

Notes from Dr. Silvan Urfer's Presentation to the PVIWC, February 10, 2008

taken by Mary O.

Note to readers: I had read Dr. Urfer's paper before the presentation and was not trying to transcribe word for word what was said in the presentation. I strongly suggest that these notes will make more sense if you read his paper first. Currently available at http://www.ths.vetsuisse.unibe.ch/lenya/housing/live/publications/Diss_Urfer_2007.pdf Also note I am not a scientist or vet and do not intend to give anyone advice via these notes.

Terminology/Basic Concepts:

locus – the place where a gene is found in the genome. Each locus contains two alleles, one from the sire and one from the dam.

alleles - you get one from each parent, randomly, at each locus on the DNA strand. You pass on one of them, randomly, to each of your offspring.

phenotype - everything but DNA (not just the visible attributes, but also things such as blood type, muscle fiber types etc.)

genotype - DNA

intermediate inheritance - e.g., red + white = pink offspring

dominant/recessive inheritance - e.g., red + white = red or white offspring. If red is dominant, can't tell if red is genetically red + red or red + white without DNA analysis or information on phenotypes of relatives.

influences on phenotype = genotype, environment and coincidence

simple heredity – Only one locus involved – genotype has the most influence on phenotype (e.g., Mendel's peas)

complex heredity Several loci involved. More equal role for all 3 influences in their effects on phenotype.

heritability - the part of a complex phenotype that is not influenced by environment or coincidence and therefore passed on to the offspring. It is expressed in percent or as a number from 0 to 1.

If you select parents who are above the population's mean for a selected trait and the offspring's mean is also higher than the mean in the population, the trait is heritable. Heritability is calculated by dividing the offspring's difference to the population mean by the parents' difference to the population mean.

Large populations (several hundred individuals and data on complete litters) are needed to accurately determine the mode of inheritance.

(for more definitions see <http://www.genome.gov/10002096>)

Important: A healthy animal does not necessarily have healthy genes – it could be a “healthy carrier”

Four Important Causes of Death in IWS

No genetic test available for any of them yet.

Dilated Cardiomyopathy (DCM) - 20-25% mortality, Dominant major gene with minor modifiers expressed in phenotype as age of onset. Atrial Fibrillation (AF) in IWS will eventually become DCM if the dog lives long enough. Since age of onset is determined by modifiers you can't assume that because a parent has late onset that the offspring will, too. Males seem to be more prone to DCM even when size is excluded as a contributing factor so it may be partly sex-based. DCM is treatable but not curable, and it is extremely difficult to predict how long a dog will survive on treatment.

Osteosarcoma - another 20-25% of IW deaths. Has been shown to be heritable in Deerhounds and St. Bernards; there is an ongoing study in the heritability in IWs. Probably complex inheritance with environmental factors. 2x greater risk in castrated males (see also Rottweiler study).

GDV/Bloat - 10-15% of IW deaths but many survive so actual occurrence is higher. Complex inheritance; having a first degree relative with GDV increases risk by 63%.

PSS - 3% of IW puppies, 18% of litters. Simple recessive; ~25% of IWs are carriers. There is a 50% survival rate with surgery.

Aging in Dogs

Aging is an accumulation of DNA damage. Dog aging is paradoxical compared to other mammals (large dogs have shorter lives than small dogs; yet elephants live longer than mice). Oxidative damage occurs during aging and is caused by things like natural and artificial radiation, toxins in the environment and many other factors. Dogs have mechanisms for inhibiting oxidative damage but during rapid growth periods these mechanisms are overwhelmed. Damage accumulation continues through life but slows after maturity is reached. Large dogs grow rapidly for a longer period of time than small dogs. This means that the damage is largely done and irreversible at the end of growth. Cumulative damage eventually causes cell breakdown. Slower growth may give the body a better ability to compensate for oxidative damage. The latter is a hypothesis; not yet studied.

Dr. Urfer's Paper

It is unknown whether biological lifespan is heritable in and of itself in the dog, although the current evidence suggests a low heritability. Therefore it is suggested to look at factors which affect lifespan (e.g., heart disease, etc.; if you can decrease the incidence of heart disease you may see a correlated increase in average lifespan).

1400 dogs with known lifespan in his database. Data sources listed in paper, then corrected for right-censored data before analysis. When looking at lifespan, right-censored data doesn't account for dogs alive at study end. More accurate to track, say, all litters born in a certain year for 12 years or so; very few IWs live to 12 so data would be complete for almost all lifespans. Different way of looking at the data than previous studies which grouped dogs by year of death. Re-analyzing data yielded different results. Grouped by DOB there is a low life expectancy before 1960, followed by a rapid increase in lifespan during the 1960's, then a decline through 1993. No more recent data was analyzed due to right censored data.

Other factors affecting or thought to affect IW lifespan

Gender – females live longer. Castration appears to increase lifespan in females but is neutral or negative for male lifespan (studies have been inconclusive on the latter). At present we don't have data on if/how the age at castration correlates to shortened lifespan.

Inbreeding – COI (coefficient of inbreeding) is a number expressing the probability that both alleles at any given locus are from the same ancestor. There are several different formulas for calculating it. COI over time stabilized in IWs in the 1960's; since about 1980, it has been decreasing when calculating over 10 generation due to population growth. Nevertheless, true inbreeding has increased over time. Age at death does NOT correlate to COI in IWs.

Theory on negative effects of inbreeding: if a trait is partially dominant then inbreeding will accumulate recessive weak alleles in the population. Compensate by allelic purging: a strong selection pressure for fitness will reduce weak alleles and recover fitness in the population in

about 5 generations.

There have been 4 important genetic bottlenecks in IWs since 1860. The last inbreeding bottleneck was Sanctuary Rory of Kihone. (Note: see chart on p.97 of thesis for very cool visual graphic of IW inbreeding over the years using a pedigree of an IW born in 2000. Made with Pedigree Explorer.)

Hypothesis: pre-1960's there was great pressure to select for fitness; lots of animals died from infection and disease and were thus removed from the breeding population. The breed thus had good genetic fitness, which it could realize as better veterinary care (antibiotics, antiparasitics, vaccinations) became available in the 1960s. At the same time, this reduced selection pressure and allelic purging, causing lifespan to decrease again. We may currently be accumulating weak alleles, which are no longer under selection pressure for purging due to a lack of selection for fitness traits.

Calculated probability of gene origins for PSS in 20 affected litters representing worldwide sources and compared them to a reference population of 400 randomly selected IWs from identical countries and birth years. (Also see charts on pages 86-90 in thesis.) It appears that one ancestor in the early 1960's explains all the PSS cases in the study population. Generation intervals in the PSS population were significantly shorter than they were in the reference population.

Need complete data on all littermates for several generations to find mode of inheritance. While the hereditary nature of PSS could be proved once again, it was impossible to test the published mode of inheritance due to the lack of complete litter data.

Breeding to decrease disease

Take into account mode of inheritance, frequency and clinical severity to assess the potential positive impact of breeding measures. For DCM and PSS we know enough to do this.

Osteosarcoma and GDV have a more complex inheritance, so it is more difficult to select against them.

Since we don't have genetic tests, we can try using Estimated Breeding Values (EBVs), which are based on phenotype, for complex diseases such as OS and GDV. The EBVs must be calculated based on a central database. Data includes the dog, its siblings, half-siblings, parents and offspring, as well as other available relatives, so becomes more accurate as more data becomes available. The result is an EBV score per disease, which breeders then can use for selection.

Assuming the mean breeding value for a given disease risk is 100, if your bitch has a score of 105, you'd want to breed to a stud with a score of less than 95 for that disease, with your goal being a reduction in the average EBV score in every generation. EBV will change over time as more data is added to the database, so you would re-calculate when making a breeding decision even if the bitch or dog had been bred before. This method was used successfully in Hovawarts in Germany to practically eliminate genetic hip dysplasia in the breed. Started in the 1980s and took about 5 generations. It can be used on any complex trait with environmental and coincidental influence.

In order for this to work, there needs to be a central repository of data, based on which EBVs are made available to breeders, and target EBV values defined for heritable diseases. Logical for breed parent clubs to do this, but not currently being done for IWs.

Ethics in breeding

Canine and human interests can be identical in many aspects, but sometimes there is a conflict between the two. When this occurs, put the dog(s) first (their interests are related to primary needs such as survival, absence of suffering and improving of well-being); human interests are secondary in comparison.

Future research

How heritable is biological lifespan in IWSs?

Does inbreeding affect: litter size, puppy mortality, and other fertility traits?

Find a genetic marker for DCM

Test whether giving antioxidants during growth impacts lifespan (note: don't experiment on your puppies without the support and advice of your vet!)