



Pathway to Progress

WHO'S WHO

LARS MOE

Professor of Companion Animal Internal Medicine in Norway; published data showing PN is a simple recessive trait in 1989.

VICKY MACLEAN/EDIE THOMAS

Malamute breeders in the US; each bred a litter with PN-affected dogs. Worked for years to educate fanciers; saved DNA on their dogs that helped identify the mutation.

KARIN HULTIN JÄDERLUND

Veterinary neurologist in Norway; heads the Scandinavian PN Research Group that found the gene for PN.

TURID TEIGEN

Malamute breeder in Norway; performed extensive pedigree analyses, documenting cases of PN; created the www.ampoly.info website.

TODD MCGUIRE

Pet owner in Australia; lost his first mal to PN. Launched the Facebook page *Alaskan Malamutes with Polyneuropathy*.

MERETE FREDHOLM

Professor in Denmark; heads the molecular genetics section of the Scandinavian PN Research Group.

MARC KENT

Veterinary neurologist in the US; diagnosed Edie's dogs with PN; wrote *A Clinician's Perspective* for the AMCA.

SANDI SHRAGER

AMCA Health Committee Chair; facilitated collaboration between researchers.

JIM MICKELSON/KATIE MINOR/DIANE SHELTON

Researchers in the US; shared samples from PN-affected dogs; collaborated with the Scandinavian Research Group.

Celebrating the International Team

That Defeated Polyneuropathy

Editor's Note: *The summer of 2012 had its inspirational moments, many of them at the Olympics in London. But to me, the advance made for the future health of Alaskan malamutes by the advent of a genetic test for Polyneuropathy (PN) is the most breathtaking international achievement of this summer. By working to create the "Perspectives on Polyneuropathy" article that was published in the June 2011 issue of the Alaskan Malamute Club of America newsletter, I became aware of people around the world who were striving to solve this devastating inherited health problem in our breed. It was my privilege to be in the loop as the breakthrough happened and the mutation was identified. I'm going to share with you the "behind the scenes" story of PN and the teamwork it took to get us the genetic test. ~Karina Burger, DVM*

The story as I know it begins in Norway in about 1980, when veterinarian Lars Moe realized that the illness seen in the offspring of the first malamutes in Norway (dogs that had been imported from the US in the 1970s) was a breed-specific, distinct genetic disease. He named the disease Polyneuropathy and conducted a test breeding to determine if it was inherited. Dr Moe presented his conclusions that PN is inherited as a simple autosomal recessive trait at the 3rd Annual Symposium of the European Society of Veterinary Neurology in Bern, Switzerland, in October 1989.

It is important to note that PN did not begin in Norway. Malamutes with these kinds of symptoms had been seen earlier in the US, but the disease had never been named or recognized as inherited. Descriptions of dogs with the signs of PN exist in old malamute publications. It was normal to inbreed more closely at that time, but back then the breeders and owners purportedly believed that the ground was poisoned, not that they were seeing an inherited disease in their

dogs. PN is often difficult to diagnose even today, due to the variation in the age of onset and the range of clinical signs and severity.

Based on what he had learned, Dr Moe created a program for the Norwegian Alaskan Malamute Club to avoid producing PN-affected puppies. The system of breeding dogs in Norway is much different than that in the US. A breeder needed the approval of the club to mate two dogs. Dr Moe's research resulted in assigning a statistical probability that each malamute in Norway was a carrier, and the club did not permit two dogs of high risk to be mated to each other. The malamute population was small and very stable due to the difficulty of importing dogs from other countries, and artificial insemination and frozen semen were not widely used then. The program was successful, and for 20 years, no PN-affected mals were known to be produced in Norway. However, Dr Moe warned breeders that the gene was still present in the population. He predicted that PN would return with time, which is typical when you control a recessive genetic disease in this way, and with the introduction of dogs or semen where their risk of carrying the gene was unknown.

In the US in the early 1990s, breeder Vicky MacLean was coping with a troubling illness in her dogs. Two littermates and a half-sibling were affected. Vicky took the dogs to the College of Veterinary Medicine at Washington State University, where PN was diagnosed. Vicky recalls, "About the time my dogs were diagnosed, several very closely related dogs were reported to have shown similar symptoms but were never tested. When I started researching PN, I recollected that there had been a case of an undiagnosed similar problem in some

dogs related to mine, probably in the early 1980s. In talking to the owners involved, it appeared to be the same thing.” Vicky wrote a description of the disease for breeders, which was published by the AMCA and is posted on the AMCA website.

Despite all of the evidence about PN, many fanciers did not want to believe the disease existed. People claimed that it was very uncommon or confined to just a few bloodlines; others declared it was not inherited as a simple recessive. Another theory was that PN in Norway was a different disease entirely than PN in the US, despite the common ancestors seen in many cases. Very few breeders disclosed cases or had their dogs diagnosed by a neurologist. The disease was cloaked in secrecy. Vicky recounts, “The hard part was the vehement denial by some breeders and owners who were producing PN from the same source as I had, but who made every excuse possible for it not to be genetic: insecticides, lead paint, vaccinations, etc.” Vicky was a true leader on health. Her decisions to have cases diagnosed, publicize what she had seen in her dogs, educate breeders, save DNA, and work toward a way to test for carriers represent the gold standard for ethical breeding practices. Vicky never stopped working on PN, even though her fear that she would produce more affected dogs resulted in the end of her malamute breeding program. She continued to drive malamute health forward; the *Perspectives on Polyneuropathy* article was undertaken at her request and urging.

In 2001, US breeder Edie Thomas had the first PN-affected dog diagnosed in a litter that she had bred. Eventually four of the seven pups would be diagnosed with PN. Edie wrote about her experience in *A Breeder's Perspective* for our 2011 PN article. Her accurate description of what this disease looks like and its impact helped many people to better understand PN. In her article, she leaves the culture of blaming and secrecy behind; instead she is honest and forthright and pleads that we do right by the dogs. Edie invited people to contact her to discuss PN after her dogs were diagnosed with it and

became an invaluable resource for information about the disease.

Meanwhile, back in the Scandinavian countries, two new cases of PN were diagnosed just a few months apart in 2009. One was seen at the Norwegian School of Veterinary Medicine, and the other was diagnosed by Dr. Mette Berendt at the small animal clinic at the University of Copenhagen. These cases sparked collaboration between the Scandinavian countries. DNA samples from other PN cases and from normal dogs were sent to Denmark, from Norway by Dr. Karin Hultin Jäderlund, and later, from Finland by Dr. Hannes Lohi. In 2010, Dr Berendt assembled a team of clinicians, veterinary neurologists, pathologists, and a geneticist from Denmark, Norway, and Sweden, to study and document new cases of PN in Scandinavia. (The Scandinavian PN Research Group includes Professors M. Berendt, M. Fredholm, I. Bjerkås, A. Espenes, and L. Moe; Associate Professors Ø. Stigen and K. Hultin Jäderlund; and C. Rohdin, Dipl ECVN.) Dr Karin Hultin Jäderlund led the team.

Norwegian breeder Turid Teigen became involved when a US sire that she had used for breeding produced a litter affected with PN. Turid comments, “I knew of Dr Moe’s work, but when I talked to other breeders, I realized that the simple recessive inheritance of PN was not widely understood.” She started assembling veterinary records and pedigree data on affected and related dogs from around the world. Working closely with several fanciers (including Vicky MacLean, Jody Glenister, Todd McGuire, Edie Thomas, Knut Møllerud, Tove Tveiten, and the Alaskan Malamute Club of Finland), she found evidence that PN exists in all lines of mals. Turid compliments the Alaskan Malamute Club of Finland, stating, “The club had a very systematic approach to address the disease. They thoroughly educated puppy buyers and breeders about PN through their home page and through breeder’s meetings. Anyone with an affected dog received practical, financial, and moral support to test the dog. In addition, blood samples were stored for future research.”

Turid collected documentation on suspect PN cases, sometimes 30+

pages of veterinary reports, pedigrees, and statistical analysis per dog. At the request of the genetic researchers, including Drs Merete Fredholm and Lars Moe, Turid sent them her pedigree analyses. When she distributed the researchers’ email address to breeders, asking breeders to disclose cases of PN they had seen or heard of, the mailbox quickly filled to capacity! Most breeders wanted to know which dogs were carriers, but this proof of fancier interest in PN helped to begin the search for the mutation.

Turid’s painstaking work resulted in several affected dogs being identified and included in the PN study. Dr Karin Hultin Jäderlund states, “Turid has really helped us in many ways with this research. Her ability to establish contact between breeders and owners all over the world, as well as the information, pedigrees, and databases she shared with us, was as good as gold for a researcher in this field of science.” At Turid’s request, the Chair of the AMCA’s CCC Committee, Dan Anderson, sent the Alaskan Malamute Assistance League pedigree database to the research team in Denmark, an invaluable tool in this type of work. As more people started discussing PN, the denial and misinformation in the malamute world often created tension and slowed progress. In response, Turid launched and today maintains a website on PN (www.ampoly.info), which contains all the research articles available about PN. In addition, owners of a sick dog could list their dog and its pedigree publicly, if they showed proof that the dog had PN. Providing this avenue for factual, constructive communication about PN helped to identify common ancestors in new cases and guide breeding decisions to avoid breeding carriers to each other. Today, Turid offers to post the PN genetic test results on the website. To participate, contact her through the site.

In Australia in 2010, first-time mal owner Todd McGuire was struggling to figure out what was wrong with his beloved Mia. His search for answers led him to Vicky’s article on PN and put him in touch with Vicky, Edie, and Turid. Losing Mia to PN inspired Todd to take action to help our breed. He wrote and published his experience in

OUTSTANDING SERVICE AWARD NOMINATION

Breeders Vicky MacLean and Edie Thomas have given many years and tears to advancing our understanding of Polyneuropathy (PN) in Alaskan malamutes. Both Vicky and Edie faced one of the most character-defining decisions a breeder can encounter: What do you do when you produce a devastating and life-threatening, genetically-inheritable disease in your dogs? These ladies handled the situation with honesty, integrity, and class. They not only met the challenge, they conquered it. Crucial actions that they took, including disclosing cases of PN in their breedings and saving/banking DNA samples from affected dogs, helped the research team to identify the mutation and to develop the genetic test.

Resolutely leading us forward, Vicky's story on PN (published on the AMCA website) was some of the most helpful information in existence on the disease. Vicky made us believe that the disease existed and shared pedigrees with owners around the world that identified common ancestors in affected dogs. Her determination that there would ONE DAY be a DNA test for this disease never wavered; she worked toward a solution for PN since the early 1990s.

Edie stepped up to the plate and wrote the article "A Breeder's Perspective," published in the June 2011 issue of the AMCA Newsletter. Few breeders would disclose to the world in this way that a major genetic problem had been found in their dogs. Edie's accurate descriptions of the appearance and the impact of this disease have helped many people to better understand PN and led to more malamutes being diagnosed and their DNA sent to the researchers.

Vicky's and Edie's years of work to educate malamute owners about Polyneuropathy and to find a way to prevent it have paid off for all of us and will benefit the health of the Alaskan malamute for generations to come. For their tireless efforts to improve malamute health, Vicky MacLean and Edie Thomas deserve to be recognized with the AMCA's Outstanding Service Award.

the Alaskan Malamute Club of Victoria's newsletter and granted reprint permission to the AMCA (*A Pet Owner's Perspective*). By starting the Facebook group *Alaskan Malamutes with Polyneuropathy*, he took on a role to coordinate efforts and share information internationally about the disease. Todd's efforts to facilitate communication resulted in more dogs with PN being identified and included in the research.

In Denmark, geneticist Merete Fredholm headed the molecular genetics section of the research team, and was awarded funding to look for the gene that causes PN. The mutation that causes PN in Greyhounds had just been identified, and the team looked at that gene in the first two DNA samples that they had, on one affected and one normal dog. Amazingly, they found that the mal with PN had a different mutation in the same gene that causes Greyhound PN. The results looked promising that they had found the mutation that causes malamute PN, but the number of samples they had was much too small to be statistically certain that this finding was not just a coincidence. The team restricted their research to only include dogs in the Scandinavian countries that they themselves diagnosed with PN, knowing that if a dog were misdiagnosed with PN and included in the study, it would confuse the results and make it hard to tell if they had really found the mutation. Wary of being overwhelmed by emails from breeders again, the team was reluctant to share their preliminary data. However, Drs Karin Hultin Jäderlund and Lars Moe agreed to write *A Research Perspective* for the AMCA's PN article.

Edie persuaded her veterinary neurologist, Dr Marc Kent at the University of Georgia College of Veterinary Medicine, to write *A Clinician's Perspective* for the PN article. Ten years before, Dr Kent had done a study on Edie's litter for free after the second affected dog was found. Dr Kent's generous deeds paid big dividends for Alaskan malamute health. Because Edie's dog Petey had been diagnosed by a veterinary neurologist, with all of the diagnostic testing explained in the article he wrote for us, and because

Edie had banked DNA, the Scandinavian research team accepted his DNA to their study - the first dog from the US to be included in the search to find the gene! Turid contacted the Canine Health Information Center (CHIC), and they immediately sent a small amount of the DNA they had to the Scandinavian researchers. Petey's result helped validate that they had found the right mutation. Turid notes, "This was a very valuable sample because Petey's pedigree was different from the other PN-affected dogs that had been analyzed at that point in time."

At this point, the researchers had very promising results, with all the affected mals showing one form of the gene they were looking at and non-affected dogs having a different form of that gene. But they really needed more affected and related dogs to achieve statistical certainty. An unexpected impact of the *Perspectives on Polyneuropathy* article and the hard work of its co-authors was that the researchers began accepting samples from the US for their study.

AMCA Health Chair Sandi Shrager had asked University of Minnesota College of Veterinary Medicine researcher Dr Jim Mickelson, who had found the PN mutation in Leonberger dogs, about starting a study to try to find the gene in mals. Together, they had located DNA samples from several PN-affected mals. Dr Mickelson credits his canine genetics laboratory manager, Katie Minor, as "the force driving our efforts to get samples. The other person to single out is Dr Diane Shelton at the University of California San Diego Department of Pathology Comparative Neuromuscular Laboratory. A world leading canine neuropathologist, Dr Shelton maintains a database of samples from cases she has seen. She provided us with her samples, and she had performed the diagnostic testing proving these mals were affected with PN." Upon learning of the Scandinavian team's promising results from Sandi, Dr Mickelson contacted Dr Fredholm and immediately offered to share the samples he had. Dr Fredholm enthusiastically accepted and offered to include all relevant scientists from

Dog: "Tundra" - Ruby Mtn's Tundra
Owner: Jody Glenister



Dog: "Nunaka" - Amaguç's Braveheart
Owners: Joni Engström/Kati Bruce



Dog: "Kaya"
Owner: Karen Mohr



Dog: "Petey" - WindStar's Pistol Pete
Breeder: Edie Thomas



Dog: "Valtti"-Hauenkuonon God Only Knows
Breeder: Sisko Nurminen



Dog: "Una" - Inupiat's Tikilik Una
Breeder: Turid Teigen



Dog: "Bo" - WindStar's Gunsmoke
Breeder: Edie Thomas

LEAVING A LEGACY

MEET THE DOGS BEHIND THE BREAKTHROUGH

DNA from about 100 malamutes was the key to identifying the mutation that causes Polyneuropathy. The genetic test that is now available to us would not exist if not for these dogs and their owners who sought a diagnosis, disclosed the illness or relationship to a PN-affected dog, and banked DNA. 22 of these dogs had PN; the rest were healthy and related by pedigree to affected dogs. Some of these dogs are alive today, while some died more than 15 years ago. Yet they all left our breed a legacy of better health, through their DNA.

the US groups in the publication of the research. For their immediate agreement to work together as collaborators and move us forward on PN, every fancier in our breed owes all of these researchers a debt of gratitude.

The story now returns to and fittingly ends with Vicky MacLean, who had saved cheek swabs on her affected and related mals for years. She stored them in her closet at home, and every time she had to evacuate due to wildfire risk, she always evacuated with these swabs! She had only a couple of swabs left on each dog, having sent some over the years to researchers that had found the PN gene in other breeds to check if

malamute PN was the same as those breeds. As the Scandinavian research group included more dogs in their study, the value of Vicky's swabs went up. Several of the samples that she had were expected to test as carriers. When Vicky forwarded us the report from the research team that the six samples she had sent to Denmark had tested as expected (two affected and four carriers), it was incredibly moving. That those samples, which Vicky faithfully saved for almost 20 years, ended up helping to make a major advance in the health of our breed is a real testament to what it means to "do right by the dogs."

How do we find ways to unite and work together to solve health problems

in our breed? The PN story shows that progress is made by those who stand up and take the actions they can take, whatever those actions may be, to accomplish something. Each person named in this story did whatever actions he or she could do and found ways to work together across countries, across languages, across clubs, and across research institutions. The summation of all these parts is how this important milestone was achieved for the benefit of the Alaskan malamute.

Now it will be up to all of us in the fancy to do right by the dogs and to breed Alaskan malamutes that are not affected with polyneuropathy.