

## Life Expectancy and Genetics

### Is it possible to breed for longevity?

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Life expectancy is the period of time an individual can be expected to live. The term can be used interchangeably with average lifespan and average longevity. Typically an individual takes some time to reach sexual maturity, then lives through a reproductive phase, and finally enters the complex process of aging. In humans aging is composed of several features:

- An exponential increase in mortality with age, that is the probability of dying at age 30 is much smaller than dying at age 70.
- Physiological changes that typically lead to a functional decline with age. Aging often is accompanied by unpleasant features such as loss of hearing or loss of eye sight.
- An increased susceptibility to certain disease with age. Such diseases causing death are heart diseases, cancer or neurological disorders, to name the most frequent ones.

The process of aging can not only be observed at the individual level but all the way down to the single cell. Factors influencing aging cannot easily be separated from those influencing longevity as in most organism aging is an integral part of longevity. In the following we do not pretend to be able to dissect this complex of longevity and aging but rather focus on the question whether there is enough genetics behind longevity in the Bernese Mountain Dog to breed for longevity. For this purpose we first should look at what is known in other organisms about longevity and aging.

There can be no doubt that environmental factors do have an impact on longevity as accidents or diseases can terminate a life. But there must be a strong genetic component as well. Otherwise it would be difficult to explain why a mouse should live no longer than 4 years but a bat of similar body mass should live up to 34 years. The life span of the calico rockfish is about 12 years whereas its close relative, the rougheye rockfish lives over 200 years with no signs of aging. All salmon die shortly after reproduction but for the steelhead trout this holds not true. Although most of them die after reproduction some are able to return to the sea and reproduce another year. The female of the plaice, a flounder-like fish, continually grows and shows no sign of aging while the male ages and dies. These examples suggest that a genetic background must be rather complex. Despite these obvious differences in aging, the process of aging, at least in mammals, appears as a consistent process albeit proceeding at different rates.

Independently of the environmental conditions a mouse will age 25 to 30 times faster than a human being. Nutrition and exercise can make you live longer and attenuate certain age-related diseases, but you will not be able to live as long as a rougheye rockfish because humans age according to their genetic plan. This does not imply that aging evolved with a purpose that we easily could recognize. Also cancer has a strong genetic basis but it did not evolve with an apparent purpose. The greatest evidence in favor of seeing aging as a genetic plan is that many genes that modulate aging have been identified in model organisms such as yeast, a worm called *Caenorhabditis elegans*, fruit fly, and mice. In the GenAge database 61 genes are listed for yeast, 255 for *Caenorhabditis elegans*, 44 for the fruit fly and 47 for the mouse. All these genes seem to have an impact on aging and therefore on longevity. In the following table some of the genes investigated in these organisms are listed. The column "Life span" refers to the difference in the mean life span of mutants in comparison to wild-type individuals.

Species	Mutation	Gene description	Life span	
C. elegans	age-1	human P(3)K homologue	65% increase	
	daf-2	human insulin-receptor homologue	100% increase	
	spe-10	unknown	40% increase	
	spe-26	unknown	65% increase	
	old-1	putative receptor tyrosine kinase	65% increase	
	ctl-1	cytosolic catalase	25% decrease	
	mev-1	cytochrome b subunit of succinate dehydrogenase	37% decrease	
	fruit fly	mth	putative G-protein-coupled receptor	35% increase
	mouse	prop1	prophet of pit1	49% increase
pit1		pituitary-specific transcription factor 1	49% increase	
ghr		growth hormone receptor	38% increase	
ghrhr		growth hormone releasing hormone receptor	23% increase	
plau		plasminogen activator, urokinase	20% increase	
shc1		src homology 2 domain-containing transforming protein C1	30% increase	

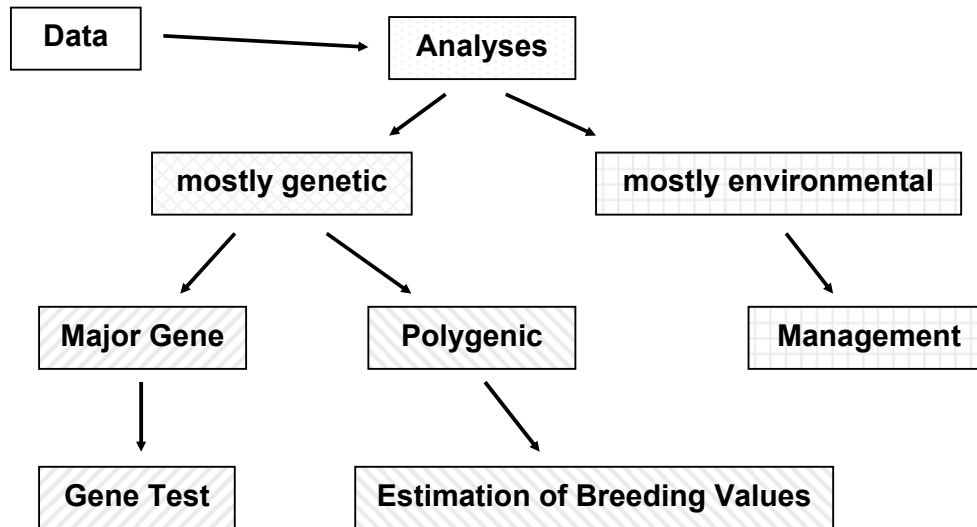
In humans the Cockayne syndrome type I seemingly leads to premature aging due to a recessive mutation in the ERCC8 (excision repair cross-complementing rodent repair deficiency, complementation group 8) gene. The Hutchinson-Gilford's progeroid syndrome is characterized by features resembling accelerated aging and caused by a dominant mutation in the LMNA (lamin A/C) gene. In Werner syndrome, caused by mutations in the WNR gene, the age-related changes of patients are remarkably similar to normal aging, only they occur at earlier ages. Further, apolipoprotein E has been implicated in human aging. The variant e2 seems to be associated with longevity, whereas the variant e4 is associated with early onset Alzheimer's disease. Besides the genes already mentioned, there are 15 other genes, among them interferon gamma, insulin receptor and tyrosin hydroxylase, which are significantly associated with aging in humans.

With the availability of the dog genome sequence it is now possible to directly identify all the genes, that have been implicated in the aging process in model organisms or humans, in the dog as well. For instance, ERCC8 is located on canine chromosome 2 covering the region 50'368'759 bp to 50'423'886 bp, LMNA on canine chromosome 7 covering the region 44'673'637 bp to 44'691'143 bp, and WNR possibly on canine chromosome 16 covering the region 36'120'426 bp to 36'257'633 bp. In the future this knowledge could be useful to elucidate the genetic background of longevity in the Bernese Mountain Dog. But would the knowledge of a single mutation in a gene modifying longevity allow us to better the present situation by breeding?

The fact that wild-derived mouse strains take longer to reach sexual maturity and live significantly longer than common laboratory strains suggests that longevity indeed can be altered by breeding. It is conceivable that in the Bernese Mountain Dog we unknowingly selected for gene constellations unfavorable for longevity. But if we can push longevity in one direction by breeding we should be able to reverse the process.

In order to increase the longevity we first have to know about the factors modifying life expectancy in the Bernese Mountain Dog. As in different species several hundred genes have been implicated in aging and, by extension in longevity, we have to assume that longevity in the Bernese Mountain dog is a rather complex trait too. Complex traits have in common that they include a genetic and an environmental component. The genetic part can be purely polygenic, but often one or more major genes can be identified. A major gene explains a large part of a phenotype but not the whole phenotype. In order to determine the nature of a complex trait a series of analyses is necessary. Variance component analyses will show whether environmental factors play a major role in the longevity problem. When including the relationships between the animals in the analyses, heritabilities,

maternal effects and genetic correlations can be estimated. Further, segregation analyses will reveal the nature of the genetic component if present. If a major gene can explain a substantial part of the variation in longevity we can go back to our list of genes involved in aging and try to narrow down that list in order to investigate one or a few such candidate genes. If a polygenic inheritance is most likely then the best way to tackle the problem would be to estimate breeding values for longevity.

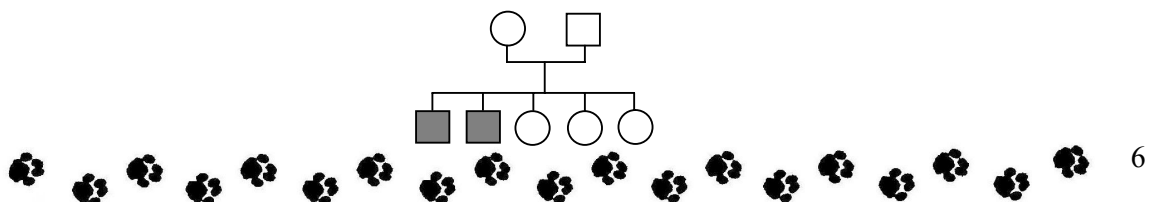


Up to here we have discussed possible factors influencing longevity and analyses able to reveal such factors. Once we know the factors we can develop strategies to improve longevity in the Bernese Mountain Dog. But before we enter this discussion we first have to think about the data needed to perform the analyses. Do we have the data necessary at hand or could the data be generated in a reasonable way? This is not a straightforward task as causes and effects of aging are not easily separated. For instance, the occurrence of hereditary diseases can interfere with longevity. Does, for example, malignant histiocytosis play a major role in decreasing the average longevity or would the dogs die anyway because of an altered genetic plan for aging? The problem boils down to the question of what information should enter the analyses to ensure meaningful results. The following list does not claim to be complete but it shows the basic information needed.

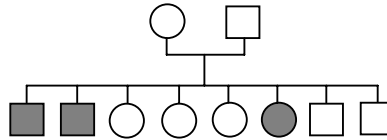
- Identity of individuals
- Pedigree
- Date of birth
- Sex
- Litter size
- Date of death
- Cause of death
- Kennel

For dogs registered with a kennel club information on identity, sex, date of birth and kennel is readily available. Also pedigree information poses no problem as the ancestry generally is well documented, often reaching back to the beginning of the breed. These data can be easily retrieved if stored in a computer database.

The litter size usually reported is the number of live registered puppies. But the true litter size often is larger as reported in the studbook, because there are puppies either stillborn or destroyed right after birth that do not appear in the studbook. This missing information usually can be obtained from the Kennel Club but often is incomplete. Consider a trait that is either present or absent at birth and the following pedigree:



Looking at this pedigree you immediately would suspect an X-chromosomal mode of inheritance of the trait as only the two male offspring are affected. Any decent computer program would come to the same conclusion. But now you learn that there were another three stillborn puppies in this litter. The stillborn female was affected but the two stillborn males were not affected.



Now you certainly would dismiss an X-chromosomal mode of inheritance in favor of an autosomal recessive mode of inheritance. Even if the phenotypes of the three stillborn puppies were not known they would allow for an autosomal recessive model. In a segregation analysis not only monogenic models but also more complex models including a polygenic component are tested. Therefore it is important to have the true litter size whenever possible in order to come up with the correct model.

The date of death is not available for most dogs, but a prerequisite if we want to find out about longevity. The same holds true for the causes of death. In most instances they simply are not available. But if we want to find out about the genetic background of longevity we need to have both, the date of death and the cause of death. These data are not easy to generate in the field as the majority of dogs of a breed belong to the non-breeding part of a given population. These dogs usually are kept as family or working dogs and their owners most often take not part in the activities of the kennel club. Therefore these owners cannot easily be enrolled in collecting data on a genetic disease even if it benefits their breed. With respect to longevity the real problem is that an owner should remember to report the date and cause of death at a time of mourning for a dear companion.

The cause of death rarely is established and only in context with accidents or a disease. The cause of death most often is based on the owner's opinion or a clinical diagnosis. Diagnoses based on necropsy findings virtually are not available as they cost additional money and often owners do not want to submit their dogs for a necropsy, especially in the case where the obvious reason for death was old age. But it is essential to know about the causes of death in order to find out whether we have a longevity problem or not. It is conceivable that by removing some of the causes of death the normal longevity could be restored. But it is also possible that some causes of death merely coincide with the natural time of death meaning that the genetic plan of dying indeed has been altered.

As we believe longevity to have a genetic basis, environmental factors should not play a crucial role. But as we do not know this for a fact it is worthwhile to evaluate possible environmental factors. For instance longevity could differ among different geographic regions which can be defined by the location of the different kennels. Or maybe dogs die more often in winter than in summer, which would be a seasonal effect defined by the dates of death.

Based on the prior knowledge on longevity it is safe to assume that we deal with a strong polygenic component which includes environmental factors and possibly one or more major genes. Getting a handle on such major genes even today with the availability of DNA microarray technology is a challenge and involves considerable time and money. Should the hypothesis of a strong polygenic component hold true the estimation of breeding values as basis for selection promises a faster and more cost-efficient way to deal with the longevity problem. It could be argued that by selecting for longevity we indirectly select against diseases which are leading to premature death. So all we would need would be the date of birth and the date of death to address the problem. But we have to keep in mind that the trait longevity could be correlated with other traits important in Bernese Mountain dogs. Therefore we cannot simply look at longevity but we have to monitor all the other traits as well in order to avoid improving longevity at other important traits' expense.

In conclusion, based on the knowledge on longevity in other species, it should be possible to increase longevity in dogs by breeding, provided the data necessary for the analyses is available or can be generated.

The statements on longevity in model organisms and humans are based on <http://www.senescence.info>; Partridge L and Gems D, 2002, Nature Reviews Genetics 3, 165-175; Finkel T and Holbrook NJ, 2000, Nature 408, 239-247.

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Studied Agronomy at the Swiss Federal Institute of Technology (ETH) in Zurich, majoring in Animal Production and specializing in Animal Genetics, graduated as Dipl.Ing.-Agr. ETH (1976-1980). Thereafter Assistant at the Institute of Animal Sciences at the ETH in Zurich (1980-1986) obtaining the Doctorate in 1984. Further studies at the University of Texas System Cancer Center, MD Anderson Hospital and Tumor Institute, Department of Molecular Genetics, Houston, Texas, USA (1986-1988). Since 1988 working at the Institute of Genetics at the University of Berne, and since 1999 Lecturer in Animal Genetics.

Research activities originally concentrated on Genome Analysis of farm and companion animals using molecular genetic methods. In the last 10 years there has been a strong emphasis on statistical genetics with the main focus on coupling und segregation analysis and genetic epidemiology. His research resulted in over 90 publications in peer reviewed scientific journals.

Member of the Scientific Advisory Committee of the Swiss Kennel Club, member of the Vetsuisse Research Commission of the University of Berne, member of the Advisory Board of Swissgenetics, Member of the Board of the Swiss Association of Animal Production, member of the Scientific Advisory Council of FUGATO (Functional Genome Analysis in Animal Organisms) of the Federal Ministry for Education and Research in Germany.

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