10th Bernese Mountain Dog

International Health Symposium

30.8.2015 Helsinki Finland

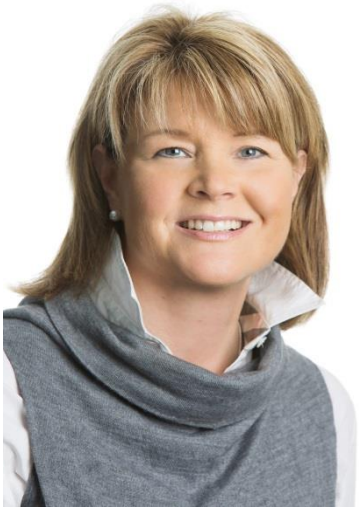
SUOMEN SVEITSINPAIMENKOIRAT –
FINLANDS SENNENHUNDAR ry

Program

9.00	**Opening** Ilona Jaanu
9.03	**Appearance of the Bernese Mountain Dog in the past and today** Jens Ramsing and Satu Ylä-Mononen
9.45	**Longevity and histiocytic sarcomas in Bernese Mountain Dogs - Results from genomic breeding values, practical experiences and new insights from whole genome sequences** Prof Ottmar Distl, Dr Norbert Bachmann, Christel Fechler
10.55	**Coffee**
11.15	**Increasing longevity by EBVs (estimated breeding values)** PhD Katariina Mäki
12.00	**IPFD and DogWellNet.com: A Collaborative Platform to Improve Dog Health** BSc DVM PhD Brenda N Bonnett
12.30	**Lunch**
13.30	**The Finnish Kennelclub as a guide for breeding** Kirsi Sainio (SKL-FKK)
14.00	**The French genetic risk test for Histiocytic sarcoma, pre-test SH: validation on different populations and state of the art on research** Dr Catherine André and Dr Benoit Hedan
15.00	**Coffee**
15.20	**A brief update from the President of the Berner-IWG** Martha Cehrs, President Berner International Working Group
15.30	**Genetic research and testing in dogs including Bernese Mountain Dogs** Prof Hannes Lohi
16.30	**Discussion**
17.00	**Closing**

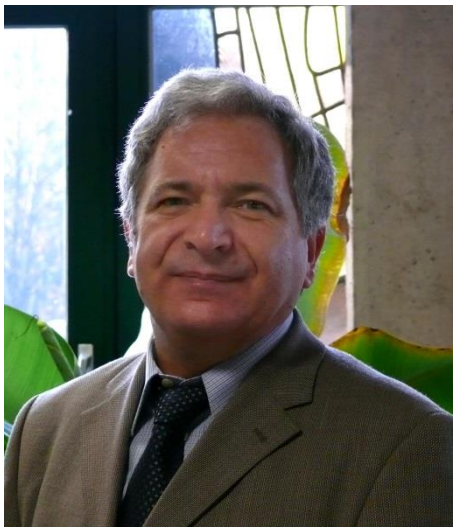
Appearance of the Bernese Mountain Dog in the past and today

Mr Jens Ramsing has been a breeder of Bernese Mountain Dog since 1970, first under the name ”Danettas”, and together with his wife Lisbet since 1984 under the present name ”Sennetta’s”. He has from the start been showing own dogs in nearly all Europe, where he has been able to win many big shows during the years, and also been able to obtain several World and European Winners as well as National and International Champions. In 1977, he founded the Danish Bernese Mountain Dog Club (DBSK), and for a period was president for the club. In 1980 he was educated as judge both in Denmark and Germany for Bernese Mountain Dog. His work for the Bernese Mountain Dog breed has given him the following honors: In Switzerland as a veteran for the breed, in Germany with the silver pin and later the gold pin, in Austria for his special efforts for the breed given at the clubs 20 year anniversary, and in Denmark as a honorary member of the club. (pic Soren Wesseltoft)



Ms. Ylä-Mononen began to breed and exhibit Bernese Mountain Dogs in her native Finland in 1982. She has been awarded several plaques for her work within the breed.
She became a judge in 1999 and is licensed to judge several Working, Sporting and Herding breeds. Ms. Ylä-Mononen has judged in multiple specialties and also in numerous countries all over the world. She is very active within the breed. She served as a secretary for the Swiss Mountain & Cattle Dog Club of Finland for 10 years and as the president of the club’s Breeding Commission for 9 years.
She has held several posts in the Finnish Kennel Club’s breeding and veterinary committees. Currently she is a secretary of Finnish Dog Show Judges' Society.

Longevity and histiocytic sarcomas in Bernese Mountain Dogs - Results from genomic breeding values, practical experiences and new insights from whole genome sequences



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The breeding objectives of the Swiss Mountain Dog Breeding Association for Germany (SSV-Germany) are aiming at to significantly improve length of lifetime and to reduce risks to death caused by histiocytic sarcoma (CHS) and degenerative myelopathy (DM) as well as to decrease prevalence of hip dysplasia (CHD) and elbow dysplasia (CED). Our studies on life expectancy support that length of lifetime is an inherited condition and heritability estimates (h2) were at 0.30-0.35 using animal models for right censored and uncensored lifetime data. Co-evolution of dogs with humans seems to have influenced lifetime of dogs resulting in different gene variants for differently long lifetimes. Several transgenic mouse models have proven genetic variants as responsible for different lengths of lifetime. Extreme long lifetimes of humans are associated with rare genetic variants. Heritability estimates in human for extreme long lifetime have been estimated at around h2 = 0.5. Breeding strategies aiming at to increase length of lifetime and to reduce the prevalence of fatal diseases should be most effective for Bernese Mountain dogs. The project "Long-living Bernese Mountain Dog" was initiated by the SSV-Germany in 2010. A main keystone of this project was the incorporation of genomic breeding values using the canine Illumina high density beadchip. The main principles of estimation genomic breeding values for dogs have been patented in 2009 for CHD in canidae (EP2123775 A1) through the University of Veterinary Medicine Hannover, Germany. The SSV-Germany was in the position to provide the first genomic evaluations for CHD, CED, longevity and histiocytic sarcoma. The DM test was added some years later. Here, we could show a case with DM and a compound heterozygous genotype for exon 1 and exon 2 of the SOD1 gene (Pfahler et al 2014).
The project "Long-living Bernese Mountain Dog" was based on data for longevity and death reports, the preventive breeding radiographic examinations for CHD and CED as well as the biobank for Bernese Mountain Dogs of the SSV-Germany. In the start of the project the most up-to-date data was used and a total of 174 Bernese Mountain Dogs were selected as reference (training) sample. Dogs selected for genotyping were evenly grouped according to ancestry, sex, age, CHD and CED scores. The reference sample contains only dogs with full phenotype and genotype data and pedigree information and thus, is the basis for standardization of the genomic breeding values. Genome-wide association studies (GWAS) were performed for CHD and CED (Pfahler and Distl 2012) and longevity, CHS and DM using the canine Illumina high density beadchip with 173.662 single nucleotide polymorphisms (SNPs). All genomic breeding values were derived using the same high density beadchips with 173.662 SNPs. In the meantime, the reference samples were extended and actually include between 300-600 individuals in dependence of the availability of the phenotypic data for the different traits.

The genomic breeding values for longevity are standardized to a mean value of 100 with a standard deviation of 10 points. Dogs with genomic breeding values at 96-100 for lifetime carry genetic variants for an average lifetime expectancy of 8.3 ± 1.5 years. Animals with genomic breeding values >110 have an extremely long lifetime expectancy (12-15 years). Dogs with genomic breeding values <85 have a lifetime expectancy of less than 6 years. The genomic breeding values explained 74% of the phenotypic variance of the observed lifetime. The predictive reliabilities for all the different traits were >50% if independent subsamples were selected from 50% of the animals in the reference data set. The genomic breeding values are already available for younger breeding animals.

Actually, the database contains 730 Bernese Mountain dogs with genomic breeding values for longevity, histiocytic sarcoma, CHD and CED as well as DM exon 1 and exon 2 haplotypes. In addition, we use this data for estimation of genomic inbreeding coefficients. Genomic inbreeding coefficients reflect inbreeding over much more generations than captured by pedigree data and are comparable among the different individuals. The genotyping results have been supplemented with whole genome sequences of six Bernese Mountain dogs and a further batch of 3 samples will be sequenced in the next months. This data allow us to detect genetic variants associated with the traits under study, to uncover genomic regions under positive selection and genomic regions with reduced genetic variability specifically for Bernese Mountain dogs. Using stringent quality control of our next generation sequencing (NGS) data, we filtered out a total of 14.937.775 SNPs, whereof 235.964 SNPs were private for Bernese Mountain dogs. Combining different methodologies based on GWAS, regions of homozygosity and private genetic variants, we retrieved a set of candidate mutations for longevity and histiocytic sarcoma. The genetic variants are now genotyped for validation in a large sample of Bernese Mountain dogs. The objective of this study is to define a comprehensive set of polymorphisms with a strong causative correlation with the traits of the breeding objectives and to base genomic breeding values on an informative set of some millions of SNPs covering the whole canine genome. Further sequencing of Bernese Mountain dogs allows us to impute the genotype data from the canine Illumina high density beadchip onto the highly reliable genetic variants detected using NGS. This means that the millions of genetic variants from the NGS data will be made available for all Bernese Mountain dogs genotyped on the canine Illumina high density beadchip.

In conclusion, the SSV-Germany can offer the breeders genomic breeding values for hip dysplasia, elbow dysplasia, longevity, histiocytic sarcoma and haplotypes for SOD1 associated with degenerative myelopathy. In addition, genomic inbreeding coefficients can be provided and lethal mutations can be explored in order to avoid risk matings among carriers. Further traits can be included in the prediction procedures when sufficient phenotypic data are available. Through the availability of whole genome sequences millions of genetic variants in the genome of Bernese Mountain dogs can be exploited for genomic evaluations and the search for genetic variants causing specific conditions. The SSV-Germany offers all Bernese Mountain dogs breeders to submit samples for genotyping and estimation of genomic breeding values as well as estimation of genomic inbreeding coefficients. Bernese Mountain dogs are tested for free if these individuals reach a lifetime of 12 or more years or show a histiocytic sarcoma or any other specific inherited condition. We have opened a route for samples from North America. Samples from North America must be shipped directly to our contract lab in the US. More details can be obtained from the SSV-Germany or our institute.

Dr Norbert Bachmann and Christel Fechler

Breeding strategy of the SSV was based on three pillars until 2012

1. Capturing , storage and maintenance data

2. Collection, processing and warehousing Blood sample & DNA-extraction
3. Breeding with phenotypic information

Information like diagnoses, reports and age of death was collected long time. Questionnairy were used to get a larger amount of data. Breeders were awarded of the transparency of the information by mention on club's website and annually reported living report and reports of the past dogs. For the breeders was developed phenotypic breeding value for longevity.

SSV founded blood bank on 1996 to collect the samples from breeding dogs for the DNA analyst. Samples were collected also from dogs with for example a severe dysplasi, bad elbows, MH-suspicion.
Until 2012 breeding based only for the information of the phenotype.
Since 2004 this information has included confirmed information from over 10 ancestors out of 14. These are the information about living dogs (certificate not older than a year) or date of death. Breeders have given more tension to age when planning breeding which has been noted since phenotypic breeding value for longevity started to use.

Since 2011 SSV has together with Dr Distl has developed genetic breedind values for longelivity, hip dysplasia, elbow dysplasia and test for HS. After 2012 SSV there have been made voluntary genomic tests which all breeders can use.
This is base for the breeders to make breedind decisions. SSV organize annually several briefings about genetic base breeding values. In SSV Christel Fechler is the leader of the breeding and Dr. Norbert Bachmann is the projectmanager. They both answer to the questions of genetic breeding values.

Until today 729 dogs have been tested genetically. Breeders appreciate these results when making their breeding plans. In the SSV organisation over 30 % of the puppies are born have genetic tested parents. The percentage is rising all the time because these puppies are really wanted.
SSV has chosen a long and hard road to achieve the longer life expectancy of Bernese Mountain Dogs. SSV breeding managers thinks it is very important to follow and tested constantly breeding values.

Today we present to you some of the stepping stones. One of these is that in the light of current knowledge the SSV-pretest for the HS in order to achieve a longer life is not alone enough. At the same time must also be considered the progress of genetic life expectancy values.

Increasing Longevity with Estimated Breeding Values

Lifespan is a partially hereditary trait, influenced by many genes. It is not possible to use lifespan phenotypes of potential breeding dogs themselves when selecting dogs for breeding. On the other hand, phenotypes of relatives are influenced by environmental factors. These facts make it difficult to know which dogs should be chosen for breeding when the goal is to increase longevity.

Swiss Mountain & Cattle Dog Club of Finland has been gathering information on dates and causes of death of Bernese Mountain Dogs starting from 1995. Information has been gathered also from Switzerland and Germany.

In 2012, first longevity breeding values (EBVs) were estimated for the breed. EBV is an estimate of an individual's genotype (genes) in a certain trait. Longevity EBVs are estimated with BLUP animal model, which is able to include all the lifespan information of the dog's relatives, and simultaneously take into account environmental effects.

EBVs are being updated once or twice a year. They are estimated for two separate data sets: Dataset 1 includes only dogs which have died. Dataset 2 includes also so called Still Going Strong –dogs, i.e., the dogs which have been reported to be alive at 8 years or older.

In August 2015 the Club has gathered information on the dates of birth and death of 2924 dogs (Dataset 1). In addition, there are 205 Still Going Strong dogs; thus, the number of dogs in the Dataset 2 is 3129. There are 1605 females and 1472 males. The dogs have been born between the years 1959 and 2014, and they have died between 1968 and 2015. The dogs come from 1607 litters, 628 sires and 1081 dams. Mean lifespan is the same in both Dataset 1 and 2 (8.0 years). Mean lifespan of the Still Going Strong dogs is 9.1 years.

The effects that are being taken into account in the EBV estimation are at the moment

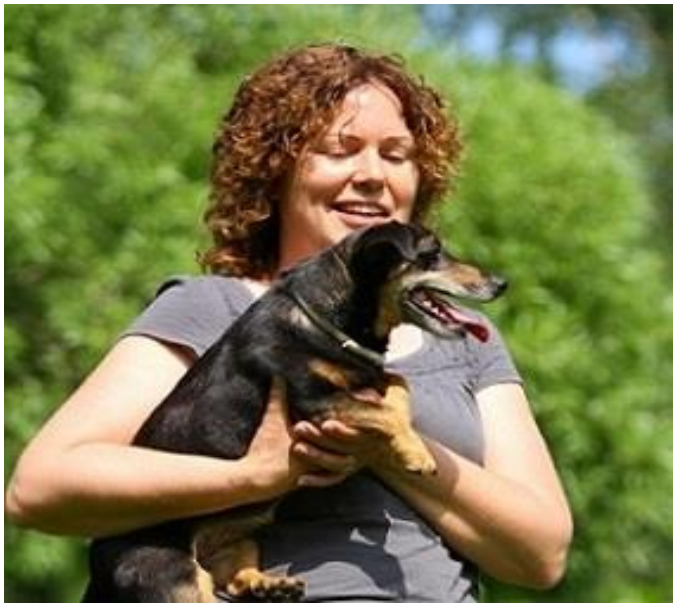
- cause of death
- country (Finland, Switzerland or Germany)
- sex
- birth year
- litter.

This makes EBVs comparable between males and females as well as between countries. Information on the cause of death is lacking for 1470 dogs, and thus this important effect cannot be taken into account for every dog.

Estimate of heritability for longevity is now lower (7-9 %) compared to the previous EBV update (11-16 %). The estimate of heritability changes all the time as more data accrues. Litter effect explains 7-8 % of the differences between dogs' lifespan. This effect includes all the environmental and some genetic effects common to the members of the same litter.

Breeding for or against a trait is always possible if there are differences between the dogs and if the heritability is larger than zero. With a low heritability (<30 %) the dog's own phenotype is not an accurate enough estimate of its breeding value, and information on the phenotypes of relatives is needed. This can easily be achieved with EBVs estimated from a comprehensive data set.

Katariina Mäki works in the Finnish Kennel Club (FKC) as a breeding expert. She takes care for example of the EBV estimation, as well as development of the breeding database. In addition she works with various affairs related to breeding and welfare of dogs. She was a member of the FKC scientific committee for ten years before she started to work in the office. Katariina studied Animal Breeding and Genetics in the University of Helsinki, and got her PhD in 2004. The title of her thesis was Breeding Against Hip and Elbow Dysplasia in Dogs. Katariina's research (and other) interests are health and welfare of dogs, maintaining and increasing genetic diversity in dog breeds, and breeding value estimation for various traits.



IPFD and DogWellNet.com: A Collaborative Platform to Improve Dog Health

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Bio: Brenda qualified as a veterinarian at the University of Guelph, in Canada. After many years as a tenured Associate Professor at the Department of Population Medicine, Ontario Veterinary College, University of Guelph in Ontario, Canada, Brenda is now a Consulting Epidemiologist and CEO of International Partnership for Dogs. She is a frequent speaker at local, national and international venues to breeders, show judges, veterinarians and others. Her research projects in Europe and North America have involved numerous species and disciplines, focusing on companion animals, population-based research using secondary data sources (most notably a large veterinary insurance database in Sweden), human–animal interactions and medical communication.

Abstract

The breeding of dogs occurs on a global scale; the challenges of the dog world would benefit from international collaboration. Sharing of knowledge, expertise, experience and information, in a form understandable by and useful for breeders, breed clubs and kennel clubs, is needed to support the health and well-being of dogs. The International Partnership for Dogs (IPFD) is a non-profit organization with a mission to facilitate collaboration and sharing of resources to enhance the health, well-being and welfare of pedigreed dogs and all dogs worldwide. Several national Kennel Clubs (Sweden, Finland, Germany, France, Norway and the UK), The Orthopedic Foundation for Animals (USA), the Agria Pet Insurance-SKC Fund (Sweden) and the Federation Cynologic Internationale (FCI) were initiating partners. The IPFD is actively engaging more collaborators from many stakeholder groups.

One of the main goals of the IPFD is creation/expansion of DogWellNet.com: both an information hub and a community-building, expertise-sharing platform. For example, the software allows for the creation of 'Forums' where Expert Panels can effectively communicate, share information, reach consensus, etc. – and then share their material with the public.

Genetic progresses in the fight against histiocytic sarcoma: Development and validation steps of the risk genetic test: SH Pre-test

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Histocytic sarcomas, both disseminated and localized, are highly breed-specific genetic disorders significantly affecting Bernese Mountain Dogs (BMD), Rottweilers and Retrievers (Affolter et al. 2000; Affolter et al. 2002). The disease is associated with both high incidence and rapid mortality (Abadie, Hédan et al. 2009; Hedan et al., 2011). While histiocytic sarcomas (HS) are clearly known to be genetic in the BMDs, Rottweilers and Retrievers, the mode of inheritance was not well understood and the number of genes likely to be involved was similarly unknown (Padgett et al. 1995). Segregation studies from the 1990s, and more recently from our lab, suggested a multigenic mode of inheritance (Abadie, Hedan et al. 2009).

To study the genetics of this cancer, we have collected over 2000 blood samples and 500 tissues samples of BMDs since 2003, mainly from dogs from France and Europe. First results, using several Genome Wide Association Studies, obtained in collaboration with Dr. E. Ostrander (NHGRI, NIH, Bethesda, US), have led to the identification of several chromosomal loci associated with a susceptibility to histiocytic cancers (Shearin, Hedan et al. 2012). We replicated these results on a new French population of BMDs (250 samples), which allowed us to confirm those loci and to identify other secondary loci. Then, 144 markers from those ten susceptibility loci were selected to discriminate at risk dogs and were genotyped on 1081 French BMDs. The analysis of the genotypes led us to select a second set of nine discriminating markers, which allowed to estimate a risk of developing and transmitting this cancer, in the context of a kennel.

In collaboration with Antagene laboratory, estimations of coefficients were made on 1081 French BMDs and according to genotypes, a probability to be unaffected or affected by HS was estimated. The distribution of this probability is significantly different between affected and unaffected BMDs. This probability was divided in three scores (A, B and C): dogs with A score were estimated to have 4 times more chance to be a healthy dog, while dogs with a C score were estimated to have 4 times more risk to be affected by and to transmit HS. We validated their use in 2013, in collaboration with the French BMD club (AFBS) and several French breeders.

Following the last IWG meeting, in September 2013, we validated the use of this index with Bernese Mountain dog samples from 8 European countries by testing 111 dogs of known status (affected /unaffected older than 10 years and old dogs):
On 59 histiocytic sarcoma affected BMDs, we observed 8,5% A, 35,6% B and 55,9% C.
On 52 healthy and older than 10 years BMDs, we observed 32,7% A, 50% B and 17,3% C.

Results of the percentage of A, B and C perfectly correlate with the status of the dogs, since > 90% of affected dogs are B or C while > 82% of healthy dogs were A or B.

We are now in the phase of validation of the pre-test SH in the American population of BMD in collaboration with the Berner Garde and Dr Vilma Yuzbasiyan-Gurkan (Michigan state University).

For research or selection purposes, 604 dogs, mainly from France, were tested with the histiocytic sarcoma pre-test. The index distribution was: 22% of A, 45% of B and 33% of C, roughly reflecting the index distribution in the general population.

Antagene and CNRS make great efforts to validate this SH pre-test in several

European countries, by testing entire litters and by testing old "unaffected" dogs (> 10 years). In the course of this year, 19 healthy dogs (>10 years) were tested. Index distribution was clearly different from the general population distribution and concordant with their healthy status: we observed 10 A (52,5%), 7 B (37%) et 2 C (10,5%). This results need to be strengthen by more old healthy dogs to be tested.

We considered that our first genetic results (Shearin, Hedan et al., 2012) were worthwhile to be used, to provide to breeders a first genetic test, estimating a risk of transmitting and developing HS, useful for selection in their kennel. This pre-test is available to BMDs breeders, to help them in their selection and breeding programs and it should be used as a selection factor among others (hip dysplasia, beauty, behaviour, other health characteristics…), not to be detrimental to genetic diversity.

Since progresses on the knowledge of this disease are still ongoing, we asked breeders who used this pre-test, to send samples and follow up of the health of their dogs to pursue research. According to research advances, new markers will be incorporated to improve the genetic pre-test. Moreover, Antagene and CNRS work together on the development of a complementary tool to help breeders for the use of the pre-test and selection of dogs. All together, this will help to improve prediction (with the pre-test itself), and further, diagnosis, and HS treatments

We want to thank owners, breeders and vets who place their trust in this research and who participated by sending samples since 2002.

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Antagene Laboratory : (http://www.antagene.com/fr/commander/pre-test-sh),

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Genetic research and testing in dogs including Bernese Mountain Dogs

Prof. Lohi spearheads a canine genetics research program in Finland and hosts one of the largest dog DNA banks in the world with > 60 000 samples from 330 breeds. This resources allows access to various genetic conditions across breeds. Dr. Lohi's laboratory has discovered a large number of new genes in different disorders in different breeds and has developed advanced infrastructure to further facilitate genetic studies, including next generation sequencing databases. Besides academic efforts, Dr Lohi has been involved also in the implementation of new diagnostic and breeding tools and concepts through his commercial endeavours in a Finnish company, Genoscoper Laboratories. The company has developed a new gene panel test, MyDogDNA test, and related online reporting system, which is transforming the genetic testing business in the field. Besides ~200 genetic conditions and traits, the test can also measure the genetic diversity and relationships of the dogs within and across breeds and therefore, help to measure, understand, maintain and develop the genetic diversity of the breeds while assisting in the systematic avoidance of genetic disorders. Dr Lohi's lecture will give an update about the current research activities in his laboratory including research in Bernese Mountain Dogs. He will also demonstrate the concept and data about MyDogDNA test for the breed.