

AUTOSOMAL DOMINANT AND A LITTLE PRACTICAL GENETICS 101

Autosomal dominant and autosomal recessive modes of inheritance...primary genes and modifiers... what does it all mean for the dog breeder?

I think it is important that I preface this section by declaring that I am not a geneticist. Nor have I played one on television. In fact, I did not even go to college. (My high school in Australia bid me a not-too-fond farewell when I was 17. They said very openly to all who would listen that I would amount to nothing. I sent them a copy of my first book, a best seller, which I wrote before my 25th birthday, with a tongue-in-cheek note asking for it to be prominently displayed in the school library as testament to the school's excellent education system. The only higher education has been at the University of Life).

As an old-fashioned dog breeder of more than 40 years, I realized way back in the beginning – when there seemed to be more emphasis on the principles of animal husbandry in the dog world – that I was tinkering in genetics and supplanting natural selection (survival of the fittest which operates in the wild) and needed to gain practical knowledge of the subject.

In my early sports writing days, an American cosmetics billionaire and tennis sponsor I was interviewing told me about his passionate hobby in purebred dogs. To achieve top quality winners he said he paid professional geneticists to visit his home with chalk and blackboard to teach him.

Without the luxury of in-house geneticists – and using skills learned from the University of Life – I simply read a lot. I devoured books, articles and studies by experts such as Hutt, Willis, Calvert, Padgett, Meurs, Battaglia, et al. I have an insatiable appetite for the subject and sometimes wonder if I was involved in biology in a previous life! Who else would give a whit and ponder about how exciting it must have been when, at the same time in history in the 19th century, Darwin was espousing his theory of evolution, mortifying theologians, and Mendel was discovering genetics in his pea garden, boring other scientists who took 35 years to discover the importance of his work?

I soak up the written word and surf the internet where genome web sites, including a federal government site, keep the world abreast of the latest developments in the frenetic race to unlock every mystery of man's evolution and existence. I am sure it is not a dinner table topic of conversation, but did you know that evolutionary anthropologists recently estimated, after DNA testing two varieties of lice – one of which is

known to live in clothes – that man first donned clothing 114,000 years ago? Who knew?

With the sequencing of the human, animal, plant and bacteria genomes, we are closing in on the complete recipe for reproduction of a human and other organisms. We are living in a historic time, right up there with man's conquest of space and walking on the Moon, and I want to be swept along with the wave.

All breeders should have a basic working knowledge of genetics but I know from experience that few truly understand – or maybe even care – what happens when they put dog to bitch. For too many it is all about the beauty aspects and as long as the quest for the Holy Grail of best-in-shows and all kinds of rankings is not interrupted, and the puppy sales and the stud fees keep coming, then the “unfortunate by-products” – dogs affected by problems which are kept out of sight or eliminated – are tolerated.

Some even go so far as to falsify death announcements to fend off the perceived “stigma” of having DCM or some other disease in their kennel. When it comes to prominent animals who die young, I am always wary of bloat, choke, brain aneurysms and those hit by a truck.

There is also the state of denial of many breeders who will not face clear genetic facts or will palm off problems on lack of scientific evidence or somebody else's bloodline or stud.

All of the above has allowed the problem of DCM in Dobermans to go virtually unchecked for some 50 years and we have now reached a real crisis point.

This is not a scientific study on genetics, merely a passionate layman's overview to try to help breeders understand what is at stake and how to possibly tackle the problem. For some it will be like preaching to the choir because they will understand it from their professional lives or biology classes. But by discussing the genetics I thought it may help some, and nudge others, into looking at this important issue and other breeding matters with a more searching and professional eye.

Genome Sequencing

Scientists completed the monumental task of sequencing the human genome in 2001 (first the rough draft and then the finished product) and the canine genome in 2003 and 2004 (first a Standard Poodle and then a Boxer were used to sequence). A question that I am often asked: “As there is now a genome sequence,

how come we don't already have a DNA test for cardiomyopathy?"

While sequencing is a historical triumph, it is only part of the decoding and there is a long, long way to go to isolate specific genes. Sequencing produces a huge linear message with an alphabet of just four letters – A, C, G and T – which stand for adenine, cytosine, guanine and thymine, which are molecular units called nucleotides – the four bases of DNA (deoxyribonucleic acid). After pieces of DNA have been dissected, copied, chemically modified and marked with dyes representing the four genetic letters, high-tech sequencing machines scan the DNA to tabulate the continuous order of the four bases, or letters...and then a tedious "finishing" process is undertaken to record the entire genome.

So how big is the sequencing message of the human genome? There are an estimated three billion of these four letters in a linear message. Science writer Matt Ridley in his book "Genome" (Harper Perennial, 2006), said: "If I read the genome out to you at the rate of one word per second for eight hours a day, it would take me a century." It has also been described as the equivalent of 800 bibles in one long succession of four letters with no paragraphs, sentences or punctuation.

The genomes — human, canine and almost 200 others, which are mostly smaller genomes of plants and bacteria — are public knowledge for scientists all over the world to use. The scientific community now has to figure out the loci of an estimated 50,000-plus genes (some say it could be as high as 150,000) on the 46 human chromosomes (23 pairs) – and an estimated 80,000-plus genes on the 78 chromosomes (39 pairs) of the canine. Obviously they do not yet know the exact number of genes.

I do not know how far canine geneticists have come in identifying their massive number of genes, but I have read that those working on the human genome have identified close to 8,000 and on average add about 100 each month.

In layman's terms, the achievement of sequencing the human genome is akin to the British explorer Captain James Cook circumnavigating my home country of Australia in 1770, mapping the coastline for the first time but having no real knowledge of what lay inland across the entire landmass except that it had mountains, rivers and plains. He never did know about the desert!

Today there are certain markers on the genome which aid the genetic detectives. It is like having a map, of say New York, with major markers for Times Square, Broadway, Central Station, Central Park, Madison Square Garden, etc...but not knowing all the streets and business houses in between. Geneticists first have

to find where say, the Waldorf Astoria or Tiffany's are, and then work outwards.

Let us imagine that in our New York map our genetic detective is looking for a villain gene (code name DCM) in the Bronx. The geneticist knows it is close to Yankee Stadium so he or she begins the process of knocking on every door in the borough to find the culprit. But what of the "modifiers," or minor genes involved in dilated cardiomyopathy? So while the key villain is in the Bronx, his accomplices, living under assumed names, may be hiding somewhere in Brooklyn, Queens or Manhattan? Could well be the case...

The scientific community around the world is moving at breakneck speed compared to the first 100 years after the discovery of genetics by the Austrian monk and scientist Gregor Mendel who officially recorded his findings from experiments with peas in 1865. But the harsh reality is that a test for dilated cardiomyopathy in Dobermans may be way in the future.

The late Dr. George Padgett, a renowned authority on the subject of canine genetics, wrote in his book "Control of Canine Genetic Diseases" (Howell, 1998) that he thought most people who read his book would be dead before DNA analysis would be available for the majority of diseases in dogs. He wrote that 10 years ago and it is still sobering stuff for those who think the scientific community must surely be close to finding the genes.

It is also painfully true that there is inadequate funding for projects like finding a heart disease gene in the Doberman. It is not glamorous and high profile like genetic research in other publicized fields which attract much bigger grant money. Researchers are normally not paid by the university. They may get an office and a phone but have to attract their own grant money to do research. Dr. Meurs could use funding help for DCM gene research at Washington State University.

So we, the breeders and owners, have to also tackle it ourselves as best we can...and the place to start is regular cardiac testing – certainly before breeding of stock —and an open registry with rudimentary genetic analysis of our dogs through the dissection of pedigrees (see the accompanying article: Rod Humphries Writes).

Practical application of autosomal dominant

So what does it really mean that the mode of inheritance of DCM is autosomal dominant? What do modifier genes have to do with it? What are the practical applications for a caring Doberman breeder?

Autosomal dominant is one of four modes of inheritance which determine how a gene (allele) expresses itself in the phenotype (the outward appearance and measurable traits). The other modes are autosomal recessive, X-linked (often called sex-linked) and polygenic. There are other factors which geneticists point to as variables in determining inheritance, including the aforementioned incomplete penetrance, incomplete dominance, etc, but as this is a general overview I hope the scientific community will cut me some slack.

An autosomal trait is one which develops from the autosomes — any of the 38 pairs of non-sex chromosomes in the nucleus of a canine cell. An X-linked trait is one which comes on the 39th pair, or sex chromosomes, commonly referred to as XX in females and XY in males. Polygenic traits involve multiple primary genes and in dogs are responsible for such things as head type; shoulder construction; etc.

Hip dysplasia is a product of the polygenic mode and breeds with high incidence of this problem will have a long, long wait while the genetic detectives search for the multiple primary genes to develop a DNA test. If there were two primary genes involved in a polygenic disease there would be 16 possible genotypes (the genetic make-up) in the offspring while a three gene trait would produce 64, and so on.

Genes are the basic unit of heredity which are situated on chromosomes in the nucleus of the canine cell. In the autosomes, a pair of matching chromosomes is inherited — one from the mother and one from father — and the genes from both parents are found at the same location on that pair. Pairs of like genes from each parent are called “homozygous.” Pairs of unlike genes are called “heterozygous.”

Dog breeders are mostly familiar with autosomal recessive (Doberman breeders deal with it in the red coat recessive gene) where a dominant gene masks a recessive, or hidden gene. The only time the recessive gene surfaces is when two animals with the same recessive are bred. Animals in this mode can be “clear” (phenotypically and genotypically normal); “carriers” (phenotypically normal and genotypically a carrier of a defective gene) or “affected” (phenotypically and genotypically defective).

But not so with autosomal dominant. In this mode only one mutant gene is needed for transmission and the disease is therefore also expressed in the heterozygous state. So there are no classic carriers, and dogs with unlike genes will have DCM. As stated earlier, other characteristics of autosomal dominant include affected dogs in every generation; only one affected parent is needed to pass on the disease; two affected parents can produce normal, unaffected animals; and it is an equal opportunity mode for males and females.

Because a single parent with one copy of the gene can pass it on, the transmission rates are high. If one parent is homozygous with two mutant genes for DCM, then all the offspring will be affected. A heterozygous parent will pass it to at least 50 per cent of its offspring even if bred to a clear mate. Devastating numbers...

If, for example, DCM was an autosomal dominant trait like merling in Collies, which is known at birth, it could be easily eliminated by not breeding an affected animal. But DCM has a late onset.

While there is truly nothing to be thankful for in the fight against DCM, there are small mercies in the autosomal dominant mode because it is easier to track than an insidious recessive gene which can lie in the weeds for a generation or two then jump up and bite the breeder. It is much harder to eliminate hidden recessives, particularly if you also throw in the late onset factor.

Autosomal dominant translates to the powerful warship steaming above water while autosomal recessive translates as the deadly submarine cruising beneath the waves with the ability to torpedo you at any given time. Trying hard to find something positive in all this I look at it as the devil you can see is better than the devil you cannot see.

Analyzing pedigrees is somewhat simpler because the disease absolutely needs an affected parent in each generation to keep the warship afloat. There is no need to guess if parents are carriers and even with the late onset a breeder can at least do retrospectives on sire and dam and grandparents to determine if there was an affected dog.

The catch here is that the breeder has to determine beyond any doubt that the dog who died of say, cancer; or one who lived a long life and the sudden death was categorized as “old age,” did not harbor the disease. It would also be difficult if the disease eventually proved to have incomplete penetrance in which a percentage of dogs would have the gene but not the disease.

I was convinced that a sire and dam in my kennel were unaffected and therefore had to be carriers when they both lived 12 years and produced a five-year-old victim of DCM. Both parents were euthanized with diminishing motor skills and one with some cancer. It was a test case which, at the time, I thought proved that I was dealing with autosomal recessive.

After Dr. Meurs’ team determined the mode as autosomal dominant, I searched my memory banks and remembered some minor incidences such as sluggishness and a loss of weight late in life of the sire. When that was coupled with the fact that he produced affected offspring in two other litters — and that autosomal dominant must have affected animals in consecutive generations — I knew he must have had the

disease. I just did not know it at the time...a scenario which can be very disconcerting when trying to track the disease in a kennel.

There was also a case of a dog I bred who died at 13 years of age with symptoms which to me sounded ominously like DCM, but the owner and the attending veterinarian were looking elsewhere. When a dog becomes sluggish; goes off its food; has spells of disorientation and then drops dead, the alarm bells sound very loudly for me. It is important to know the real truth because older dogs with the disease clearly can produce very young dogs which die of DCM.

And what of the modifying genes in this equation? I can best describe modifiers by quoting from a report written in 2000 by the National Heart, Lung and Blood Institute on "Genetic Modifiers of Single Gene Diseases."

"All diseases are variable in their presentation due to differences in the genetic makeup and the environmental exposure of the affected individual. For disorders inherited in a Mendelian fashion, a single gene plays the predominant role in the development of a disease phenotype. However, phenotype variation occurs even among those who have identical genotypes at a disease locus. To further our understanding of the molecular basis of monogenic disorders, it will be necessary to find other genes that contribute to phenotype variability."

The study said that cardiac myopathies are affected by modifying genes. "Although individuals may have single gene defects (the primary gene), there can be tremendous variation in the progression, complications and outcome of the disease (even in an extended family) that may be due to the interaction of the disease gene with other genes, impacting on the final disease presentation."

The study said that in human diseases a number of primary genes had been identified in the genome, "now the difficult process of finding the modifier genes and their relative mutations must be undertaken. The number of biologically plausible candidate genes may be very large."

It is the same situation in canines. The modifier genes for DCM in Dobermans, which will be spread across the genome, could possibly be responsible for the differences in heart rhythm disturbances, which trigger sudden death in some and congestive heart failure in others. The task of pulling it all together will be difficult at best.

The Punnett Square – Establishing Breeding Percentages

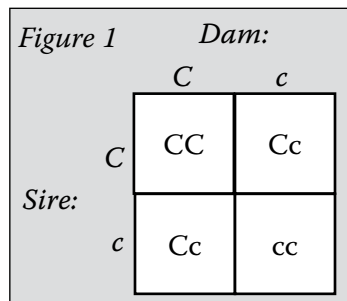
For as long as I can remember I have used Punnett squares to determine the probability of heredity in pup-

pies. Professor Reginald Punnett (1875-1967), creator of crossing (or checkerboard) squares, was a famous British geneticist who wrote the first full textbook on genetics in 1905. The Punnett square is a major tool of geneticists to this day, and while I will give some simple examples, the professionals work with more intricate squares of multiple traits in each box.

The classic difference between autosomal recessive and autosomal dominant is illustrated in the first two Punnett squares. Autosomal recessive is what many breeders thought was the mode of inheritance for DCM – but with autosomal dominant "carriers" are no longer applicable.

Autosomal Recessive

Figure 1: The mating of two heterozygous animals or "carriers" of a deleterious gene. Dominant genes are always designated a capital letter, and the recessive a lower-case letter. In this instance, if cardiomyopathy had been an autosomal recessive trait, then capital "C" (for cardiomyopathy) would have been the normal dominant (or wild type) gene and lower case "c" would be the mutant recessive.

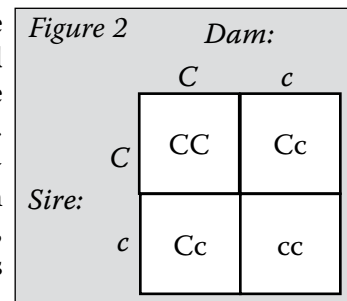


The percentages are obviously applicable over a large sample and would not be exact in each litter, but in this case a breeder could expect 75 percent of the offspring to be phenotypically normal: 25 percent "clears" (CC, or normal — offspring whose phenotype and genotype would not be affected) and 50 percent "carriers" (Cc — offspring who would not have the disease but would carry the deleterious gene in recessive form). There would be 25 percent "affected" (cc - offspring who would have two copies of the bad gene).

Below is an illustration of the actual mode, autosomal dominant, also illustrating two heterozygous animals. Affected animals produce affected offspring in every generation and because there are no "carriers" the disease will not skip a generation.

Autosomal Dominant

Figure 2: In this mode the disease is expressed by the dominant gene and the recessive is clear. Because this mode produces affected animals in the heterozygous state, the two breeding animals



are themselves affected. It is clear that everything in this pattern is the opposite of autosomal recessive. In this case 75 percent of the animals will be affected (25 percent CC which is the homozygous dominant animal and 50 percent of Cc which are the heterozygous animals) and 25 percent clear (cc the homozygous recessive dog). This was the clincher for Dr. Meurs in her study: two affected dogs producing clear offspring.

Figure 3: A heterozygous (affected) male bred to a clear female. 50 percent of the offspring would be affected (Cc) and 50 percent would be clear (cc).

Figure 3

		<i>Dam:</i>	
		<i>c</i>	<i>c</i>
<i>Sire:</i>	<i>C</i>	Cc	Cc
	<i>c</i>	cc	cc

Figure 4: A homozygous dominant (affected) male bred to a heterozygous (affected) female. All the offspring are affected...but the 50 percent homozygous dominant (CC), and 50 percent heterozygous (Cc) offspring would transmit in different percentages in future breedings.

Figure 4

		<i>Dam:</i>	
		<i>C</i>	<i>c</i>
<i>Sire:</i>	<i>C</i>	CC	Cc
	<i>C</i>	CC	Cc

Figure 5: Two homozygous dominant (affected) parents will produce 100 percent homozygous dominant (affected) offspring.

Figure 5

		<i>Dam:</i>	
		<i>C</i>	<i>C</i>
<i>Sire:</i>	<i>C</i>	CC	CC
	<i>C</i>	CC	CC

Figure 6: The sire is a phenotypically and genotypically normal homozygous recessive male bred to a homozygous dominant (affected) dam. All the offspring will be heterozygous (affected) and would be expected to eventually die of the disease.

Figure 6

		<i>Dam:</i>	
		<i>C</i>	<i>C</i>
<i>Sire:</i>	<i>c</i>	Cc	Cc
	<i>c</i>	Cc	Cc

This is another of the quirky combinations of autosomal dominant. If this was an autosomal recessive Punnett square, then all four offspring would be unaffected heterozygous animals and would never manifest the disease but would be “carriers” of the bad gene. ■

The author opens his heart to fight cardiomyopathy in the following Rod Humphries Writes.