Basic Genetics

Sue Ann Bowling

The basis for order in life lies in a very large molecule called deoxyribonucleic acid, mercifully abbreviated to DNA. A related molecule, ribonucleic acid (RNA) provides the genetic material for some microbes, and also helps read the DNA to make proteins.

Read?

Yes, read.

DNA has a shape rather like a corkscrewed ladder. The "rungs" of the ladder are of four different types. The information in DNA comes in how those types are ordered along the molecule, just as the information in Morse code comes in how the dashes and dots are ordered. The information in three adjacent rungs is "read" by a kind of RNA that hooks onto a particular triad of rungs at one end and grabs a particular amino acid at the other. Special triads say "start here" and "end here" and mark off regions of the DNA molecule we call discrete genes. The eventual result is a chain of amino acids that makes up a protein, with each amino acid corresponding to a set of three rungs along the DNA molecule. There are also genes that tell the cell when to turn on or turn off another gene. The proteins produced may be structural or they may be enzymes that facilitate chemical reactions in the body.

We now know that chromosomes are essentially DNA molecules. In an advanced (eukaryotic) cell, these chromosomes appear as threadlike structures packaged into a more or less central part of the cell, bound by a membrane and called the nucleus. What is more important is that the chromosomes in a body cell are arranged in pairs, one from the father and one from the mother. Further, the code for a particular protein is always on the same place on the same chromosome. This place, or location, is called a locus (plural loci.)

There are generally a number of slightly different genes that code for forms of the same protein, and fit into the same locus. Each of these genes is called an allele. Each locus, then, will have one allele from the mother and one from the father. How?

When an animal makes an egg or a sperm cell (gametes, collectively) the cells go through a special kind of division process, resulting in a gamete with only one copy of each chromosome. Unless two genes are very close together on the same chromosome, the selection of which allele winds up in a gamete is strictly random. Thus a dog who has one gene for black pigment and one for brown pigment may produce a gamete which has a gene for black pigment OR for brown pigment. If he's a male, 50% of the sperm cells he produces will be B (black) and 50% will be brown (b).

When the sperm cell and an egg cell get together, a new cell is created which once again has two of each chromosome in the nucleus. This implies two alleles at each locus (or, in less technical terms, two copies of each gene, one derived from the mother and one from the father) in the offspring. The new cell will divide repeatedly and eventually create an animal ready for birth, the offspring of the two parents. How does this combination of alleles affect the offspring?

There are several ways alleles can interact. In the example above, we had two alleles, B for black and b for brown. If the animal has two copies of B, it will be black. If it has one copy of B and one of b, it will be just as black. Finally, if it has two copies of b, it will be brown, like a chocolate Labrador. In this case we refer to B as dominant to b and b as recessive to B. True

dominance implies that the dog with one B and one b cannot be distinguished from the dog with two B alleles. Now, what happens when two black dogs are bred together?

We will use a diagram called a Punnett square. For our first few examples, we will stick with the B locus, in which case there are two possibilites for sperm (which we write across the top) and two for eggs (which we write along the left side. Each cell then gets the sum of the alleles in the egg and the sperm. To start out with a very simple case, assume both parents are black not carrying brown, that is, they each have two genes for black. We then have:

	B	B
B	BB (black)	BB (black)
B	BB (black)	BB (black)

All of the puppies are black if both parents are BB (pure for black.

Now suppose the sire is pure for black but the dam carries a recessive gene for brown. In this case she can produce either black or brown gametes, so

	B	B
B	BB (pure for black)	BB (pure for black)
b	Bb (black carrying brown)	Bb (black carrying brown)

This gives appoximately a 50% probability that any given puppy is pure for black, and a 50% probability that it is black carrying brown. All puppies appear black. We can get essentially the same diagram if the sire is black carrying brown and the dam is pure for black. Now suppose both parents are blacks carrying brown:

	B	b
B	BB (pure for black	Bb (black carrying brown)
b	Bb (black carrying brown)	bb (brown)

This time we get 25% probabilty of pure for black, 50% probability of black carrying brown, and - a possible surprise if you don't realize the brown gene is present in both parents - a 25% probability that a pup will be brown. Note that only way to distinguish the pure for blacks from the blacks carrying brown is test breeding or possibly DNA testing - they all look black.

Another possible mating would be pure for black with brown:

	B	B
b	Bb (black carrying brown)	Bb (black carrying brown)
b	Bb (black carrying brown)	Bb (black carrying brown)

In this case, all the puppies will be black carrying brown.

Suppose one parent is black carrying brown and the other is brown:

	B	b
b	Bb (black carrying brown)	bb (brown)
b	Bb (black carrying brown)	bb (brown)

In this case, there is a 50% probability that a puppy will be black carrying brown and a 50% probability that it will be brown.

Finally, look at what happens when brown is bred to brown:

	b	b
b	bb (brown)	bb (brown)
b	bb (brown)	bb (brown)

Recessive to recessive breeds true - all of the pups will be brown.

Note that a pure for black can come out of a mating with both parents carrying brown, and that such a pure for black is just as pure for black as one from ten generations of all black parentage. THERE IS NO MIXING OF GENES. They remain intact through their various combinations, and B, for instance, will be the same B no matter how often it has been paired with brown. This, not the dominant-recessive relationship, is the real heart of Mendelian genetics.

This type of dominant-recessive inheritance is common (and at times frustrating if you are trying to breed out a recessive trait, as you can't tell by looking which pups are pure for the dominant and which have one dominant and one recessive gene.) Note that dominant to dominant can produce recessive, but recessive to recessive can only produce recessive. The results of a dominant to recessive breeding depends on whether the dog that looks to be the dominant carries the recessive. A dog that has one parent expressing the recessive gene, or that produces a puppy that shows the recessive gene, has to be a carrier of the recessive gene. Otherwise, you really don't know whether or not you are dealing with a carrier, bar genetic testing or test breeding.

One more bit of terminology before we move on - an animal that has matching alleles (BB or bb) is called homozygous. An animal that has two different alleles at a locus (Bb) is called heterozygous.

A pure dominant-recessive relationship between alleles implies that the heterozygous state cannot be distinguished from the homozygous dominant state. This is by no means the only possibility, and in fact as DNA analysis advances, it may become rare. Even without such analysis, however, there are many loci where three phenotypes (appearances) come from two alleles. An example is merle in the dog. This is often treated as a dominant, but in fact it is a type of inheritance in which there is no clear dominant - recessive relationship. It is sometimes called overdominance, if the heterozyote is the desired state. I prefer incomplete dominance, recognising that in fact neither of the alleles is truly dominant or recessive relative to the other.

As an example, we will consider merle. Merle is a diluting gene, not really a color gene as such. If the major pigment is eumelanin, a dog with two non-merle genes (mm) is the expected color - black, liver, blue, tan-point, sable, recessive red. If the dog is Mm, it has a mosaic appearance, with random patches of the expected eumelanin pigment in full intensity against a background of diluted eumelanin. Phaeomelanin (tan) shows little visual effect, though there is a possibility that microscopic examination of the tan hair would show some effect of M. Thus a black or black tan-point dog is a blue merle, a brown or brown tan-point dog is red merle, and a sable dog is sable merle, though the last color, with phaeomelanin dominating, may be indistinguishable from sable in an adult. Merle has no obvious effect on recessive red. What makes this different from the black-brown situation is that an MM dog is far more diluted than is an Mm dog. In those breeds with white markings in the full-color

state the MM dog is often almost completely white with a few diluted patches, and has a considerable probablity of being deaf, blind, and/or sterile. Even in the daschund, which generally lacks white markings, the so-called double dapple (MM) has extensive white markings and may have reduced eye size. Photographs of Shelties with a number of combinations of merle with other genes are available on this site, but the gene also occurs in Australian Shepherds, Collies, Border Collies, Cardiganshire Welsh Corgis, Beaucerons (French herding breed), harlequin Great Danes, Catahoula leopard dogs, and Daschunds, at the least.

Note that both of the extremes - normal color and double merle white - breed true when mated to another of the same color, very much like the Punnett squares above for the mating of two browns or two pure for blacks. I will skip those two and go to the more interesting matings involving merles.

First, consider a merle to merle mating. Remember both parents are Mm, so we get:

	M	m
M	MM (sublethal double merle)	Mm (merle)
m	Mm (merle)	mm (non-merle)

Assuming that merle is the desired color, this predicts that each pup has a 25% probability of inheriting the sublethal (and in most cases undesirable by the breed standards) MM combination, only 50% will be the desired merle color, and 25% will be acceptable full-color individuals. (In fact there is some anecdotal evidence that MM puppies make up somewhat less than 25% of the offspring of merle to merle breedings, but we'll discuss that separately.) Merle, being a heterozygous color, cannot breed true.

Merle to double merle would produce 50% double merle and is almost never done intentionally. The Punnet square for this mating is:

	M	M
M	MM (sublethal double merle)	MM (sublethal double merle)
m	Mm (merle)	Mm (merle)

Merle to non-merle is the "safe" breeding, as it produces no MM individuals:

	m	m
M	Mm (merle)	Mm (merle)
m	mm (non-merle)	mm (non-merle)

We get exactly the same probability of merle as in the merle to merle breeding (50%) but all of the remaining pups are acceptable full-colored individuals.

There is one other way to breed merles, which is in fact the only way to get an all-merle litter. This is to breed a double merle (MM) to a non-merle (mm). This breeding does not use a merle as either parent, but it produces all merle puppies. (The occasional exception will be discussed elsewhere.) In this case,

	M	M
m	Mm (merle)	Mm (merle)

m	Mm (merle)	Mm (merle

The problem with this breeding is that it requires the breeder to maintain a dog for breeding which in most cases cannot be shown and which may be deaf or blind. Further, in order to get that one MM dog who is fertile and of outstanding quality, a number of other MM pups will probably have been destroyed, as an MM dog, without testing for vision and hearing, is a poor prospect for a pet. In Shelties, the fact remains that several double merles have made a definite contribution to the breed. This does not change the fact that the safe breeding for a merle is to a nonmerle.

Thus far, we have concentrated on single locus genes, with two alleles to a locus. Even something as simple as coat color, however, normally involves more than one locus, and it is quite possible to have more than two alleles at a locus. What happens when two or more loci are involved in one coat color?

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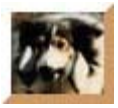

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Basic Genetics II: Multiple Loci

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Usually more than one gene locus is involved in coat color. We'll take one of the simplest, in which the two loci each have two alleles, with a simple dominant-recessive relationship. The model we will use is the Labrador Retriever. One locus we have already examined: the brown locus. We will now add a second locus, on a different chromosome, called E. An EE or Ee dog will show whatever eumelanin pigment is possible. An ee dog apparently can manufacture only phaeomelanin in the hair, though the skin and eye pigment still includes melanin (of whatever color is allowed by the B series).

A black Lab may be BBEE, BBEe, BbEE or BbEe - any combination that includes at least one B and one E gene.

A chocolate (brown) Lab may be bbEE or bbEe.

A yellow Lab with a black nose may be BBee or Bbee

A yellow Lab with a liver nose is bbee - but since ee dogs tend in many cases to lose nose pigment in winter, this may not be easy to distinguish from BBee or Bbee.

Suppose we mate two BbEe dogs, both blacks carrying brown and yellow:

	BE	Be	bE	be
BE	BBEE (pure for black)	BBEe (black carrying yellow)	BbEE (black carrying brown)	BbEe (black carrying brown and yellow)
Be	BBEe (black carrying yellow)	BBee (pure for yellow, black nose)	BbEe (black carrying brown and yellow)	Bbee (yellow carrying brown)
bE	BbEE (black carrying brown)	BbEe (black carrying brown and yellow)	bbEE (pure for brown)	bbEe (brown carrying yellow)
be	BbEe (black carrying brown and yellow)	Bbee (yellow carrying brown)	bbEe (brown carrying yellow)	bbee (brown-nosed yellow)

Each puppy has one chance in sixteen of having the combination shown in any section of the table above. In this mating between two black dogs both carrying brown and yellow, there is a 9/16 probability that a particular pup will be black, a 3/16 probability that the pup will be brown, a 3/16 probability that the pup will be a black-nosed yellow, and a 1/16 probability of a brown-nosed yellow. Since nose color does not come into registration, the registered colors would be 9 black:3 brown:4 yellow.

What happens if more than two loci are involved? The basic principle is the same - put all of the possible combinations in a sperm cell along the top and all of the possible combinations in an egg cell along the left side. The problem is that the number of possible combinations doubles for each additional locus. For a single locus, we had a 2 x 2 square with 4 cells. For two loci, we had a 4 x 4 square with 16 cells. With three loci, we have an 8 x 8 square with 64 cells. Besides, we've pretty well exhausted the acceptable colors for Labs.

Shetland Sheepdogs might be a good model for our three-locus model. For the moment we'll omit the recessive black, and consider that Sheltie color is determined by three loci.

At the A (agouti) locus, a^y is sable and a^t is tan-point (black and tan = referred to as tricolor if a white spotting gene is present.) An a^ya^t dog is sable, but generally somewhat darker than an a^ya^y dog. The difference is generally of the same order as the difference within a^ya^y or within a^ya^t, so it is not possible to be absolutely sure whether a^t is present by looking at the dog.

At the M locus, Shelties have both M and m, as discussed earlier. Mm produces blue merle in a^ta^t dogs and sable merle on a^ya^t and a^ya^y.

At the S (spotting) locus most correctly marked Shelties have two copies of s^i, Irish spotting. A s^is^i dog generally ranges from white on the chest and feet to high white stockings, white tail tip, and a full shawl collar. The probability of the full collar, as well as white stifles, seems to be somewhat enhanced if the dog is s^is^w, so s^w, color headed white, tends to be maintained in the breed as well. (I am keeping it simple by ignoring s^p, piebald, which may also occur in Shelties.) s^ws^w dogs are predominantly white with color on the head and perhaps a few body spots. While healthy, they cannot be shown. Of course all of this assumes that Little's attribution of white markings to different alleles at the same locus was correct.

Suppose we mate two white-factored, tri-factored sable merles (not a likely mating, but this is an illustration!) The genetic formula for each parent is $a^ya^tMms^is^w$. There are eight possible gametes for each sex:

	a^yMs^i	a^yMs^w	a^yms^i	a^yms^w	a^tMs^i	a^tMs^w	a^tms^i	a^tms^w
a^yMs^i	DMS	DMS	SM	SM	DMS	DMS	StM	StM
a^yMs^w	DMS	DMS*	SM	WSM	DMS	DMS*	StM	WStM
a^yms^i	SM	SM	S	S	StM	StM	St	St
a^yms^w	SM	WSM	S	WS	StM	WStM	St	WSt
a^tMs^i	DMS	DMS	StM	StM	DM	DM	BM	BM
a^tMs^w	DMS	DMS*	StM	WStM	DM	DM*	BM	WBM
a^tms^i	StM	StM	St	St	BM	BM	T	T
a^tms^w	StM	WStM	St	WSt	BM	WBM	T	WT

There is no way I could fill in this chart with the detail I used in the 2-loci charts and still have it fit readably into a browser window, so I have used a shorthand to indicate the apparant color:

- S = pure for sable with irish markings (3)
- St = tri-factored sable with irish markings (6)
- T = tricolor with irish markings (3)
- SM = pure for sable merle with irish markings (6)
- StM = tri-factored sable merle with irish markings (12)
- BM = blue merle with irish markings (6)
- WS = white with pure for sable head (1)
- WSt = white with trifactored sable head (2)
- WT = white with tricolor head (1)
- WSM = white with pure for sable merle head (2)
- WStM = white with tri-factored sable merle head (4)
- WBM = white with blue merle head. (2)

- DMS = homozygous merle, dilute sable markings (12)
- DM = normal homozygous merle (4)

I have not distinguished white-factored from Irish dogs, and I have ignored the possibility that the MMs^ws^w pups (starred in chart) might not be viable. In practice such a breeding would probably never be made, as Sheltie breeders tend to avoid breeding merle to merle and white factor to white factor, but it does illustrate the variety that can be obtained with two alleles at each of three loci.

In this case, all three loci are visibly affecting the color. The only exception is the interaction between color-headed white and double merle, and this is frankly an unknown. There are times, however, when a particular gene combination at one locus can block expression of a gene combination at another locus. I will follow Searle on nomenclature and distinguish between a dominant-recessive relationship between alleles at a particular locus and an epistatic-hypostatic relationship between two loci.

The first example is very obvious, but only because the gene action is clear-cut. Consider Cocker Spaniels. They have two alleles at the S locus (S, fully colored, and s^p, piebald.) An SS dog is solid color, an Ss^p dog may have minor white marking (and is often unshowable) and an s^ps^p dog is a parti-color. The second gene is ticking. Ticking works by producing flecks of color in white areas. TT produces ticks of color in any white areas on the dog, tt has clear white areas, and Tt probably produces less ticking than TT, with considerable variation among breeds. s^ps^p and probably Ss^p dogs will show ticking if T is present, since they have white areas that are "available" for ticking, though if the base color is red, tan or cream the ticking may not be obvious. But if the dog is SS, there are no white spots for the ticking to show up on. SS is thus epistatic to ticking.

The final example involves the genes for dominant black. I will assume it is at a separate locus K, with K^B being dominant black, epistatic to anything at the A series, while k^yk^y allows the A series to show through. We also have the E series, in which E allows the A series to show through while ee allows only red-yellow pigment in the hair. Functionally we can consider that the A locus determines where eumelanin and phaeomelanin are produced, the K locus allows only eumelanin to be produced if E is at the E locus, but ee at the E locus overrides that to allow only phaeomelanin production. Sounds like a mess? You bet it does! K at the K locus is epistatic to the A locus, but ee (pure recessive at the E locus) is epistatic to both the A and the K locus. But it agrees with what is observed.

Let's look at a breed cross between two "red" dogs. We'll take an accidental breeding I know of between a Belgian Tervuran ($A^yA^yEEk^yk^y$) and a Golden Retriever ($??eeK^BK^B$). Note that ee is epistatic to the A series, so we do not know what the normal A allele is in the Golden. The gametes are A^yEk^y for the Terv and $?eK^B$ for the Golden. Every puppy inherits $A^y?EeK^Bk^y$ and is black, as was in fact observed (to the initial astonishment of the owner.) If we mated two of these pups, we would get a 16/64 probability of ee which would be red regardless of what was at other loci. Of the other 48/64 (Ee and EE dogs), 75% would be K^Bk^y or K^BK^B, and hence black. so there is a 36/64 probability that a particular puppy will be black. The remaining 12/64 will show what is present at the A locus. Of the 12, we expect that 9 will have the A^y gene in at least one dose, and with dominant black moved to the K locus A^y is dominant over all other A alleles. So there is only a 3/64 chance that a given puppy will actually show what A allele is normal in a Golden - if in fact all Goldens have the same allele at A!

We still need to discuss penetrance, variable expression, and threshold traits, as well as

linkage and crossing over (and their influence on the accuracy of DNA testing), test breeding, and testing whether a suspected allele is in fact at a particular locus. Some further comments about merle are also in the works.

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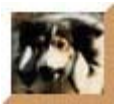

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Basic Genetics III: Linkage and Crossing Over

Up until now we have assumed that all genes were inherited independantly. However, we have also said that genes are arranged on chromosomes, which are essentially long strands of DNA residing in the nucleus of the cell. This certainly opens the possibility that two otherwise unrelated genes could reside on the same chromosome. Does independant inheritance hold for these genes?

To start with, we need to consider the rather complex process that forms gametes (egg and sperm cells, each with only one copy of each chromosome) from normal cells with two copies of each chromosome., one derived from each parent. I am not going to go into the details, beyond remarking that at one stage of this process, the maternally-derived chromosome lines up with the corresponding paternally-derived chromosome, and only one of the two goes to a specific gamete. If this were all there were to it dogs, having 39 chromosome pairs, would have only 39 "genes", each of which would code for a wide variety of traits. In fact, things are a little more complicated yet, because while the paternal and maternal chromosomes are lined up, they can and do exchange segments, so that at the time they actually separate, each of the two chromosomes will most likely contain material from both parents.

At this point we need to define a couple of terms. Two genes are linked if they are close together on the same chromosome and thus tend to be inherited together. Linkage in common usage, however, may apply to a single gene having more than one effect. An example which is not linkage in the sense used here is the association between deafness and extreme white spotting. White spotting is due to the melanocytes, the cells which produce pigment, not managing to migrate to all parts of the fetus. Now it turns out that in order for the inner ear to develop properly, it must have melanocytes. If the gene producing white spotting also prevents the precursors of the melanocytes from reaching the inner ear, the result willl be deafness in that ear. In other words, the same gene could easily influence both processes. Thus deafness and white spotting are associated, but they are not linked. They are due to what is called pleiotropic (affecting the whole body) effects of a single gene.

In true linkage, there is always the possibility that linked genes can cross over. Imagine each chromosome as a piece of rope, with the genes marked by colored stripes. The matching of the maternal and paternal chromosomes is more or less controlled by the colored stripes, which tend to line up. But the chromosomes are flexible. They bend and twist around each other. They are also self healing, and when both the maternal and paternal chromosomes break, they may heal onto the paired chromosome. This happens often enough that genes far apart on long chromosomes appear to be inherited independantly, but if genes are close together, a break is much less likely to form between them than at some other part of the paired chromosomes.

Such breaks, called "crossing over" do occur, and occur often enough that they are used to map where genes genes are located on specific chromosomes. In general, neither linkage nor crossing over is of much importance to the average dog breeder, though one should certainly keep in mind the possibility that the spread of an undesirable gene through a breed is due to the undesirable gene being linked to a gene valued in the breed ring. Crossing over is also important in the use of marker genes for testing whether a dog carries a specific gene, most often a gene producing a health problem.

There are two distinct ways of using DNA testing to identify dogs carrying specific, undesirable genes. The first (and preferable) is actually to sequence the undesirable gene and

its normal allele. This allows determination of whether the dog is homozygous normal, a heterozygous carrier, or homozygous affected. Since the genes themselves are being looked at, the results should be unambiguous. (The breeding decisions based on these results are still going to depend on the priorities of the breeders.)

In some tests, however, a marker gene is found that appears to be associated with the trait of interest, but is not actually the gene producing that trait. Such a marker is tightly linked to the gene actually causing that trait. This does not work at all badly providing that the group on which the test was validated is closely related to the group to which the test was applied. Use of this type of test on humans usually requires that the test be validated on close relatives, and applied only to people closely related to the validation group.

It is true that dogs of a given breed tend to be closely related to each other. However, the breed-wide relationship is generally through more distant ancestors than most people can trace in their own genealogy. In Shetland Sheepdogs, for instance, almost all US show stock can be traced to dogs imported from the British Isles between 1929 and 1936, with only a tiny influence of imports after 1950. This means that a crossover appearing on one side of the Atlantic since 1950 (20 or so dog generations) might not show up on the other side. Marker tests that work on U.S. populations might not work at all on British dogs, or on a dog with recent British ancestry.

Even without physical separation here is always the possibility that at some point in the breed history a crossover occurred. Quite a large fraction of the breed may have the original relationship between the marker gene and the problem gene, but if a crossover occurred in an individual who later had a considerable influence on the breed, the breed may also contain individuals in which the marker gene is associated with the opposite form of the problem gene. Since the relationship between individuals of the same breed may go back 30 generations or more, and there is a chance of a crossover occurring in each generation, linked markers need to be used with caution and with constant checking that marker test results correlate with clinical results.

Let's look more closely at this.

Let our marker gene be ma, with ma^a being the gene associated with the healthy gene, and ma^b being the marker that seems to be associated with the defective gene, both being true for the test population. For the genes actally producing the problem, we will use H, with H^h being the normal, healthy gene and h^d being the recessive gene which causes the problem. In the original test population, ma^a was always on the same chromosome with H^h, and ma^b was on the same chromosome with h^d. In other words, chromosomes are either ma^aH^h or ma^bh^d, never ma^ah^d or ma^bH^h. If a dog has ma^a on both chromosomes, it is also H^h on both chromosomes, a genetic clear. If it has ma^a on one chromosome and ma^b on the other, it also has one H^h gene and one h^d gene, and is a carrier. If it has ma^b on both chromosomes, it has h^d on both chromosomes and is a genetic affected. At least, that is the assumption on which marker tests are based.

Now suppose that at some point a crossover occurred between the ma and H loci. The probability of a crossover may be very small in any individual breeding, but remember that there are a lot of breedings behind any particular dog. We can still assume that most of the chromosomes will still be of the ma^aH^h or ma^bh^d type, or the original validation of the marker test would have failed. But now suppose that a small fraction of the chromosomes are of types ma^ah^d and/or ma^bH^h. We now have four chromosome types, and sixteen possible combinations. Some of these will test the same, since the only difference is in which

chromosome comes from the mother and which from the father, but there are still sixteen possible outcomes. In the table below both the marker results (upper) and the true results (lower) are shown for each possible combination:

	ma^aH^h	ma^bh^d	ma^ah^d	ma^bH^h
ma^aH^h	clear ma^ama^a	carrier ma^ama^b	clear ma^ama^a	carrier ma^ama^b
	clear H^hH^h	carrier H^hh^d	carrier H^hh^d	clear H^hH^h
ma^bh^d	carrier ma^ama^b	affected ma^bma^b	carrier ma^ama^b	affected ma^bma^b
	carrier H^hh^d	affected h^dh^d	affected h^dh^d	carrier H^hh^d
ma^ah^d	clear ma^ama^a	carrier ma^ama^b	clear ma^ama^a	carrier ma^ama^b
	carrier H^hh^d	affected h^dh^d	affected h^dh^d	carrier H^hh^d
ma^bH^h	carrier ma^ama^b	affected ma^bma^b	carrier ma^ama^b	affected ma^bma^b
	clear H^hH^h	carrier H^hh^d	carrier H^hh^d	clear H^hH^h

Note that in only six of the sixteen possible types is the marker indication of genotype correct. If the crossover genotypes are rare (as would normally be the case if the marker test verified at all) most of the population will be in the upper left quarter of the table, where the marker will correctly predict the true genotype. But if any of the chromosomes trace back to a crossover, a marker test may give a false sense of security (carrier or affected shows clear by marker testing) or result in discarding a healthy dog (carrier or clear shows affected or carrier by marker testing.)

If only three chromosome types are available, the two verifying types plus one crossover, then if the marker gene is associated at times with the healthy allele, (ma^bH^h) the result will include dogs which are affected or carriers by marker analysis which are genetically carriers or clears (false positives.) If the other chromosome type has the undesirable allele not always associated with the marker (ma^ah^d) the results will include dogs clear or carriers by marker analysis that are actually carriers or affected (false negatives.) However, the existance of one crossover chromosome type would make me suspicious that the other might also exist in the breed.

So are marker tests of any use at all?

Yes! In the first place, they demonstrate that the actual gene is on a relatively limited portion of a known chromosome. The marker gene can thus assist in finding and sequencing the gene actually causing the health problem.

In the second place, marker tests are accurate so long as neither parent of an individual has a crossover chromosome. In humans, such tests are most likely to be used when a problem runs in a particular family. The linkage of a marker with the genes actually producing the problem is generally based on studies of how the marker is linked to the genes in that particular family. With dogs, the verification is normally done on a breed basis, and the fact that breeds may actually be split into groups (color, size, country of origen) which interbreed rarely if ever is likely to be ignored. Dogs closely related via close common ancestors to the test population are the best candidates for marker testing. In general, keep up conventional testing side by side with the marker testing. If the marker testing and the conventional testing disagree (e.g, affected dog tests clear or clear dog tests affected) consider the possibility of a crossover, and notify the organization doing the test.

Genetics index page

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Basic Genetics IV: the relationship of genes to traits (single locus)

With the exception of the few DNA tests available, we cannot know the genetic makeup of our dogs, only the physical makeup, or phenotype. We tend to break that phenotype up into traits, some breed specific, some more general. For instance, we might know that a Sheltie is 15" tall, a black-nosed sable merle with full white collar, feet and tailtip and a narrow face blaze, OFA good, is missing one premolar, has natural ears, and had double rear dewclaws. All of these "traits" are defined by human beings. Very few of them actually refer to single genes that might be inherited as dominant, recessive, incompletely dominant or co-dominant.

In some cases we can break down a trait into a specific combination of genes. In the case of color, for instance, we know of a considerable number of genes that affect color through specific processes. In some cases, this knowledge has fed back on what we consider to be traits. Thus in the case given, the dog is:

- Sable $A^y\_$ (as opposed to black with or without tan-point markings).
- Black (as opposed to brown) B_
- Merle Mm
- Irish-marked $s^i s^i$ or $s^i s^w$
- Possibly a face-marking gene

In addition, the dog's color can be affected by minor genes (such as the modifier genes determining how much of the dog is white) by random factors (which probably influence the exact pattern of both white spotting and the location of the dark patches in the merling) and by environmental factors (such as uterine environment, nutrition or excessive exposure to the sun.) The point is that very few of the traits that humans have chosen are in fact due solely to the effect of a single pair of alleles at a single locus. We have looked at some such simple traits as regards color.

However, the height of the dog, the ears, the hip rating, the missing premolar, and the double rear dewclaws are probably not single-gene traits, but rely on the interaction of several pairs of genes, with perhaps some influence from the environment.

In general I am using dominant, recessive, co-dominant or intermediate to refer to genes at the same location on a single pair of chromosomes, i.e., alleles at the same locus. There are cases where genes at one locus can "hide" genes at another locus. An example in dogs is recessive yellow, ee, in which recessive yellow, although a recessive at its own locus, can hide whatever the dog carries at the A locus and the proposed K (dominant black) locus. This type of relationship among different loci is called epistatic. The locus that is hidden is referred to as hypostatic. In some cases (e.g., E at the E locus) an epistatic locus has an allele that allows the hypostatic locus to show its effects.

We will consider a number of types of inheritance. The first group actually refer to single-gene traits. Any of these types of inheritance may also be involved in the inheritance of multiple-gene traits.

Single-locus inheritance

- Dominant-recessive
- Intermediate
- Co-dominant
- Sex-limited
- Sex-linked

More complex inheritance will be covered on the next page, and includes

- Modifier genes
- Polygenic additive
- Threshold traits
- Variable expression
- Incomplete penetrance
- Polygenic recessive or dominant
- Mixed polygenic

Dominant-recessive inheritance

Black and brown provide a clear example of a dominant-recessive relationship among alleles. Every dog has two genes at the black/brown locus. If both genes are for black, or if one is for black and one is for brown, the dog is black, most readily identified by nose color. If both genes are for brown, the dog is brown, again most readily identified by nose color. BB cannot be distinguished from Bb without genetic tests or breeding tests.

Many genetic diseases, especially those that can be traced to an inactive or wrongly active form of a particular protein, are inherited in a simple recessive fashion. van Willebrand's disease (vWD) for instance, is inherited as a simple recessive within the Shetland Sheepdog breed.

Intermediate inheritance

Warning! Although this type of inheritance is common, it has a variety of names (incomplete dominance and overdominance are two common ones) some of which are also used for other things entirely. Here I will use it to refer to the type of inheritance in which the animal carrying two identical alleles shows one phenotype, the animal carrying two different identical alleles shows a different phenotype, and the animal carrying one copy of each of the alleles shows a third phenotype, usually intermediate between the two extremes but clearly distinguishable from either.

In dogs, merle color is a good example of this type of inheritance. If we define M as merle and m as non-merle, we find we have three genotypes:

- mm non-merle, with normal intense color
- Mm merle, with normal color diluted in a rather patchy fashion
- MM homozygous merle, extreme dilution, dog mostly white if a white-spotting gene is also present, and often with anomalies in hearing, vision and/or fertility.

Note that there is really a continuum between dominant-recessive and intermediate inheritance. In Shetland Sheepdogs, for instance, sables carrying one gene for tan-point have on average more dark shading than dogs with two sable genes. However, the darkest shading on dogs pure for sable is probably darker than the lightest shading on dogs carrying a gene for tan-point. In practice, intermediate inheritance is often treated as if it were a special case of dominant-recessive inheritance, as can be seen by the symbols used for merle and non-merle - usually the capital letter refers to a dominant gene and the lower-case letter refers to a recessive gene. I think a separate name is justified because it could be equally well argued that

homozygous merle is an undesirable recessive for which the merle color is a marker that the dog carries the merle gene.

Many of the standard color genes normally treated as dominant-recessive do in fact have intermediate inheritance, the heterozygote generally much more similar to one homozygote than the other, between at least some alleles in the series. Coat color gene loci with at least some allele pairs leaning toward intermediate inheritance include A (agouti, patterning of black and tan), C (color, intensity of color), and S (white spotting). I suspect the same is true for T (ticking), G (graying) and even D (dilution) if another diluting gene, such as merle, is present. This may be much more generally true than is recognized.

Co-dominant inheritance

The dividing line between intermediate inheritance and co-dominant inheritance is fuzzy. Co-dominance is more likely to be used when biochemistry is concerned, as in blood types. Co-dominance means that both alleles at a locus are expressed. Co-domininance in X-linked genes is a special case that will be treated under sex-linked inheritance.

Sex-limited autosomal inheritance

Please, don't confuse sex-limited inheritance with sex-linked inheritance. They are two totally different things. Sex-linked inheritance is discussed below. I do include sex-influenced traits under the sex-limited heading, though some genetics texts separate sex-influenced and sex-limited traits.

A classic example of a sex-limited trait in dogs is unilateral or bilateral cryptorchidism, in which one or both testicles cannot be found in their usual position in the scrotum. Since a bitch has no testicles, she cannot be a cryptorchid - but she can carry the gene(s) for cryptorchidism, and pass them to her sons. Likewise, genes affecting milk production are not normally expressed in a male. The main problem with sex-limited inheritance is that it is impossible to know even the phenotypes of the unaffected sex in a pedigree, which makes it difficult to determine the mode of inheritance.

In sex-influenced inheritance, the genes behave differently in the two sexes, probably because the sex hormones provide different cellular environments in males and females. A classic example in people is male early-onset pattern baldness. The gene for baldness behaves as a dominant in males but as a recessive in females. Heterozygous males are bald and will pass the gene to about 50% of their offspring of either sex. However, only the males will normally be bald unless the mother also carries the pattern baldness gene without showing it (female heterozygote.) If the mother is affected with baldness (homozygous) but the father is not, all of the sons will be affected and all of the daughters will be non-affected carriers. A bald man may get pattern baldness from either parent; a bald woman must have received the gene from both parents.

Sex-linked inheritance

In order to understand sex-linked traits, we must first understand the genetic determination of sex. Every mammal has a number of paired chromosomes, that are similar in appearance and line up with each other during gamete production (sperm and eggs). In addition, each mammal has two chromosomes that determine sex. These are generally called X and Y in mammals. Normal pairing of chromosomes during the production of gametes will put one or the other in each sperm or ovum.

In mammals, XY develops testicles which secrete male sex hormones and the fetus develops into a male. An XX fetus develops into a female. Thus sperm can be either X or Y; ova are

always X. Sex linked inheritance involves genes located on either the X or the Y chromosome. Females can be homozygous or heterozygous for genes carried on the X chromosome; males can only be hemizygous.

X-linked recessive:

The most common type of sex-linked inheritance involves genes on the X chromosome which behave more or less as recessives. Females, having two X chromosomes, have a good chance of having the normal gene on one of the two. Males, however, have only one copy of the X chromosome - and the Y chromosome does not carry many of the same genes as the X, so there is no normal gene to counter the defective X.

An example of this type of inheritance is color blindness in human beings. Using lower case letters for affecteds, we have

- Affected male: xY Color blind
- Non-affected males XY Normal color vision
- Affected female xx Color blind
- Carrier female xX Normal color vision
- Clear female XX. Normal color vision

Now the possible matings:

xY to xx (both parents affected) xx females and xY males, all offspring affected.

xY to Xx (affected father, carrier mother) half the females will be xX and carriers, half will be xx and affected. Half the males will be XY and clear, half will be xY and affected.

xY to XX (affected father, clear mother) all male ofspring XY clear, all daughters Xx carriers.

Note that the daughters of an affected male are obligate carriers or affected. The unaffected sons of an affected male cannot carry the problem.

XY to xx (father clear, mother affected) xY males (affected) and xX daughters (carriers.)

XY to Xx (father clear, mother carrier) half the males affected (xY) and half clear (XY); half females clear (XX) and half carriers (Xx)

XY to XX (father and mother both genetic clears) all offspring clear.

Note that all female offspring of affected males are obligate carriers (if not affected.) Likewise, any female who has an affected son is a carrier. Non-affected sons of affected fathers are genetically clear.

This type of inheritance may be complicated by the sublethal effect of some X-linked genes. Hemophilia A in many mammals (including dogs and people) is a severe bleeding disorder inherited just like the color-blindness above. Many affected individuals will die before breeding, but for those who are kept alive and bred for other outstanding traits, non-affected sons will not have or produce the disease. All daughters, however, will be carriers.

X-linked dominant:

Here I will use X^+ for the dominant gene on the X chromosome, and X for the gene on the normal X chromosome. The actual possibilities are similar to those for an X-linked recessive, except that X^+X females are now affected. In X-linked dominant inheritance, more femals

than males will show the trait. Possible matings are:

Affected to homozygous affected (X^+Y to X^+X^+): All offspring affected.

Affected to heterozygous affected (X^+Y to X^+X): All daughters affected; half of sons affected.

Affected to homozygous normal (unaffected female): (X^+Y to XX): All daughters affected, all sons normal.

Normal to homozygous affected (XY to X^+X^+): all offspring affected, but daughters are heterozygous affected.

Normal to heterozygous affected: (XY to X^+X): Half of offspring affected, regardless of sex. Affected daughters are heterozygous.

Normal to normal (XY to XX) all offspring affected.

X-linked co-dominant:

Mammalian cells, even in females, get along fine with just one X chromosome. In fact, more than one X chromosome within a cell seems to be a problem if both are active. So in female cells, one or the other X chromosome must be inactivated. This occurs more or less at random, so any female mammal has patches of cells with one X chromosome inactivaed, and patches with the other not active. If the gene being discussed codes for an enzyme that is spread throughout the body, it may not be obvious that the different patches of cells are behaving differently, and we will get what looks like dominant, recessive, or intermediate inheritance.

However, if the gene is expressed directly within the cell, the mosaic nature of the female may become obvious. The tortoiseshell cat provides an excellent example of this.

In cats, the orange color is on the X chromosome. It is designated as O, and the "wild-type" gene that allows black (eumelanin) to appear in the coat is designated +. Note that a cat homozygous or hemizygous (male) for + may be solid or tabby with the eumelanin pigment showing only in the tabby stripes, ticks and blotches (in extreme cases only on the tips of the hairs) and the "black" may just as well be chocolate or blue. A cat with only O genes will be some shade from cream to deep red., with no black/blue/chocolate pigment in the coat, but usually with tabby markings.

However, a cat with the gene for orange on one X chromosome and the gene for non-orange on the other is neither orange nor non-orange, but has patches of both colors. This color is known as tortoiseshell, and I am going to use the broad definition, including blue/cream or chocolate/yellow tortoiseshells. Most of the time cats with two X chromosomes are female, and since two X-chromosomes are required for tortoiseshell, most tortoiseshell cats are female.

Now and then a cell does not divide properly when it is making a germ cell, and you might, for instance, get an XY sperm cell. This would produce an XXY male, which would look male (he has a Y chromosome) but also have two versions of X and thus could be a tortoiseshell. However, the XXY makeup, corresponding to Klinefelter's syndrome in human beings, is believed to produce sterility. A similar syndrome involving females with only one X chromosome but no Y is called Turner's syndrome in human women, and again appears to produce sterility. We will therefore consider only matings between animals with two sex

chromosomes.

Non-orange male to non-orange female (+ to ++): all non-orange offspring.

Non-orange male to tortoiseshell female (+ to +O): Males 50% orange and 50% non-orange; females 50% non-orange and 50% tortoiseshell.

Non-orange male to orance female (+ to OO): all males orange; all females tortoiseshell.

Orange male to non-orange female (O to ++): All males non-orange; all females tortoiseshell.

Orange male to tortoiseshell female (O to O+): males 50% orange and 50% non-orange; females 50% orange and 50% tortoiseshell.

Orange male to orange female (O to OO): All offspring orange.

Y-linked inheritance:

The Y chromosome in most species is very short with very few genes other than those that determine maleness. Y-linked inheritance would show sons the same as their fathers, with no effect from the mother or in daughters. In humans, hairy ears appear to be inherited through the Y chromosome. Padgett does not list any known problem in dogs as being Y-linked.

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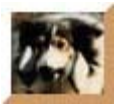

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last updated March 29. 2010

Test Breedings II

Purpose: to determine the genetic basis for a trait.

Sue Ann Bowling

Suppose we have a list of various types of a particular trait, and we want to know how they are inherited. The first step is to make a guess. It should be an informed guess - for instance, you may know that in other mammals a particular trait is inherited in a particular way, so as a first guess you assume that the inheritance is similar in the animal you are investigating. The point is, this first guess is just that - a guess. In order to elevate that guess to the level of a hypothesis, you need to work out what your guess predicts in terms of what parents can produce what, and then breed (or investigate breeding records) to see if that is really what happens.

Let's take a first guess we know is wrong. Labrador Retrievers come in black, brown and yellow, as explained earlier. Suppose we don't know the genetics of this. We have observed the three colors, and a reasonable initial assumption is that there a locus for color which has three alleles: black, brown and yellow. As we start to look at Stud Book data, we find that;

1. Black to black can produce any color
2. Yellow to yellow can produce only yellow
3. Brown to brown usually produces browns, but can produce yellow
4. Black to any other color can produce black.

This information adds to our initial guess. If black to black can produce any color then black must be the top dominant in the series. Likewise, if yellow to yellow can produce only yellow, then yellow must be the bottom recessive. Brown looks as if it is recessive to black but dominant to yellow. Our tentative hypothesis, then, is that we have a locus, J, with three alleles:

- J^{blk} black
- j^{brn} brown
- j^{yel} yellow.

Now we set up our Punnett squares and work out what each mating will produce. We find that

1. $J^{blk}J^{blk}$ x $J^{blk}J^{blk}$ gives black to black producing all blacks
2. $J^{blk}J^{blk}$ x $J^{blk}j^{brn}$ gives black to black producing all blacks
3. $J^{blk}j^{brn}$ x $J^{blk}j^{brn}$ gives black to black producing black and brown
4. $J^{blk}J^{blk}$ x $J^{blk}j^{yel}$ gives black to black producing all black
5. $J^{blk}j^{yel}$ x $J^{blk}j^{yel}$ gives black to black producing black and yellow.
6. $J^{blk}j^{brn}$ x $J^{blk}j^{yel}$ gives black to black producing black and brown
7. $J^{blk}j^{brn}$ x $j^{brn}j^{brn}$ gives black to brown producing black and brown
8. $J^{blk}j^{brn}$ x $j^{brn}j^{yel}$ gives black to brown producing black and brown

9. $J^{blk}j^{brn}$ x $j^{yel}j^{yel}$ gives black to yellow producing black and brown
10. $J^{blk}j^{yel}$ x $j^{brn}j^{brn}$ gives black to brown producing black and brown
11. $J^{blk}j^{yel}$ x $j^{brn}j^{yel}$ gives black to brown producing black, brown and yellow
12. $j^{brn}j^{brn}$ x $j^{brn}j^{brn}$ gives brown to brown producing all browns
13. $j^{brn}j^{brn}$ x $j^{brn}j^{yel}$ gives brown to brown producing all browns
14. $j^{brn}j^{yel}$ x $j^{brn}j^{yel}$ gives brown to brown producing brown and yellow
15. $j^{brn}j^{yel}$ x $j^{yel}j^{yel}$ gives brown to yellow producing brown and yellow
16. $j^{yel}j^{yel}$ x $j^{yel}j^{yel}$ gives yellow to yellow producing all yellows

The key point is that none of the black to black or black to yellow matings can, on this hypothesis, give us a litter with all three colors represented. Three colors is only possible if black carrying yellow is mated to an animal which is brown carrying yellow. Blacks always have the potential to produce some blacks, but if a brown is produced than the black must carry brown, and there simply isn't room for the yellow allele at the locus, which can hold only two alleles at once. While the individual matings seem to agree with with our incorrect hypothesis, the hypothesis falls down when it is applied to colors within a single litter.

The problem is that while it's fairly easy to go through a stud book and determine what parent color combinations can give a particular puppy color, it is much harder to pull out a whole litter. In the AKC Stud Books it is almost impossible, as the only dogs listed are those who have produced registered litters. The point is that without determining whether the observed distribution of phenotypes within a litter agrees with the hypothesis, the hypothesis is still little more than a guess.

There are two possible test breeding strategies to expose this problem. The first involves looking at as many litters as possible in which one parent is the top dominant (black) and the other is the bottom recessive (yellow). If such a litter includes both browns and yellows, then our one locus - three allele hypothesis cannot be true.

The second case is a variant - identify blacks with one parent yellow or chocolate, so you "know" that the black is $J^{blk}j^{yel}$ or $J^{blk}j^{brn}$, and examine litters to yellow and to brown mates. Again, the presence of all three colors in one litter disproves the hypothesis, but it will take fewer litters in total, as the initial selection of the blacks eliminates those that are pure for black.

Note that in most cases, this means a fair number of breedings. This again is a case where there is no way to prove the hypothesis correct. You may have nine litters with black to yellow producing only yellow or brown (with black in each case) but that doesn't prove the hypothesis is correct. Only a few black to yellow litters may even have the right parental genotypes, and especially if the number of puppies is small, one possible color may be missing by pure chance. As usual with scientific hypotheses, the hypothesis cannot be proven, but it can be disproven.

In this particular case, I knew the thypothesis was incorrect. I have friends who breed Labs, and one bred a black to a black and got all three colors in the litter. It's not considered unusual in Labs. I even used the litter in a genetics Science Forum article. There are, however, other loci in dogs where the assignment of one or more

genes to the locus is questionable. Probably the most important are the A series and the E series.

Dominant black is a very unlikely top dominant of the A series. This series is known in a number of mammals, and more yellow is almost always dominant over less yellow. The key breeding here would need a breed with dominant black, sable and tan-point. Basenji breedings of this type (black to tan-point) have been reported to include all three colors. The only remaining doubt comes in whether the "reds" from these breedings are sable or ee reds. e is not known to occur in the breed, but without further test breeding of the red offspring, there remains some uncertainty. Still, I am inclined to treat A^s at this point as belonging to another locus entirely. This hypothesis agrees with recent DNA work, and in fact dominant black is now assigned to the K locus.

There was another possible problem in the A series, this one involving the recessive black seen in Shelties and German Shepherds. If the recessive black was in the A series, with sable dominant to tan-point which in turn is dominant to recessive black, then it shoud not be possible to get a litter with all three colors from a sable to sable or a sable to recessive black breeding - a sable could be black-factored or tanpoint factored but not both. There was some evidence from Shelties that such three-color litters do occur. This suggests that the presence or absence of tan points in the classic tan-point pattern may depend on a extra locus.

DNA work has now established that Sheltie black is indeed aa, so the three-color litters are now suspected to be (1) cases where the true parents are not those on the registration, (2) misidentification of the colors of one or more pups, or (3) rare mutations. However, the A (agouti) locus is still under study.

E is defined to include E, which allows the agouti series to show through, and e which in double dose makes the dog produce only phaeomelanin in the hair coat, effectively hiding what is present at the A locus. The two other proposed members of the E series, E^{br} (brindle) and E^{ma} (masked) are still at the hypothesis stage. Even Little, who is often quoted as the source for putting brindle and mask in this locus, prefaced almost everything he said with "if they are at the same locus." In particular, none of the test matings he carried out really clarified the relationship of e to E^{ma} or to his proposed E^{br}. Test breeding is definitely needed at this locus. Some work has been done in greyhounds that suggests that the brindle gene might be at the same locus (called "K" by the researcher) with dominant black, but this was preliminary at the time this website was first put together. The hypthesisthat both brindle and dominant black are at the K locus has since been shown to agree with DNA studies.

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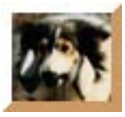

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Last updated May 11, 2010

Population Genetics I: Random breeding

Sue Ann Bowling

Ordinary genetics looks at how one selects breeding stock to produce the best possible offspring. Population genetics looks at the statistical distribution of genes in a particular breeding population, such as a breed of dog, and how different kinds of selection can affect that gene distribution. (Increasingly, population genetics also involves looking at the relationship between species by using gene sequencing as a tool.) You can think of ordinary genetics as predicting the phenotypic makup of the next generation, while population genetics predicts the genetic makeup of the breed as a whole, often several generations away.

This article is based on the assumption that the population is random breeding - an animal is equally likely to mate with any other animal in the population. This is obviously not really true - a dog in California is much more likely to mate with another California dog than with one in New York, a Great Dane is more likely to mate with another Great Dane than with a Papillion, and many breeders of domesticated animals practice deliberate breeding to relatively close relatives. We'll look at possible effects of this later on (if I get around to it). Random breeding with selection based on a single gene is the simplest case, with which other possibilities can be compared.

Unfortunately, I'll have to use a little algebra to do this. I promise I'll try to explain the results in non-mathematical terms.

We need to start by defining a few things.

A gene pool refers to the sum total of genes (and how many of each combination) found in a breeding population. The breeding population may be a single kennel that changes its gene pool every time it breeds to an outside dog, in which case the gene pool can be considered leaky, or at the other extreme may be all of the animals within a pure breed. One can speak of the gene pool of an entire species, but it is simply not true that any member of the species can mate with any other member with equal probabilty. There are species with continuous ranges where a particular gene is very rare at one end of the range and very common at the other - any member of the species can mate with any other, but by far the most likely matings are of relatively near neighbors.

We will deal with a single autosomal locus (no sex-linked genes) with a single pair of alleles, which we will call K and k. Our breeding population is made of of three different types of animals:

KK, which are genetic clears. We will call the fraction of clears in the population n, for normal.

Kk, which are carriers, meaning that they can produce affected animals. We will call the fraction of carriers in the population c, for carrier.

kk, which we will call affected, meaning that they show the effect of the k gene in double dose. We will call the fraction of affecteds in the population a, for affecteds.

Note that n + c + a = 1 = 100%, as every animal in the population is one of the three states.

Note also that "affected" can mean something as innocuous as brown rather than black pigment or something as serious as blindness, bleeding disorders or even prenatal death. I am

also making no stipulation at this point as to whether the Kk state can be distinguished from KK. There are a rapidly increasing number of cases in which Kk, once distinguisable from KK only by imperfect breeding tests, can now be identified by genetic testing.

A gene frequency refers to the fraction of the genes in the breeding population that is of a particular type. The gene frequencies of all of the different alleles at a locus must add up to 100%, or 1. We are dealing with a two-allele locus (K and k) so we will define f as the frequency of the k allele and (1-f) as the frequency of the K allele. How does this relate to our clear-carrier-affected numbers?

Each dog has two genes. A fraction n is normal, and has two K genes. They contribute nothing to f. A fraction c are carriers, with one half of their genetic makeup k; they contribute c/2 to f. Finally, the affecteds contribute a to f. This gives

$$f = c/2 + a.$$

As a general rule, we do not know the value of c, as not all carriers are identified. But if we assume random breeding, the probabilities of the nine types of breedings possible (normal male to normal female, normal male to carrier female, normal male to affected female, carrier male to normal female, carrier male to carrier female, carrier male to affected female, affected male to normal female, affected male to carrier female, and affected male to affected female) can be calculated if we know c, a and n. specifically, we get these fractions:

1. Normal to normal: n x n.
2. Carrier to carrier: c x c.
3. Affected to affected a x a
4. Normal to carrier (combining the cases where the male or female is the carrier): 2 x n x c
5. Normal to affected: 2 x n x a.
6. Carrier to affected: 2 x c x a.

We also know the expected results of each kind of breeding:

1. Normal to normal all normal.
2. Carrier to carrier 25% normal, 50% carrier, 25% affected.
3. Affected to affected all affected.
4. Normal to carrier 50% normal, 50% carrier.
5. Normal to affected all carrier.
6. Carrier to affected 50% carrier, 50% affected.

If we multiply the types of offspring by the fraction of the breedings in each category, and then group the offspring by their genetic makeup, we get some surprisingly simple numbers:

1. n (fraction of normals) = (1-f) x (1 - f)
2. c (fraction of carriers) = 2 x f x (1-f)
3. a (fraction of affecteds) = f x f.

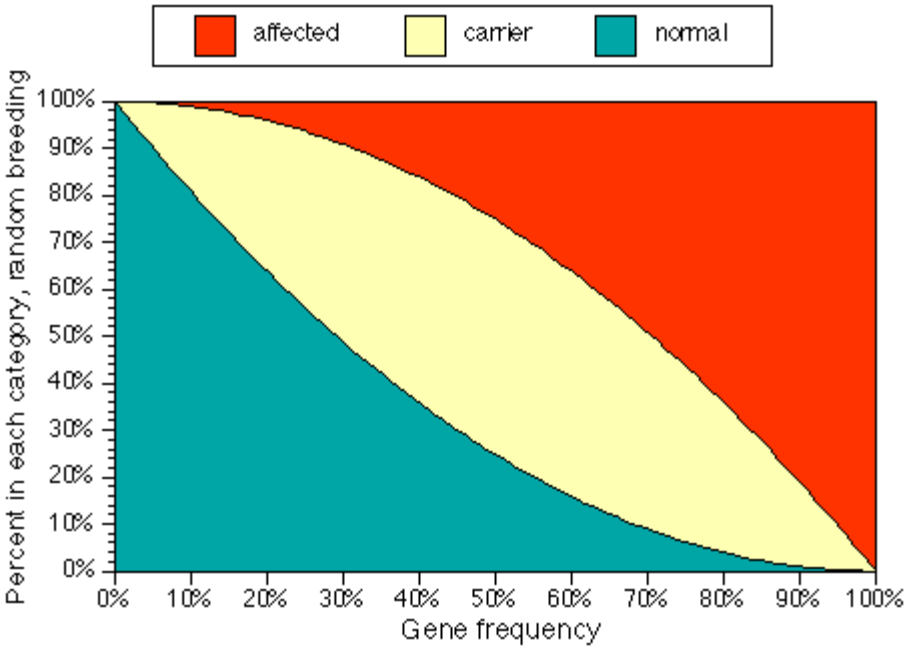
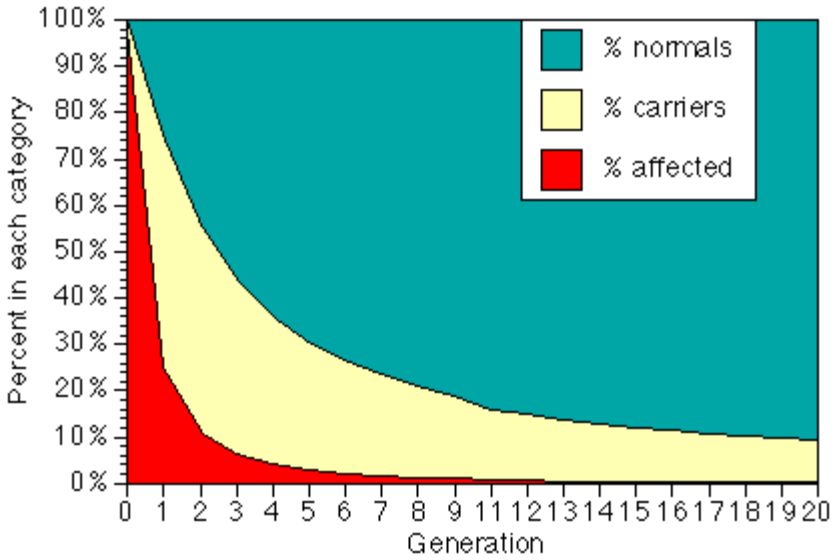


Figure 1. Percents of normal, carrier and affected individuals for a random-breeding population with a given gene frequency.

If we recalculate f from these values of n, c and a, it will be the same as the f we started with. **Completely random breeding without selection does not change gene frequencies, unless the breeding population is so small that the assumption of a predictable distribution of types within litters of the same type or types of matings within a gene pool breaks down**.

Until now we have assumed that there is no differential breeding based on whether the animal is a normal, a carrier, or an affected. Now let us assume that the kk genotype is undesirable. It does not matter whether the kk animal is a color the breeder does not like or has a lethal defect that results in its death before it reaches breeding age. For breeding purposes it is a lethal gene, i.e., all kk (affected) animals are removed from the breeding pool in each generation. For the moment we will also assume that Kk (carriers) cannot be distinguished from KK (normals.) What does this do to the frequency of the gene? (If you can't stand algebra an want to go straight to Figure 2 you can.)

We will use subscripts (numbers below and to the right of the symbol) to indicate the generation. Thus f_0 is the gene frequency in our starting generation, f_1 is the is the gene frequency in the first generation after all affected animals in the initial generation are removed, f_2 is the gene frequency in the next generation after the affecteds are removed, and so on. For illustrative purposes, suppose that f_0 is so large that the population is effectively made up only of affecteds and carriers. After all of the affecteds are removed, however, the remaining gene pool is made up almost entirely of carriers, which by definition have a gene frequency of 50%. When these dogs are interbred, they produce 25% genetic normals, 50% carriers, and 25% affecteds, which again are discarded from the breeding pool. Our new gene pool is 2/3 carriers (f=50%) and 1/3 normals (f = 0), so f_2 = 1/3. Breeding these dogs gives 1/9 affecteds, and when these are removed we have a population with equal numbers of carriers and normals, for a gene frequency of 1/4. Note that while selection solely by removing affecteds is very fast if the original percent of affecteds is high, the continued reduction after the 4th or 5th generaltion is slow.



Percent of normals, carriers and affected in each generation of a program of removing all affected animals, assuming affected condition is autosomal recessive. It doesn't show on the graph, but generation 20 would still have a quarter of a percent - one puppy in 400 - affected.

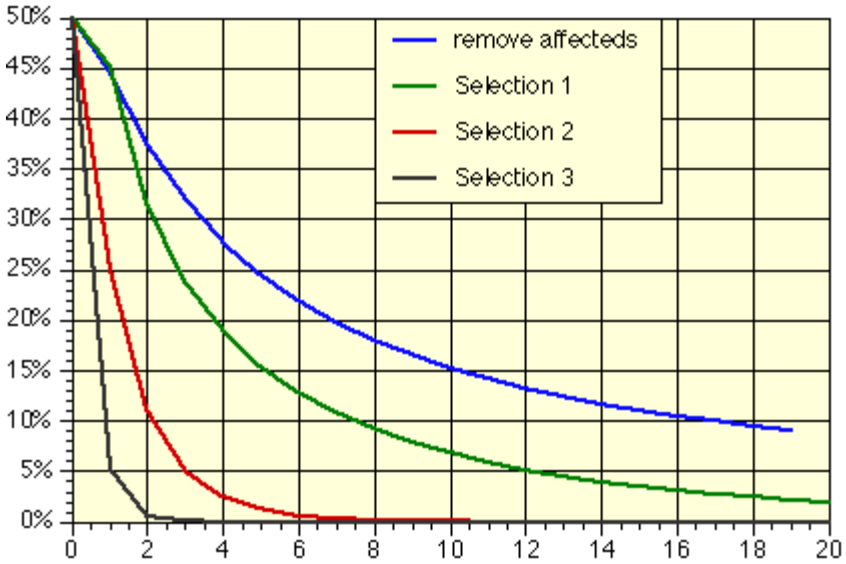
Can anything be done beyond this? Yes, provided the mode of inheritance (autosomal recessive) is known. Assume at first the carrier state cannot be distinguished from the affected state, i.e, that Kk cannot be distinguished from KK except through breeding results. (This has historically been the case with most recessive problems.) Use the breeding results to identify the carriers, and limit (not necessarily avoid at this stage) the breeding of carriers. In other words, if an animal produces affected offspring, it is a carrier and should be bred again only if it has other traits that are truly outstanding and hard to get. Full siblings of an affected animal have two chances in three of being carriers, and one in three of being normal, and these animals are less likely than the parent to produce the problem. Removing animals from the breeding pool that have produced affected animals is the next step in lowering the gene frequency.

Between test breeding and DNA sequencing, the number of conditions in which the carrier state can be unambiguously identified is increasing rapidly, and the obvious answer is not to breed carriers. However, I hesitate to recommend any breeding strategy which would remove over 10% of the gene pool due to a single gene. This could easily happen if the carrier state is identified, and has resulted in health problems in the past when the few genetic clears for one problem turned out to carry a different problem. However, there are a couple of intermediate strategies which will lower the gene frequency to the point that carriers can be eliminated safely, while at the same time minimizing the number of affecteds produced.

First, breed carriers only to tested normals. This will eliminate the production of affected offspring, but it does nothing in itself to reduce the gene frequency of the unwanted gene.

Second, treat carrier status as a fairly serious fault. The idea is to reduce the use of carriers while not eliminating them entirely until the carrier frequency drops below 5 to 10%. The figure below is based on how the carrier frequency would change with time if various percents of the carrier-normal breedings that would take place on a random basis were not made.

All Selections based on no affecteds bred, no carrier to carrier matings.
Selection 1: carriers allowed to produce at 90% of general breed rate.
Selection 2: carriers allowed to reproduce at 50% of breed rate;
Selection 3: carriers reproduce at 10% of breed average rate.



The point of this figure is not to select heavily against carriers, as that will result in too much loss in genetic diversity if the carrier frequency is high. Rather, it is that not making carrier to carrier breedings, while cutting down on the total number of offspring produced by carriers, is an effective means both of eliminating the production of affected animals and of reducing the gene frequency in the population. The type and severity of selection used at any given point in time should depend on both the gene frequency and the severity of the problem.

Note that the figures all relate to a population that starts with 50% gene frequency. In practice this means that even the mildest selection, that of removing affecteds, will start out by removing more than 10% of the breeding population due to a single gene. In cases where the breeding pool has a high incidence of affecteds, a different kind of selection becomes important - aimed not so much as reducing the number of affected and carrier animals as of increasing the frequency of the normal gene. Only after the gene frequency of k has been reduced by these earlier steps can the stonger selection suggested here be applied.

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Population Genetics II: Reducing High Gene Frequencies

Sue Ann Bowling

Suppose you have an undesirable recessive gene that is affecting most of a population. This gene is clearly not lethal in the normal sense, as there is no way that a naturally lethal gene can exceed a gene frequency of 50% (every animal in the breed a carrier, and that is unlikely unless there is strong selection against both homozygotes.) But it can easily be a gene which affects health (e.g., deafness, blindness, bleeding tendencies, metabolic disorders) but does not appear obvious to the eye of the breeder without tests. It is possible for such an undesirable recessive to affect an entire breed; and once this happens it is not possible to eliminate the condition without crossing to another breed. For breeds which have not quite reached this 100% frequency, then, it is of extreme importance to preserve the normal gene.

Suppose we start with a breed gene frequency of 95%. We will again assume random breeding, modified only by the breeding strategy of the breeders. With a 95% gene frequency, we would expect 90.25% affected, 0.25% genetic clears, and about 9.5% carriers, for an unaffected rate of slightly less than 10%. (In practice, some breeders will normally have been testing and removing carriers, so the fractions of affecteds and clears will increase at the expense of carriers.) We assume that in any generation we want to remove no more than 10% of the gene pool due to this single gene. The exact value of 10% can be argued - it should depend on the severity of the unwanted gene - but removing much more than 10% in a single generation due to a single gene can have dangerous effects on the overall genetic diversity of the breed.

In the first few generations, you forget about selection *against* the undesirable gene and concentrate - hard - on selection *for* the normal gene. In effect, unaffected status - be it carrier or simply non-affected - is treated as an extremely positive virtue and bred for. Almost all unaffected dogs should be bred, and they should be bred to the best mates available. This means that owners of top quality dogs must be willing to mate them to bitches which are of poor quality by show standards if these bitches are non-affected. Affected, poor-quality offspring of such matings can and should be removed from the breeding pool; non-affected offspring, like their non-affected parent, should be kept in the gene pool. A more difficult goal is to get owners of top quality bitches to mate them at least once in their lives to the best non-affected male available. The goal at this point is to increase the number of carriers at the expense of affecteds. Unfortunately the show ring provides no reward for this kind of long-range thinking.

How fast will this have an effect? It depends on how strong the selection for non-affecteds is, and how rare non-affecteds are to start with.

It is clear, however, that it will take some time to get a reasonable spread of K genes in the breed (remember most of the breed starts out kk) especially if we want those K genes to come from as wide a range of individuals as possible. Note that at this time we are distinguishing only between affected (kk) and non-affected Kk and KK) individuals. To a first approximation, the percent of affected individuals is the square of the gene frequency. (This is exact only for random breeding.) The gene frequency is then the square root of the percent of affected individuals in the breed. This is an easy calculation on a $10 pocket calculator - punch in the fraction of affecteds as a decimal (e.g., 70% is put in as 0.70) and hit the square root key. (In this case the gene frequency is about 0.84 = 84% - the gene frequency will always be greater than the percent of affecteds.)

By the time the gene frequency has dropped to around 80% (64% affecteds) some mild selection against affecteds should be added to the mix. Affected to affected breedings should be looked on with an increasingly critical eye - not actually banned yet, but limited. Affected dogs (both sexes) without any great virtues to offer should be removed from the gene pool.

As the gene frequency continues to drop, the selection against affecteds should grow stronger. Actual removal of all affecteds should wait until the observed frequency of affecteds drops below the critical value of 10% (gene frequency about 32%), but affected to affected breedings should be eliminated and non-affected to non-affected breedings encouraged as far as possible. At this stage it is premature to worry about carriers, but an affected dog should have really great virtues to offer if it is kept in the breeding pool. Once the gene frequency drops below about 30%, it is safe to start removing all affected individuals from the breeding pool. By this time, 90% of the animals in the breed will be non-affected, and there should be no problem in finding good non-affected mates.

Until now, we have assumed that we cannot differentiate KK from Kk - both are simply non-affected. In most cases, however, there are ways of identifying carriers. The simplest is simply to continue to test for the condition, and pay attention to normal breeding results. If a breeding produces any affected individuals, both parents are carriers and non-affected littermates have 2 chances out of three of being carriers. One in three of the littermates, however, are genotypic normals. Thus the littermates of affected pups, if of exceptional type otherwise, should be tested for carrier status. If such an animal tests as a genetic normal, it cannot pass on the gene for the problem, even though a littermate was affected.

Testing for carrier status beyond what comes out of normal breeding has changed sharply in the last few years. The old method (still needed for some genes) is to breed the questionable dog to an affected one. Some affecteds will still be produced at this stage, and some should be retained for test breeding if that is necessary. This type of test breeding, however, has considerable uncertainty and required several known carrier offspring to be produced (around 10) before a dog could be pronounced to be a non-carrier with a reasonably high degree of confidence. In fact, a dog could never be proven to be a non-carrier; it could only be demonstrated that he could not be proved to be a carrier.

Increasingly, gene sequencing is offering an alternative in determining carrier status. This has great advantages over test breeding: no carriers or affected dogs need be

produced to determine the status of the dog, and the production of affected individuals can be entirely avoided if the carrier status of all individuals in the breeding population is known. It does produce problems as well: the temptation is to say that no carriers should be bred right from the start, when a large number of dogs, could be removed due to a single gene. Suppose that the test becomes available when the fraction of affected individuals in the breed is on the order of 4%. This corresponds to a gene frequency of 20% and a carrier frequency of 32%. Even with an affected frequency of 1% we can expect a carrier frequency of 18%. Yet we do not want to elminate more than 10% of the breed due to this single gene. How do we prodeed?

We can avoid producing affecteds by breeding carriers only to dogs genetically tested as non-carriers - genetic normals. This in itself, however, does nothing to reduce the gene frequency. For the best benefit of the breed as a whole, the avoidance of carrier to carrier matings should be accompanied by some selection against carriers, but not by actual elimination of carriers from the gene pool when such elimination would lead to too rapid a restriction of the gene pool A limitation on the number of litters produced by carriers would be appropriate, as would removal of those carriers whose virtues could be found in non-carriers. Figure 3 in part I of this series shows how rapidly selection will reduce the gene frequency using this strategy. Probably the initial approach would be to allow carriers to reproduce at around 90% of their expected rate, then reduce the reproductive rate with each generation until the carriers make up less than 10% of the population. At that point the remaining carriers could be removed from the breeding pool.

How long should testing continue? Certainly as long as occasional affecteds are being produced. More practically, offspring from normal to normal breedings should all be normal. Until the test is throroughly established, breeding stock from normal to normal breedings should still be checked, but carrier status for these dogs is not expected. Once the test is fully validated, all pups from matings involving a carrier as a parent should be tested. Once all carriers are removed, in theory no more testing is needed - but to catch any new mutations, it is still a good idea to check widely used animals - any dog bred to produce more than two litters a year, I would say. Also all relatives of any affected pups that show up after the gene is apparently eradicated.

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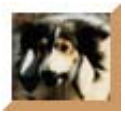

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Inbreeding and linebreeding

What are inbreeding and linebreeding, and what effect do they have?

In genetic terminology, inbreeding is the breeding of two animals who are related to each other. In its opposite, outcrossing, the two parents are totally unrelated. Since all pure breeds of animal trace back to a relatively limited number of foundation dogs, all pure breeding is by this definition inbreeding, although the term is not generally used to refer to matings where a common ancestor does not occur behind sire and dam in a four or five generation pedigree.

Breeders of purebred livestock have introduced a term, linebreeding, to cover the milder forms of inbreeding. Exactly what the difference is between linebreeding and inbreeding tends to be defined differently for each species and often for each breed within the species. On this definition, inbreeding at its most restrictive applies to what would be considered unquestioned incest in human beings - parent to offspring or a mating between full siblings. Uncle-niece, aunt-nephew, half sibling matings, and first cousin matings are called inbreeding by some people and linebreeding by others.

What does inbreeding (in the genetic sense) do? Basically, it increase the probability that the two copies of any given gene will be identical and derived from the same ancestor. Technically, the animal is homozygous for that gene. The heterozygous animal has some differences in the two copies of the gene Remember that each animal (or plant, for that matter) has two copies of any given gene (two alleles at each locus, if you want to get technical), one derived from the father and one from the mother. If the father and mother are related, there is a chance that the two genes in the offspring are both identical copies contributed by the common ancestor. This is neither good nor bad in itself. Consider, for instance, the gene for PRA (progressive retinal atrophy), which causes progressive blindness. Carriers have normal vision, but if one is mated to another carrier, one in four of the puppies will have PRA and go blind. Inbreeding will increase both the number of affected dogs (bad) and the number of genetically normal dogs (good) at the expense of carriers. Inbreeding can thus bring these undesirable recessive genes to the surface, where they can be removed from the breeding pool.

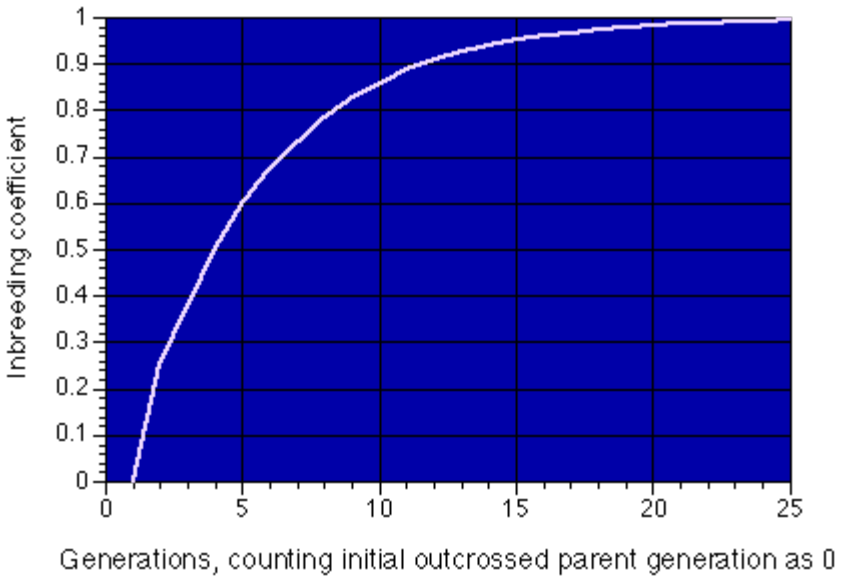
Unfortunately, we cannot breed animals based on a single gene - the genes come as a package. We may inbreed and rigorously remove pups with PRA or even their parents and littermates from the breeding pool. But remember inbreeding tends to make all genes more homozygous. In at least one breed, an effort to remove the PRA-causing gene resulted in the surfacing of a completely different and previously unsuspected health problem. It is easier and faster to lose genes (sometimes very desirable genes) from the breeding pool when inbreeding is practiced than when a more open breeding system is used. In other words, inbreeding will tend to produce more nearly homozygous animals, but generally some of the homozygous pairs will be "good" and others will be "bad".

Furthermore, there may be genes where heterozygosity is an advantage. There are several variant hemoglobin types in human beings, for instance, where one homozygote suffers from some type of illness, the other homozygote is vulnerable to malaria, and the heterozygote is generally malaria-resistant with little or no negative health impacts from a single copy of the non-standard hemoglobin gene. A more widespread case is the so-called major histocompatibility complex (MHC), a group of genes where heterozygosity seems to improve disease resistance.

Is there a way of measuring inbreeding? Wright developed what is called the inbreeding coefficient. This is related to the probability that both copies of any given gene are derived

from the same ancestor. A cold outcross (in dogs, probably a first-generation cross between two purebreds of different, unrelated breeds would be the best approximation) would have an inbreeding coefficient of 0. Note that this dog would not be heterozygous at every locus. There are genes shared with every multicellular organism, genes shared with all animals, genes shared with all animals with backbones, genes shared with all four-limbed animals (including most fish and all amphibians, reptiles, birds and mammals) and with all mammals. Although the DNA might differ slightly, the proteins produced would be functionally the same. Further, the chances are that our dogs with inbreeding coefficient = 0 would still be homozygous for some genes shared by all dogs. The inbreeding coefficient thus specifically refers to those genes that are variable (more than one possible form) in the species and even the breed being considered.

An inbreeding coefficient of 1 (rare in mammals) would result if the only matings practiced over many generations were between full brother and full sister.



The figure shows how the inbreeding coefficient chages with generations of brother-sister matings. As a general rule, this type of mating in domestic animals cannot be kept up beyond 8-10 generations, as by that time the rate of breeding success is very low. However, the rare survivors may go on to found genetically uniform populations.

This has been done in laboratory rodents, producing inbred strains of mice and rats so similar genetically that they easily tolerate skin or organ grafts from other animals from the same inbred strain. However, the process of inbreeding used to create these strains generally results in loss of fertility (first seen in these mammals as a reduction in litter size) which actually kills off the majority of the strains between 8 and 12 generations of this extent of inbreeding. A handful of the initial strains survive this bottleneck, and these are the inbred laboratory strains. However, very little selection other than for viability and fertility is possible during this process. You wind up with animals homozygous for a more or less random selection of whatever genes happened to be in the strains that survived, all of which derive from the parents of the initial pair.

Note that two very inbred parents can produce offspring that have very low inbreeding coefficients if the inbred parents do not have ancestors in common. This, however, assumes that mates are available who are not strongly inbred on a common ancestor. If the parents are related to each other, their own inbreeding coefficients will indeed increase the inbreeding coefficients of their offspring. The critical factor is the coefficient of kinship, which is the inbreeding coefficient of a hypothetical offspring of the two individuals.

Inbreeding has become an important consideration for wildlife conservationists. Many wild populations are in danger of extinction due to some combination of habitat destruction and hunting of the animals, either to protect humans or because the animal parts are considered valuable. (Examples are ivory, rhinorcerus horn, and infant apes for the pet trade, as well as meat hunting.) For some of these animals the only real hope of survival is captive breeding programs. But the number of animals available in such captive breeding programs, especially at a single zoo, is often limited. Biologists are concerned that the resulting inbred populations would not have all of the genes found in the wild populations, and thus lose some flexibility in responding to change. In reaction to this threat they have developed networks such that animals can be exchanged among captive breeding poplulations in such a way as to minimize the overall inbreeding of the captive population. The idea is to select pairs in such a way that the inbreeding coefficient of the offspring is kept as low as possible.

Most elementary genetics books have instructions for calculating the inbreeding coefficient from the pedigree. (For more information, see Dr. Armstrong's site, Significant Relationships.) However, these procedures have two major limitations. First, they are not really designed for cases where there are multiple common ancestors, though they can be used separately for each common ancestor and the results added. Second, they become impossibly complex as the length of the pedigree increases. It is by no means uncommon in dogs, for instance, to have pedigrees which can be researched in the AKC stud book and the KC Gazette and which go back to foundation dogs born around the turn of the century - perhaps 30 or even 40 generations earlier. With this type of long pedigree, foundation animals may appear a million times or more in the pedigree.

With this in mind, a computer program called GENES was developed by Dr. Robert Lacy for the calculation of the inbreeding coefficient, kinship coefficients among animals in the breeding pool, percent contributions of varying founding ancestors, and related output, assuming full pedigrees to the foundation stock were available for all animals currently in the breeding population. For captive breeding populations, the less inbreeding the better, and this is the way the program is used.

In purebred livestock the situtation is a little different - we want homozygosity for those genes which create a desirable similarity to the breed standard. Wright's defense of inbreeding was based on this fact. However, inbreeding tends to remove those heterozygotes which are beneficial (e.g., the MHC) as well as increasing undesirable as well as desirable homozygotes. The practice is most dangerous in the potential increase of homozygous health problems which are not obvious on inspection, but which shorten the life span or decrease the quality of life for the animal.

I do not at the present time have other dog breeds for comparison, but I recently submitted a Shetland Sheepdog pedigree database to Dr. Armstrong for calculation of true inbreeding coefficients. This database was based on full pedigrees of all AKC Shetland Sheepdogs that had sired 10 or more breed champions (males) or produced 5 or more (females.) These top producing animals were set up as the current living population (a somewhat artifial assumption, as the dogs involved where whelped from 1930 to after 1990.) I would love to see some comparisons with other breeds.

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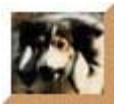

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updated March 8, 2010

Size as an example of additive inheritance

Sheltie breeders, as a group, tend to be hung up on size. We have reason to be. The breed was produced by mixing large and small breeds, few if any of which were in the size range we accept as correct today (13" to 16", with preference for 15" and up). Size, however, is not a simple genetic trait. At a minimum, it depends on the genetic codes for growth hormones, the genes that dictate when and how much growth hormone is produced, probably genes that code for receptor proteins that respond to growth hormones, genes that control bone shape and angulation between bones, and other genes affecting various metabolic processes. We don't even know the whole list, or how to determine what makes a particular dog large or small. In some cases the gene for larger size would be dominant, in some cases recessive, in some cases the dog heterozygous at a particular locus would be intermediate is size. It is, however, possible to use a very simple model to explain some of the oddities of Sheltie size. Remember this is a greatly simplified model! The real situation is almost certainly more complicated. We may even have a few genes for correct size hidden in there somewhere!

Suppose we assume we have four loci affecting size. Assume also that each locus has two alleles, one derived from the Collie part of our breed's ancestry, and the other from the original small island Sheltie (remember that at one time 12" was pushed as the maximum height) and toy breeds crossed in late in the 19th Century. We'll call these loci f, i, j, and k. The alleles for large size will be f^+, i^+, j^+ and k^+; those for small size will be f^-,i^-, j^-, and k^-. The size of the dog will be a base of 15" plus 3/4 times the sum of the "+" genes minus 3/4 times the sum of the "-" genes. A dog with all "+" genes, for instance, would be 21" tall, while a dog with all "-" genes would by 9" tall.

Suppose a breeder, breeding fairly close within her own line and related dogs, winds up with a consistent size genotype of f^+f^+ i^+i^+ j^-j^- k^-k^-. All gametes will be $f^+i^+j^-k^-$. All puppies will have the same size genotype as their parents, and will be 15" tall. But she's had to inbreed quite a bit, and she is looking for an outcross that will give her back what she's lost without sacrificing her predictable size.

She finds another breeder, again breeding fairly closely within her own line, who also gets all 15" Shelties, and whose line is strong for exactly the traits she needs. Breeder A breeds her best bitch to breeder B's best stud dog, and breeder B, who is missing a couple of things A has managed to fix, breeds her own bitch to a stud from breeder A's lines. The puppies arrive, grow up, and all are 15".

Then two of these 15" pups, from litters level in size stemming from strains level in size, are bred to each other. The result could easily be puppies all over the map in size. What happened?

Breeder B had a consistent size genotype of f^-f^- i^-i^- j^+j^+ k^+k^+, and her dogs consistently produced $f^-i^-j^+k^+$ gametes. The uniformly in -size puppies from the

strain cross, then, all had the genotype $f^+f^-i^+i^-j^+j^-k^+k^-$ and could produce any of 16 types of gamete, ranging from $f^+i^+j^+k^+$ to $f^-i^-j^-k^-$. I'm not going to try to draw a 16 x 16 Punnett square, but the expected size distribution in 256 puppies is:

1- 9 inch (all -)
8- 10 1/2 inch (7 -, 1 +)
28- 12 inch (6-, 2+)
56- 13 1/2" (5-, 3+)
70- 15" (4+, 4-)
56- 16 1/2" (5+, 3-)
28- 18" (6+, 2-)
8- 19 1/2" (7+. 1-)
1- 21" (all +)

If we assume some minor size genes as well, so the various categories are smeared out somewhat, the results don't look too unfamiliar. Note that if you breed the 16 1/2" but do not breed the 13 1/2", the result will be a gradual loss of - genes, and an overall upward creep in height. Also, there is no way to look at a 15" dog and determine whether it is fully heterozygous ($f^+f^-i^+i^-j^+j^-k^+k^-$) or homozygous (f^-f^- i^-i^- j^+j^+ k^+k^+, for instance) It's not as simple as breeding only from in-size dogs with in-size littermates!

How about genes for correct size? Could we have an additional allele, f, i, j, k at each locus, with ffiijjkk dogs being uniformly 15", and dogs with 7 normal genes and one + gene being 15 3/4"? It would certainly be nice, as then we'd just have to eliminate the + and - genes to have a breed that breeds true for size. It would be a slow process, if only because dogs with the alleles for correct size would so easily be confused with dogs with a balance of + and - genes. Given the background of our breed, though, the source of such genes for correct size is an open question. Most of our breed's ancestors were larger or smaller than 13" to 16". The standard advice on breeding for size, though, is to breed to correct size, which is based on the unstated assumption that the alleles f, i j and k exist.

Other complications undoubtedly occur. The hypothetical small and large genes may differ in their effect - f^+ might contribute more to oversize than j^- does to undersize, for instance. There may be additional loci that have a dominant-recessive effect - NN or Nn might add 2" to the height while nn would allow the fjkl loci to control size. On the other hand, QQ or Qq might allow the fjkl loci to control size while qq would be 2" less than the fjkl size. The important thing to remember is that size is based on more than one gene pair, and as a result can do some very strange things.

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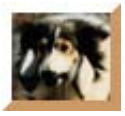

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