There was a little girl, who had a little curl right in the middle of her forehead,
And when she was good, she was very good, but when she was bad she was horrid!

A child's nursery rhyme

OR THE STORY OF NDG, A LETHAL MUTATION

For the past year, the Pyrless family has been devoted to the problem of trying to identify a lethal mutation in my line. In the summer of 2011, I sold a pup as an LGD for an alpaca farm. The owners had previously adopted 2 adult bitches that had been returned to me. When Big John was 18 months old he was taken to the U. of Pennsylvania veterinary hospital for an assessment of an ongoing apparent neurological condition. The diagnosis was polyneuropathy with associated laryngeal paralysis. I didn't pay much attention to it, but noted it as one of those problems "that happens". Late in 2012, I replaced Big John with a full brother named Jesse, who at the age of 6-8 months, began to develop the same symptoms as Big John. Since the older bitches had lived a long healthy life, I associated the condition with perhaps something environmental – maybe a toxin – on the farm, that would affect a growing pup.

In the summer of 2013, a 3rd pup in a different home, began to show signs of what her owner believed to be some form of muscular weakness, again at about 6 months. Keelee was euthanized in the Fall of 2014 at 21 months. A detailed necropsy indicated widespread degeneration in both the central and peripheral nervous systems.

On December 1st 2013, a beautiful litter of 7 pups was born that I co-bred with Susan Blevens. Sue kept 3 of the pups; 2 others were sold as show potential, and 2 as family pets. Despite a continual problem with pacing, the pick of the litter – Chief, won his first 2 points at 7 months of age. Another sibling, Thor also paced, and a litter sister named Ellie was also fighting an apparent panosteitis. I saw Chief when he was 10 months old, and noticed some mild ataxia in his rear. Chief had an excellent PennHIP rating and therefore Sue thought my laminate floors might be the problem. Shortly thereafter, Sue had Ellie seen by her vet, and he determined that her problem was neurological, not orthopedic. All 3 were evaluated by a neurologist and an MRI for Ellie indicated that she demonstrated cerebellar atrophy secondary to degenerative disease. All demonstrated similar observable symptoms.

During the time between Keelee's necropsy, and Ellie's MRI, it became obvious that I was dealing with a genetic defect that first appeared in pups between the ages of 4 and 6 months. I was devastated learning at the end of my breeding career, that I had, granted unknowingly, introduced a lethal gene mutation into the population. There was a close relationship between all of the 6 affected dogs. They all shared the same sire. Two of the dams were half-sisters. The third dam was a daughter of one of the other two. A Google search on canine polyneuropathy led me to Leonbergers who have 2 different mutated genes causing polyneuropathy. More importantly, that search led me to a group at the University of Minnesota, College of Veterinary Medicine that isolated the mutated Leo genes, and developed a test for them. I contacted the lead researcher of the group, Dr. James Mickelson, Ph.D. Professor of Biochemistry. Since Pyrs contributed to the formation of the Leonbergers as a breed, I asked if he would consider testing blood samples from Chief & Ellie for the Leo mutations they had identified. He thought they would be negative, but agreed to test them anyway. As predicted, they were negative for the LPN 1 and 2 mutations. However, the interdisciplinary team at UMN consisting of Dr. Mickelson, Dr. Kari Ekenstedt, DVM, Ph.D, Assistant Professor, and Katie Minor, RN, became interested in trying to identify the gene causing the neurological problem in the Pyrless dogs.

From that point on, fortune smiled. Closely related families of affected and unaffected dogs that included the parents and siblings, were available for blood sample submissions. Early on I assumed

the disease was inherited in an autosomal recessive manner, but that still had to be proven. My Pyrless family not only contributed the blood samples for the study, but also kept the process confidential in an attempt to prevent idle speculation, mis-information, etc.. We agreed that once factual information was available, the data would be published in the Bulletin. Pet owners were simply told we were participating in a genetic study so as not to alarm them into thinking their adult dogs would become ill.

The Minnesota group had enough grant funds to support the initial preparation of the samples for DNA analysis. A total of 36 samples were analyzed, and In August we were informed that the specific gene mutation had been identified, and that the disease was in fact inherited in an autosomal recessive manner. The results for each of the samples submitted were forwarded to the owners, and to Sue Blevens and myself as alternate contacts. The Minnesota group is currently preparing a scientific paper for publication describing the identification of a gene mutation in Great Pyrenees responsible for Neuronal Degeneration (NDG), as well as listing the syndrome on their website. Through Sue Bleven's employee matching gift funds, we were able to make a significant contribution to the final studies. It is anticipated that a test for carriers will be available by the end of the year for an approximate $65 fee. Testing will enable those dogs identified as carriers to be bred to dogs identified as clear. This combination on average will produce 50% Normal, 50% Carriers and NO Affected dogs. A breeding between 2 carriers will on average produce 25% Normal, 50% Carriers, and 25% Affecteds. By careful breeding policies no more Affecteds should be produced. Testing will allow the Carriers to be safely bred, and kept in the gene pool. On the other hand, breeding 2 Carriers on average will produced 25% Affecteds, and should not be undertaken.

Where do we go from here? The results of the analysis of DNA from 133 Pyrenees in the CHIC DNA bank, indicate that there are other carriers (approximately 5% of the test population) out there. These carriers are distantly related to my dogs – at least 6 generations back. When known Carriers are bred, owners of potential sires & dams will be asked to have their dogs tested for the mutation. When genetic testing is available, any of you who may have dogs distantly related to mine, or had a similarly affected puppy "that happened", should test your breeding stock to know the status of your dogs. Those of you familiar with the dwarf project may remember how far back the mutation was traced. *For this reason, not knowing the origins of the NDG mutation, should, unless both parents have been Cleared, necessitate testing all breeding stock, and in fact requiring It for CHIC registration.*

On a personal level, none of this would have happened without the involvement of those members of the Pyrless family that were directly or indirectly affected. The owner of the LGD dogs allowed us to bring a veterinary neurologist to the farm to examine and videotape the 2 dogs, euthanize them and then transport them to another neurologist for necropsy. Additional veterinarians outside of the Minnesota group performed many of the studies free of charge or for an extremely reduced fee: the veterinarian in Saskatchewan that performed the necropsy of Keelee; the veterinarian in Connecticut who performed the MRI on Ellie and necropsies on the LGD dogs; a research team at UC San Diego, and local veterinarians throughout the country who collected the blood samples. Finally, last but not least, Sue Blevens worked tirelessly organizing the entire process from our end, and maintained constant contact with the Minnesota research team, outside veterinarians, and the dog owners. While she has the angst of watching Chief & Ellie slowly decline, she also has the joy of owning their Group Winning sister!

Finally, why the nursery rhyme? The sire of the pups, and carrier of the gene is BIS, BISS GCh Pyrless No-Brainer HOF, HOF. Sadly Raleigh while boarded, tragically died from unknown causes a week after the gene was identified and before his semen had been frozen. To date he has sired 14 Champions. The carrier dams are Pyrless On My Time, HOF with 8 Champions; Ch. Pyrless Seventh Bride with 2

Champions; and GCh Pyrless Razzle Dazzle with 1 Group Winning Champion. These combinations produced many Specialty winners, a Group Winner, and Group Placers. ***When they were good they were very good……..*** **Valerie Seeley**