Review of recent genetics studies with respect to breed viability.

What is population genetics?

Award-winning author Dr. Susan Thorpe-Vargas has an up-to-date discussion in her primer on genetics.

<http://pawpeds.com/pawacademy/genetics/breedingstrategies/chapter4.html>

(The primer is a good update to general knowledge of genetics and worth reading in its entirety.)

One aspect of population genetics which has become increasingly prominent with respect to purebreds of any species has been **inbreeding depression**, especially recently as it affects the immune system.

An analogy developed by Olga Aginsky Shulman has been helpful is illustrating this process to non-scientific breeders (used with permission):

Olga Aginsky Shulman, . Metaphor on the effect on inbreeding on the MHC
(her cousin is a geneticist)

He said: think of the Breed as a team that is playing cards against Life. As a whole – the species (or original breed deck) has a formidable number of various cards and that is what allows the species to survive and adjust to the evolutionary changes. No matter what "hand" the house deals on the table your team has the cards to beat it. So the original Breed team is given a deck of, let's say, 10000 cards. Each breeder has a portion of the deck that (in most cases) originally includes the necessary variety for each team player's survival. As you start playing the "survival" game with Life (while inbreeding at the same time) you lose some of the variety in your individual Breeder hand to the process of playing and reshuffling your hand (some cards fall out of your hand forever into the discarded pile). Your own hand becomes smaller and often holds many similar cards. Your team mates also inbreed and their hands also become smaller and more uniform. At some point in the game your combined breed deck may become only 2000 cards out of the original 10000. And that is where good or bad luck comes in.

If the Breed is lucky (or have not played that long "as a team" and if there were no bottlenecks in the breed's history) – each hand (line) have possibly retained a slightly different variety of the same cards and when you outcross to another line and mix new cards all together – the whole Breed deck is still formidable enough to counter the tough cards that Life is dealing from time to time.

If the Breed is unlucky – the cards are more similar in all the hands (like that Puffin Dog) and limited to a much smaller number (the kings and queens and aces and 10s, 7s, 2s may be completely missing from all the hands :))). So when the Life suddenly deals a "tough hand" – the Breed cannot beat it with anything in its combined deck. That is when you need to go out to other decks for the cards that will beat what Life has just dealt you.

For a discussion of what happens to the immune system' ability to respond when inbred, see Dr. Heather Lorimer's "Inbreeding and its Effect on the Immune System"

<http://pawpeds.com/MCO/mchs/articles/lorimer.html>

C. A.. Sharp tackled this question of the effect of inbreeding on the immune system in an award-winning article published before the identification of the DLA haplotype.

<http://www.ashgi.org/articles/immune_rising_storm.htm>

“So why do we see all this complexity with the MHC? It is Nature?s answer to the problem of infectious disease. The immune system must be prepared to tackle many different infectious agents. A mere handful of alleles would not allow the necessary flexibility to face down an ever-evolving array of pathogens. In most cases, each haplotype a dog has will differ from the other, thus increasing its odds of having something in its immune arsenal that will work against whatever nasty bug it may encounter. A plague may kill those individuals who don't have the correct combination of MHC alleles to fight the disease. It may even kill a major part of a population, as happened with bubonic plague among humans in centuries past. While each individual has only two haplotypes, the overall population of its species will have many. Therefore, when a new plague organism comes along, as they inevitably do, the species will survive even though some or even many individuals may be lost. ”

further in the article:

“Without diversity within the MHC, the dog will catch a disease. If the disease is bad enough, the dog may die. If there were only a few possible MHC haplotypes in a breed or species, the risk of an entire population being wiped out by a virulent plague would be very high. The cheetah provides an example from nature. This wild cat species went through an extreme genetic bottleneck sometime in the last ice age. All modern cheetahs are descended from a very few individuals, possibly from a single pregnant female. Thanks to Nature's harsh culling practices,far more stringent than those applied by any dog breeder,the cheetah has survived, but even so it is extremely susceptible to some kinds of disease. ”

Dr. Irene Sommerfeld-Stur looked at inbreeding and its consequences for fertility in a presentation in 2006.

Irene Sommerfeld-Stur. Infertility and inbreeding: how veterinarians should tell what breeders do not want to hear.

<http://www.vin.com/proceedings/Proceedings.plx?CID=WSAVA2006&Category=2686&PID=16050&Print=1&O=Generic>

After the mapping of the dog's genome, One question asked was **whether DNA typing could identify dog breeds.** A number of major studies attempted to answer that question.

D. N. Irion et al. Analysis of Genetic variation in 28 Dog Breed Populations with 100 Microsatellite Markers (2003)

<http://www.ncbi.nlm.nih.gov/pubmed/12692167>

Heidi Parker et al. Genetic Structure of the Purebred Dog (2004)

<http://www.sciencemag.org/content/304/5674/1160.abstract>

In the next few years, attention turned to **the viability of dog breeds.**

A paper by G. Leroy examining French dog breeds marked several as endangered.

Leroy, G. Genetic Variability in French Dog Breeds Assessed by Pedigree Data. (2006) Full text seems only to be available from his thesis -p 151.

<http://hal.archives-ouvertes.fr/docs/00/50/10/99/PDF/TheseGL_Final.pdf#page=151>

this paper is worth reading ,especially Tables 5 and 6 and the section on Implications.

In 2009, Leroy expanded his investigations into French breeds, adding DNA analysis to pedigree analysis

Leroy, G. Genetic Diversity of Dog Breeds; within-breed diversity comparing genealogical and molecular data. He continues to calculate "effective population size" for 61 breeds.

<http://www.netsonic.fi/~soitja13/Leroy2009_2.pdf> (full text)

In the same year was published:

Bjornerfelder, S Assortative mating and fragmentation within dog breeds.

<http://www.biomedcentral.com/1471-2148/8/28>

Using the FCI Poodle in Sweden, the authors traced increasing fragmentation as a result of breed standard divisions and cumulative breeder decisions to breed within a narrow range of colour or size.

The major study linking inbreeding with gene loss was called the "Imperial Study".

Calboli, F. et al. Population Structure and inbreeding from pedigree analysis of purebred dogs (2008)

<http://www.genetics.org/cgi/content/full/genetics%3B179/1/593>

The authors found a genetic loss of alleles ranging from 70% to 97.1% in 6 generations in 10 UK breeds.

Studies on the effect of inbreeding depression on individual dog breeds do exist, starting with a paper in pre-publication at the time of the author's death. An abridged version is available online.

Armstrong, John. Longevity in the Standard Poodle. (1998, rev 2000).

<http://www.canine-genetics.com/lifespan.html>

Although never formally published, other researchers have accepted and used the paper's conclusion that the effect of inbreeding depression begins at 6.25% (10) COI.

Smid, J. Increased mortality in Rhodesian Ridgebacks; the consequences of inbreeding depression.

This graduate thesis no longer seems to be online. I do have a copy if needed. This paper established increased deaths from cancer as the COI rose; dogs who did not develop cancer had normal longevity.

Oliehoek, P. et al. History and structure of the closed pedigree population of Icelandic Shepherds. (2008)

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2736928/>

From a founder population of 36, found that only 2.2 founders were fully represented in the current breed. Suggested alternative ways of spreading the remaining genes to a more equal ratio.

In contrast, one paper on the Irish Wolfhound found no decrease in fertility despite inbreeding.

Urfer, S. Fertility and inbreeding in Irish Wolfhounds in Sweden, 1976-2007.

<http://preview.actavetscand.com/content/51/1/21>

The insurance company Agria has published extensive disease and mortality statistics on insured dogs.

Bonnett, B. N. Mortality in over 350,000 insured Swedish dogs from 1995-2000. 2 parts. (2005)
Part 2 looks at breeding practices.
<http://www.actavetscand.com/content/46/3/121>

Included are statistics on non-purebreds, which are useful for a look at a non-inbred population.

From population genetics to a DNA test.
The identification of a 3-gene haplotype within the immune system (formerly called the Major Histocompatibility Complex(MHC) now the Dog Leucocyte Antigen (DLA)) has allowed researchers to use a DNA test to assess the heterozygosity of both breeds and individual dogs.

Angles, J.M. Frequency and distribution of alleles of canine MHC-II DLA-DQB1, DLA-DQA1 and DLA-DRB1 in 25 representative American Kennel Club breeds.

<http://www.ncbi.nlm.nih.gov/pubmed/16101828>

“Forty per cent of dogs typed were homozygous at DLA-DRB1, 52% at DLA-DQA1 and 44% at DLA-DQB1:.. .Comparison of our study of North American purebred dogs to previous European DLA surveys showed a similar use of common alleles consistent with known founder effects. However, more alleles were detected in European breeds, compared to their North American descendents, indicating that additional DLA class II diversity was lost when European breeds were established in North America.”

Although the study is not yet published, Dr. L. Kennedy and Dr. John Burchard have indicated that Salukis have the highest variability among dog breeds, with 31 haplotype variations found. North American Salukis are much more homozygous than those elsewhere (73%), and there are indications that even partial homozygosity in this specific area of the dog's genome corresponds with higher disease rates.

In contrast, landrace (unpedigreed) Ibizans were found to have 6 haplotypes, based on a sample size of 58 dogs. The authors were surprised at the heterozygosity in this geographically isolated breed.
<http://www.tesisenxarxa.net/TESIS_UAB/AVAILABLE/TDX-0707108-144203//esr1de1.pdf>

Some of the individual breed studies are listed at the website for the commercial DLA test.
<http://www.genoscoper.com/in_english2/gene_tests/gene_tests/dla_diversity/>

Three studies are listed for Nova Scotia Duck Tolling Retrievers.

Hughes, A.G. Association of a dog leukocyte antigen class II haplotype with hypoadrenocorticism in Nova Scotia Duck Tolling Retrievers.

<http://www.ncbi.nlm.nih.gov/pubmed/20136772> 7 haplotypes found.

Wilbe, M. MHC class II polymorphism is associated with a canine-related SLE disease complex.

<http://www.ncbi.nlm.nih.gov/pubmed/19636550>

“Homozygosity for the risk haplotype DRB1*00601/DQA1*005011/DQB1*02001 increased the risk for IMRD (OR = 4.9; ANA-positive IMRD: OR = 7.2) compared with all other genotypes. There was a general heterozygote advantage, homozygotes had OR = 4.4 (ANA-positive IMRD: OR = 8.9) compared with all heterozygotes. . . . We conclude that DLA class II is a highly significant genetic risk factor for ANA-positive IMRD. The results indicate narrow diversity of DLA II haplotypes and identify an IMRD-related risk haplotype, which becomes highly significant in homozygous dogs.”

Maki, K. Population structure and genetic diversity of worldwide Nova Scotia Duck Tolling Retrievers and Lancashire Heeler dog populations

<http://www.ncbi.nlm.nih.gov/pubmed/20646119>

There is disagreement between geneticists K. Maki and D. Bannasch with C. Wade with respect to how significant the studies on Toller DLA are. Both have made statements on the email list Toller-L.

The Poodle MHC Study: Dr. Bannasch's statement (2/2010) during the discussions on the Toller that

Standard Poodles had 3 DLA haplotypes caused the Poodle Club of Canada's Health Officer to contact Dr. Lorna Kennedy at Manchester (UK) who had done the initial investigation. In her initial samples from the UK, 6 haplotypes were found with 2 each in one dog only. The fact that the PCC had an online health survey <www.pcchealth.ca/main.html> available encouraged Dr. Kennedy to initiate a 5-year study into the number and extent of DLA haplotype variations in Poodles worldwide, sponsored by the PCC, using grant money from Royal Canin. Each DNA sample is directly connected to a dog's record in the PCC Health Survey, so that data for further research into the Poodle will be available to scientists after the study is completed. Using population genetics calculations from the Poodle Health Registry's online pedigree/health database, the Health Officer collected 31 samples from worldwide representative Standard Poodles, including rare outlier pedigrees, which had been imported by a group of breeders concerned by Dr. Armstrong's findings of a genetic bottleneck and subsequent inbreeding depression. A preliminary report was received from Dr. Kennedy in March 2011.

10 haplotypes were found, making a total of 11 haplotypes now identified in the Standard Poodle.
(7 of the 10 found came from 1 kennel)
Only 8 dogs in the first batch of 31 did not carry haploype # 1 (the most common haplotype)
15 samples were homozygous,(13 homozygous for haplotype # 1).
Above COI (10 gen) of 7.9%, 12 out of 17 are homozygous.
Above an estimated % Wycliffe of 40% (genetic bottleneck measurement) ,9/10 were homozygous for haplotype # 1.

These results are slightly higher than were found in the original UK samples, which were collected starting in 1988.

A further 50 samples taken from the UK DNA bank will have been processed by the June Board meeting. A second batch from PCC using a directed search towards those bloodlines showing rare haplotypes and looking at Standard to moyen, klein or miniature crosses should have results by Sept.

Preliminary conclusions:

When Dr. Armstrong proved the presence of inbreeding depression in Standard Poodle, concerned breeders worldwide contributed pedigrees to expand his database. His advice at the time was to lower COI to below 10%, avoid popular sires, and track disease rates, especially cancer. His advice was echoed by the late Dr. Padgett and Dr. Jerrold Bell at breed seminars. Although voluntary except in the initial fight against SA, disease registries were set up in several countries, especially on SA and Addison's and the data applied to a master pedigree database. However, rough statistical calculations using the breed average COI, the breed average % Wycliffe of 40 and the incidence of Addison's tracked by birth date show that while COI has stopped rising and even fallen slightly, the rise in dogs having 40% Wycliffe or greater (which *may* be homozygosity for haplotype # 1) and the rise in incidence of Addison's develop in parallel, with some lag in the disease graph line. While the % Wycliffe stabilizes by 1990, disease rates of Addison's continue to rise.

It seems evident, at least from these preliminary study results, that once the genetic bottleneck in Standards reached a certain level, no effort on the part of breeders was sufficient to stop the progress of homozygosity in the breed, and Dr. Kennedy has recommended crossing to other sizes of Poodles. It may be that as a result of experience with genetic bottlenecks after World War II, some European bloodlines are less homozygous, but that does not seem particularly evident in the pedigree database.

Measurement of Breed viability:

Dr. Maki has a list of factors which must be considered in order to maintain breed viability.
They are:
Maki, K website <http://katariinamaki.com/research.html>

BLUP estimation is possible for traits when information for a sufficient number of individual dogs as well as suitable pedigree data are available. Research on genetic diversity requires extensive pedigrees and includes estimates on - the mean inbreeding coefficient in the breed

-the effective population size in the breed, estimated from the rate of inbreeding

-mean kinship or mean additive relationship within the breed

- the effect of the founder animals effective number of founders and ancestors
- the genetic relationships between the populations in different countries.
- for each animal: inbreeding coefficient, ancestor loss coefficient, as well as average relationship (or mean kinship) with the other animals in the population.

(One might also add: - testing for DLA haplotpye heterozygosity.)

There exists a review of longevity surveys for dog breeds, by Dr. K Cassidy

<http://users.pullman.com/lostriver/breeddata.htm>

Tollers are significantly shorter-lived than other retriever breeds.

Submitted by Mary Jane T. Weir

Voluntary CKC Librarian and Health Officer for the Poodle Club of Canada.