation
			Foundation
	D* Salome von Oslo	D* Peter (01/01/77)	Foundation
			Foundation
		D* Fee	Foundation
			Foundation
D* Asta av Tofteberg (09/05/82)	N* Zumack (31/01/82)	Foundation	Foundation
			Foundation
		Foundation	Foundation
			Foundation
	N* Dronning Åsa (September 81)	Foundation	Foundation
			Foundation
		Foundation	Foundation
			Foundation

Jarl av Trollsfjord pedigree

Jarl likely inherited the mutation from his mother, Asta av Tofteberg but we still don't know, whether Zumack or Dronning Åsa was carrier. We don't know too which was the GSD origin in Nano's pedigree.

A. Nano's pedigree

Nano and Princes Charles are children from Pans Tøffen & Mjavos Satie and come from the first NFO novices.

- Pans Truls (born in 1973) 4 times in the pedigree,
- Pans Trulte (1973) 3 times,
- Pippa Froken Skogpus (1972) twice,
- Josephine (1974) once,

- Shrekken (1974) once,
- and Saga (1975) only once too.

There is also a several-year gap between these novices and Dronning Åsa or Zumack, respectively born in 1981 and 82.
All GSD IV carrier novices in the NFO population are likely to be genealogically related because the GBE 1 allele corresponds to a complex and particular mutation which should be unique and comes from a single ancestor. This observation would imply that Dronning Åsa (or Zumack) is related and descends from the ancestor responsible of GSD IV in Nano's pedigree.

Nevertheless I've still not found any satisfying connection between Dronning Åsa/Zumack and Nano's pedigree. Colosseum's and Tofteberg catteries would have worked together: Jakobellas Fabian, a son from Colosseum's Anton Prikken (Josephine's son and present in Nano's pedigree) and Colosseums Fergus (another Josephine's son) were used for breeding in the Tofteberg cattery. But all Norwegian catteries were more or less related in the eighteens that's why we cannot conclude anything just with this observation.

However as there were no doubt about GSD in Europe until 2005, we can imagine that the carriers' frequency is not very high (confirmed by the first results in France and adjacent countries). That's why it's difficult for me to believe that some cats like Pans Tøffen could be the carrier in Nano's pedigree because this sire fathered lots of kittens which were used in European breeding plans. Moreover Tøffen is a son from Elin von Plysch and Pans Silver which both had numerous descendants and are children from well-known novices like Truls, Trulte or Pippa Frøken Skogpus.
Obviously Truls (or one else) could even so be the carrier and in this case he could have transmitted the mutation by chance only to a few children. It's even so possible that several descendants were carriers but breeders would have selected and only kept cats without any litters problem. However this track is undoubtedly not the most realistic.

As far as I'm concerned I think that Nano inherited the mutation from her mother, Mjavos Satie, although I did not have any official proof but only speculation.
Satie's paternal grandparents are the well-known and prolific Pans Silver and the novice **Josephine,** which had lots of descendants in Colosseum's cattery and whose some descendants were used in Tofteberg cattery. These descendants could be related with Dronning Åsa or Zumack, notably Jakobellas Fabian, Josephine's son.
On Satie's maternal side we found **Saga** and Pans Tussen, another well-known and prolific sire which came from Truls, Trulte and Pippa Frøken Skogpus.

Descendants from Josephine, Pippa Frøken Skogpus, Skrekken and Saga were estimated in order to have a more precise idea about.

1) **Josephine**: 5 breeding sons (Colosseum's Kalle, Fergus, Adrian Knur, Anton Prikken & Asopher Tippen), 99 grandchildren (respectively 15, 51, 8, 22 & 3) and 280 grand grandchildren (respectively 47, 181, 10, 42 & 0). If Josephine transmitted GBE 1 in Nano's pedigree, Anton Prikken was carrier (but maybe another too) and lots of his descendants could inherit it.

2) Pippa Frøken Skogpus: especially 2 breeding children, Pjewick Forest Troll & Nisse. This female has not less than 140 grand grand grandchildren, essentially by Pans Toma, Thomas, Tamina & Elin von Plysch (via Pjewick Forest Troll) and by Pjotr av Karibo & Pans Tussen (via Pjewick Forest Nisse). If Pippa Frøken Skogpus is the GSD IV origin in Nano, either Pjewick

Forest Nisse and Pans Tussen were carriers OR Pjewick Forest Troll and Pans Toffen. These possibilities should not be imagined because of the numerous descendants compared to the relatively low carrier frequency.

3) Skrekken: Elin von Plysch as single breeding daughter. This female is mother from Pans Tøffen & Toa. Tøffen fathered 8 breeding children, 35 breeding grandchildren and 147 grand grandchildren whereas Toa fathered 13 breeding children, 77 grandchildren and 256 grand granchildren. If Skrekken transmitted GBE 1 to Nano, Tøffen was carrier (and maybe Toa too) … an unlikely situation considering the first estimated low frequency!

4) **Saga**: 2 breeding children, Mjavos Scirpus & Sara.

- Mjavos Satie from Scirpus: all descendants are in the United States.
- Mjavos Sarabande from Sara: 4 children, 4 grandchildren and 2 grand grandchildren.
- Mjavos Sarastro from Sara: 4 children, 6 grandchildren, 31 grand grandchildren.
- Mjavos Sarda from Sara: 12 children (Enebackens Cicero, Cerina & Hannelore had lots of descendants), 64 grandchildren and 160 grand grandchildren.

If Sarda did not inherit GBE1, Saga hypothesis could be the second GSD IV lineage and that would explain why we apparently do not have so many carriers in the current NFO population. In this case Sarabande and/or Sarastro should be carrier.
Interestingly lots of GSD IV carriers have Saga numerous times in their pedigree whereas this novice had not been very used in breeding.
Obviously that are only speculations and we are likely to never understand completely all GSD IV genealogical secrets, except if we find other independent lineages in North European countries.

B. Jarl's pedigree

There isn't currently any doubt more about the GSD beginning in Jarl's pedigree. Different observations led to think that Asta av Tofteberg was carrier and transmitted it to Jarl, even though we cannot be 100% sure as we don't know if there were only two GSD lineages at the beginning. But which parents did transmit it? No idea!

(1) Zumack had 4 litters in different catteries:

- Dronning Åsa av Tofteberg : Arnt Rosmer, Alex & Asta av Tofteberg (born in 1982) but Arnt Rosmer was not bred.
- Marte av Baune : Sanddrop's Martell, Maxim & Miriam (1983), without any descendants.
- Gyda av Baune : Mjo av Baune (1983), without any descendants.
- Gretemor av Baune : Jorgen, Ludwig, Mjodulf & Silvia av Baune (1983) ; only Silvia was bred. I did not find any GSD carrier which had Silvia av Baune in pedigree.

NB: interestingly some carrier cats which don't have any Tofteberg origin have lots of Baune ancestors in their pedigree. But what should we conclude? That Zumack was carrier and probably other Baune cats? I don't think so and rather believe that Baune cats were anyway often present in pedigree at this time since it was one of the first well-known Norwegian catteries. But it's only a new personal speculation.

(2) Dronning Åsa had another litter in the Felidas cattery but without any descendants.

GSD IV and global testing in France (2007)

I unfortunately don't have access to all French Norwegian Forest Cats GSD results. We currently already know at least 4 lineages responsible of GSD IV in France:

(1) Jana av Trollsfjord which is Jarl's sister and inherited the GBE 1 allele from Asta av Tofteberg.

(2) Nikita Felis Audax

(3) La Forêt´s Imponerende Samson. A possible (but not proved) relation between Nikita and Samson could be Tähtiyön Alfa, for a common GSD origin in these both Danish lineages.

(4) Jonny av Tromsø. Other Tromsø cats are carrier and several inherited the mutation from amber cats (see below) but apparently not in Jonny's pedigree.

GSD IV and amber German lineage (2007)

The first officially affected cats in Europe were amber and enabled us to unearth a problem we have already heard about in the nineteen's.
Obviously GSD IV does not concern only amber cats! Unfortunately amber ancestors met GSD carriers and the inbreeding for fixing the recessive colour selected in the same time the **GBE 1** and **amber** alleles.
GSD IV has been described anyway for the first time in the United States but amber colour never appeared naturally over there, but only several thousands kilometres over there, in Sweden at the same time. We currently know amber and GBE genes located on two different chromosomes proving that both characters are genetically independent.

Today GDS IV testing has been led in almost all amber German catteries and showed a slightly higher carrier frequency in this lineage, undoubtedly due to inbreeding.

Population	{Nm} frequency	{NN} frequency	{mm} frequency	GBE normal allele frequency	GBE1 allele frequency
United States (1996)	15%	84,3%	0,7%	91,8%	8,2%
France (2007)	12%	87,6%	0,4%	93,6%	6,4%
Germany (2007)	9%	90,8%	0,2%	95,3%	4,7%
Amber German lineage (2007)	19,1%	79,8%	1,1%	89,3%	10,7%

NB: An appropriate selection enabled to forget GSD IV in most German amber catteries. In the future all introduced cats in these breeding plans should be tested.

I can conclude today that two well-known cats were unfortunately enough to widespread the GBE 1 mutation in amber cats, by name Jankothan av Takeskog and his sister, Jinni av Takeskog. Jankothan & Jinni are the amber lineage native foundations in Germany. Unfortunately if they inherited the amber mutation from their father, Hopeless Tribes Goran, they also inherited the GBE 1 mutation from their mother, Morky's Mathilda a descendant from Alex av Tofteberg.

NB 1: We also know another carrier female, independent from the amber lineage and which came and inherited the mutation from Morky's Maximilian (Mathilda's brother).
NB 2: S* Morky´s Mathilda/Maximilian - N* Garderåsen´s Catarina - N* Marekatten´s Miriam - N* Fanny af Gjernes - S* Bimus Apollon - N* Alex av Tofteberg. All these cats were likely carriers.

Jankothan and Jinni transmitted both mutations (amber and GBE 1) in almost all their numerous breeding children. This is the explanation for such a GSD carrier frequency in the amber lineage. Until now I'm too closely involved and cannot say if some imported amber Swedish cats were also carriers. We had doubt for some of them but there are not any informative results which could definitively confirm it.

On the contrary we identified two other GSD origins in the German amber lineage. These both origins are obviously less important than Jankothan and Jinni but exist with Icecat's A Star is Born, a descendant from Asta av Tofteberg (fourth generation) and Holly von der Grafschaft which doesn't have neither Asta, nor Alex, nor Dronning Åsa and nor Zumack in pedigree. On the contrary, she presents several times Odin av Æsene.
I personally supposed that this sire could have been carrier: interestingly his mother, Kløfterhagen´s Babuschka, comes from Saga and Odin also has Colosseum's Anton Prikken and Josephine on the paternal side, like in Nano's pedigree.
Kløfterhagen´s Babuschka is the amber "mother" in the NFO population that's why I personally don't believe that she also carried the GBE 1 mutation. Indeed in such a case, we would likely have a higher GSD carrier frequency than 20%, in all amber lineages and not only in Germany …
It's obviously too early for concluding which was the carrier in Nano's pedigree, even though Josephine gathers several disconcerting elements together. Is it only by chance?

GSD IV and other German carrier lineages (2007)

A. Av Tromsø

This lineage unfortunately collected several different GSD origins, firstly Mister X av Takeskog (Jinni av Takeskog son). Two other cats are also carriers but don't descend from the amber lineage.

<table>
<tr><td rowspan="8">D* Smedjebacken´s Sören</td><td rowspan="4">D* Smedjebacken´s Eiric Blabär</td><td rowspan="2">D* Smedjebacken´s Avion</td><td>D* Afjord´s Nils</td></tr>
<tr><td>D* Små-Troll´s White Dorina</td></tr>
<tr><td rowspan="2">D* Lilja-Larosa av Tromsø</td><td>N* Snørre av Huldrepus</td></tr>
<tr><td>S* Brånegårdens Dolly Parton</td></tr>
<tr><td rowspan="4">S* Glofax Dottir</td><td rowspan="2">S* Gistvikens Rasmus</td><td>S* MorrHoppans Lurige Ludde</td></tr>
<tr><td>S* Gistvikens Mona Lisa</td></tr>
<tr><td rowspan="2">S* Glofax Blikfaxa</td><td>S* Gistvikens Silver Red</td></tr>
<tr><td>S* Segersjös Hoppetozza</td></tr>
<tr><td rowspan="8">S* Cicceorina´s Illustra Irina</td><td rowspan="4">S* Cicceorina´s Buggande Brynolf</td><td rowspan="2">S* Janillas Champis</td><td>S* Forest Lov´s Lilla Grå</td></tr>
<tr><td>N* Frida av Elvatun</td></tr>
<tr><td rowspan="2">S* Qvistas Cicceorina</td><td>S* Sarosgards Eddie</td></tr>
<tr><td>N* Torvmyra´s Hoya Carnosa</td></tr>
<tr><td rowspan="4">S* Garderasen´s Victoria</td><td rowspan="2">N* Garderåsen´s Augustus</td><td>N* Christiania´s Christian</td></tr>
<tr><td>N* Tigerstaden´s Cassandra</td></tr>
<tr><td rowspan="2">N* Marekatten´s Miriam</td><td>N* Blåbærskogens Faxe</td></tr>
<tr><td>N* Fanny af Gjernes</td></tr>
</table>

S* Brånegårdens Jonathan	N* Sekan Viko	N* Sekan Sølvtiger	N* Mirk av Calif
			N* Sekan Sitana
		N* Catania av Sultano	N* Kalle av Skogheim
			N* Ravneåsen´s Celine
	S* Qvistas Cicceorina	S* Sarosgards Eddie	S* Finngärdets Fiddler
			S* Fjordkattens Isobel
		N* Torvmyra´s Hoya Carnosa	N* Frigg av Baune
			N* Torvmyra´s Cirkeline
D* Blå Prinsess av Tromsø	NL* Caterwaul´s Trueblue Troll	DK* Alfheim´s Imzadi	DK* Dovregubbens Mischa
			S* Gomorran´s Gloria
		NL* Roosje van´t Blauwe Huis	NL* Knut Nelson av Skogalund
			NL* T´Annes Värld Visa
	S* Brånegårdens Dolly Parton	S* Sjövikens Albin	S* Havskattens Kent
			S* Sjövikens Viktoria
		S* Cicceorina´s Härliga Hanneli	S* Cicceorina´s Artige Affe
			N* Orense Von Figueras

I'm not able to bring you a definitive answer explaining the inheritance in these both pedigrees. Faults could exist in pedigrees which make the studies analysis more difficult. In my opinion there are two possibilities: either the GBE 1 mutation was inherited by the same ancestor in both pedigrees or with an independent way.

- In the first case Brånegårdens Dolly Parton and/or Qvistas Cicceorina could be the carrier.
- In the second case Garderasen´s Victoria (Garderasen´s Catarina's sister) could transmit it in the first pedigree and the second inherited it from an independent (but always unknown) way.

Testing in Swedish lineages could eventually bring interesting new results for understanding these first observations.

B. vom Haukeligrund

D* Asbjörn von Haukeligrund	D* Dino von Mosby	D* Ole von Anna-Söra	Foundation
			Foundation
		D* Fines von Mosby	Foundation
			Foundation
	D* Goldina von Birkeland	D* Odin von Birkeland	Foundation
			Foundation
		D* Swenja von Birkeland	Foundation
			Foundation
D* Haifa von Haukeligrund	N* Ellila´s Linus	N* Syverstad´s Benny	N* Svarteper
			N* Howlid´s Albertine
		N* Syverstad´s Bonita	N* Fernando av Hulder
			N* Bjølar´s Bella Tiffany
	D* Corinna von Haukeligrend	D* Pandora´s Sancho	D* Timo Edler vom Bohnenkamp
			D* Danah von Setesdal
		N* Ødegaarden´s Kaisa	N* Lucky Joker
			N* Trollfjell´s Brosna

It's difficult to analyse this new carrier pedigree and we cannot conclude definitively since Asbjörn's ancestors are not known after the third generation.
Nevertheless Pandora's Sacho came interestingly from Odin av Æsene and Jakobellas Max born in 1983, a grandchild from Colosseum's Anton Prikken and which belonged to the Trollsfjord cattery (which had Tofteberg cats).
All these remarks remain once more only personal speculation, and we do not have enough elements to say which cats were carriers in this pedigree.

To conclude I would like you to understand that studies about GSD affected lineages don't aim to condemn the catteries which unfortunately had carriers in the past it but only to better understand this disease story in the European NFO population. That's why I would be happy and interested by any results which could help me in progressing in this research.

Glycogen Storage Disease IV (GSD IV) in Pawpeds

GSD IV (also called Glycogen Storage Disease type IV) is an autosomal recessive disorder known in humans, horses and Norwegian Forest Cats.
Its pathogenic corresponds to a deficiency in glycogen stocking and most of affected kitten are still-born or die quickly after birth. Sometimes homozygous GSD IV mutated kittens survive, develop a neuromuscular affection and die before 15 months old.

Testing your cat

GSD IV has been described for the first time in United States in 1992 where Pr John Fyfe succeeded in proving that there was a genetic origin because of the narrow inbreeding for the American NFO lineages foundations.
The mutation was sequenced in the Glycogen Branching Enzyme (GBE) gene and called GBE 1 a few years later by the same researcher, J. Fyfe, and a genetic test has been developed and marketed since 1996.
If you wish to DNA test your cat(s) for the GBE 1 mutation, this is possible in several laboratories. Here are some of the laboratories who perform this test (please note that this is not an exhaustive list, there might be other labs that do this also):

1) U.S.A, University of Pennsylvania, PennGen Testing Lab
   http://w3.vet.upenn.edu/research/centers/penngen/services/deublerlab/gsd4.html

2) Germany,
   a. Laboklin - **http://www.laboklin.de/frame.php?lang=en**
   b. Biofocus - **http://www.biofocus.de/data/biofo/de/data/Link_1344_download.pdf**

3) France,
   a. Genindexe - http://www.genindexe.com/pdf/GSD4_FELINS_ENG.pdf
   b. Antagène - **http://www.antagene.com/index.php?page_id=214&rubrique_id=126&coderub1=3&coderub2=0&coderub3=9&langue=L1&menu=**

The disease prevalence was around 15% in the United States at the beginning. The first data in European laboratories enable us to estimate the prevalence around 12% for the France and adjacent countries. This mutation also does exist in Europe and we currently know surely several concerned lineages in Europe.

1) The juvenile form disease is really nightmarish for the adoptive family, because the disease is evolutive on 12 months and inevitably lethal after awful sufferings.
2) GSD IV appeared in the United States because of inbreeding, and then in Germany for the same reason. The same story will be perpetuated if carrier cats are exported in countries where the NFO genetic pool is reduced and needs inbreeding.
3) By disregarding this problem, the disease prevalence will increase as soon as well-known lineages will meet this mutation. It's already a topical problem.

Recommendations for testing

For eliminating the GBE 1 mutation from the NFO population the easiest and most reliable way is to test all breeding cats. Cats can be tested as soon as he is 2-4 weeks old and must be tested only once in life. You don't need to test descendants from homozygous normal parents.

Recommendations for breeding

- All cats used for breeding should be tested once in life OR have homozygous normal parents.
    - Homozygous mutated cats die generally before becoming sexually mature and cannot transmit the mutation.
    - Heterozygous or carrier cats have to be closely watched.
- Carrier should be neutered and his breeding descendants must be all tested.
- However if the concerned cat is very important for breeding you can mate him with homozygous normal cats. In this case all breeding kittens must be tested and the carriers reserved as pets. Before being sold such kittens should be chipped and neutered.
- Be careful, in some GSD IV lineages, it seems that even carrier kittens could be weaker and die before 2 years old. In this case carriers should be neutered.
- As you introduce a new cat in your selection plans, be careful about his GSD IV status and if he is not tested, do it even though it's just a covering with your females.
- In all cases inform all concerned breeders about your GSD IV results, even and especially for the carriers. In Germany and France we succeeded in identifying several lineages and with results from North-Europe, we should be able to go further.

Contact

If you have any questions regarding the health programme against GSD IV you are very welcome to contact one of us:

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