

Genetics and Behavior:

A Guide for Practitioners

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KEYWORDS

- Canine • Feline • Behavioral genetics • Temperament • Personality • Dog behavior
- Cat behavior

KEY POINTS

- Phenotyping behavior is difficult, partly because behavior is almost always influenced by the environment.
- Using objective terms/criteria to evaluate behaviors is always best; the more objective the assessment, the more likely any underlying genetic patterns will be identified.
- Behavioral pathologies, and highly desirable behavioral characteristics or traits, are likely to be complex, meaning that multiple genes are probably involved, and therefore simple genetic tests are less possible.
- Improvement in breeds can be accomplished using traditional quantitative genetic methods; unfortunately, this also creates the possibility of inadvertently selecting for covarying undesirable behaviors.
- Patterns of behaviors within families and breed lines still provide one of the best guidelines for genetic counseling in dogs.

INTRODUCTION: WHY SHOULD PRACTITIONERS CARE ABOUT BEHAVIORAL GENETICS?

Dogs have a relationship with humans unlike that of any other domestic animal. Dogs have been selected over time for true collaborative work with humans, and this selection has historically resulted in dog breeds and groupings based on the dog's ability to work with humans on certain tasks (eg, herding). As result, most of the emphasis on behavioral genetics in veterinary medicine has been on dogs, and that bias is reflected in this article.

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With respect to domestic dogs:

- Molecular data suggest that dogs separated from wolves 10,000 to 135,000 years ago.¹⁻⁷
- Dogs have lived together with humans for 15,000 to 30,000 years,⁸⁻¹⁰ as supported by anthropologic evidence.^{11,12}
- Breed clusters of dogs of different shapes/sizes who engaged in different tasks have existed at least 3000 years.

Only in the past 150 years has selection/breeding emphasis largely shifted from what a dog could do to how society wanted that dog to look. Dog breeds represent pools of canalized genetic variation. Historically, they have been the result of many generations of selection for certain specific tasks, and therefore it is no accident that dogs bred for conformation may have more reliable looks than behaviors, and that those bred for work may have more reliable performance than looks. Understanding this pattern and how it shapes modern genetics is important for veterinarians who wish to provide the best information about genetic factors contributing to behavior.

GENOTYPE VERSUS PHENOTYPE

We are how we behave, and behavioral phenotypes are defined by the behaviors the dog exhibits under varied conditions. All phenotypes (what the behavior looks like) are influenced by the genetic, physical, and maternal (*in utero* and rearing) environments. The behavioral phenotype of any dog is also influenced by the interaction of the environment on the dog's neurochemistry, activity of various regions of the brain, and molecular responses to stimulation, within any given genotype. This fact is why even littermates from tightly tested and controlled breeding lines can be so variable (eg, one is terrified of storms and the other is not).

The genetic background (the genotype or genomic code) of the patient only tells what could happen in terms of behavior and personality, not what will happen. The genotype is a catalog of coded sequences of instructions, not all of which will be activated, used, or expressed. This concept is essential because it means that behavior is not deterministic. Even when diseases are heritable in a simple manner, their phenotypes and presentations can be altered through interaction with the environment. Nowhere is this truer than for behavior: it occurs when pharmacologic treatment and behavior modification are used for behavioral problems, and when problems are prevented simply because the patient is in a household that may not promote them. Unfortunately, misconceptions about determinism and the role of genetics have driven myths about breed-based behaviors and unfortunate breed-specific legislation. Given these limitations, on what should we focus with respect to behavioral genetics?

All behaviors are the result of the interaction of the genetic background with the physical and cognitive environments found in the individual patient. The concept of a response surface can help practitioners understand how patterns of behavior can individually vary with exposure to different environments depending on genetic background.

The response surface in [Fig. 1](#) represents a simple space created by behavioral traits, the environments in which they are displayed, and the genotype affecting them. In [Fig. 1](#), dogs A and B seem to behave the same (they are the same color). Their responses to different environmental manipulations will expose how they are different. As dog A is exposed to a range of environments from right to left on the environmental axis, she remains unchanged; however, when dog B is similarly exposed, her behaviors alter dramatically (B1 in [Fig. 2](#)).

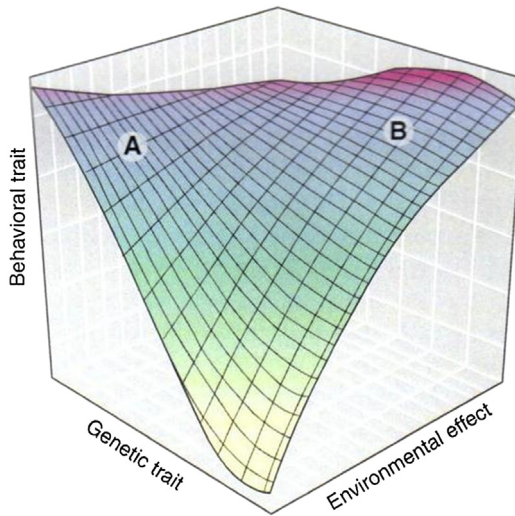


Fig. 1. A response surface for a series of expressions of a behavioral trait across different genetic and physical environments. A and B represent dogs whose behaviors seem the same (same color), but for whom the genetic and environmental contributions to their behaviors are vastly different. (From Overall KL. Proceedings of the Dogs Trust Meeting on Advances in Veterinary Behavioural Medicine London; 4th–7th November 2004. p. 65: Veterinary behavioural medicine: a roadmap for the 21st century. *Vet J* 2005;169:134; with permission.)

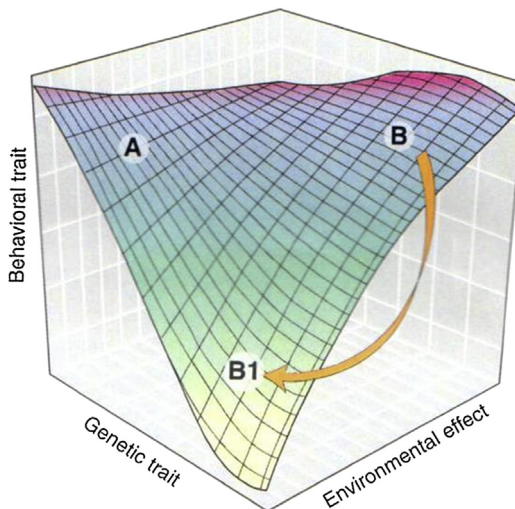


Fig. 2. Two dogs, A and B, who look alike in their behaviors. The underlying contribution of their genes to their behavior differs here, and when exposed to a series of environments, one of them alters her behavioral response surface considerably (patient B1) when compared with the other (patient A). This difference in response suggests that the underlying mechanisms (which are genetically determined in this example) for the 2 responses differ. A and B displayed the same behavioral phenotype in one environment, but they are not the same genetically and therefore do respond differently to different environments, such as tasks, training, and interventions. (From Overall KL. *Manual of clinical behavioral medicine for dogs and cats*. St Louis (MO): Elsevier; 2013. p. 66; with permission.)

Phenotyping behaviors is difficult, but phenotype is key to understanding genetic associations, complex mechanisms, or differential response to more specific treatments, particularly those involving medication. A diagnosis is almost never a phenotype, but it can help to develop the characterization of one. When done well, using rigorous criteria, behavioral diagnoses provide probabilistic associations among behaviors, pathology, and environment that can be represented using some kind of a decision tree reflecting possible outcomes. In behavior, diagnosis must rely on some objective representation of the behavior (eg, behavioral types, responses, transitions, and counts taken from video), evaluated over different contexts. Because many behaviors and behavioral sequences are nonspecific, they can only be interpreted within a context provided by the interaction of pattern (sequence of behaviors, duration, frequency, intensity), associated physiology, and species, breed, and ontogeny-typical behaviors. The more tightly these distinctions cluster, and the more diverse the measures of the clusters (eg, behavioral assay, plus physiologic assay, plus provocative test), the better the phenotype.

MEASURING BEHAVIOR

Temperament, Personality, and Behavioral Assays

Temperament can be broadly defined as the relatively stable individual characteristics of behavior that show some consistency over time and across situations,¹³ and as differences in behavior between individuals that are relatively constant given similar evaluation situations.¹⁴ Personality traits have been documented in several species. The concepts of temperament, personality,¹⁵ and character¹⁶ have been used to identify breeds or individuals suitable for specific behavioral tasks.¹⁷ These terms provide only a summary characterization of the dog's behavior: the components used for assessment still must be defined, objective, and measurable.

Temperament/personality measures are often used to predict an association or correlation with a defined outcome, like succeeding as a working dog. Svartberg¹⁸ found that the use of dogs as conformation show dogs (measured as the amount of merits of the breeding stock from dog shows) negatively correlated with 4 personality traits (playfulness, curiosity/fearlessness, sociability, aggressiveness) he had found to be stable in a standardized behavioral test that involved 13,097 Swedish dogs. However, using the dogs as working dogs in trials (measured as the amount of merits of the breeding stock from working dog trials) correlated positively with playfulness and aggressiveness in sires. These results were significant, regardless of breed. How the dog is used matters; breeding for different criteria (eg, for conformation vs field or other working trials) causes changes in the breed.

Certain personality traits may render humans vulnerable to psychiatric disorders, including anxiety disorders.¹⁹ Anxiety disorders of genetic origin have been documented in dogs. One nervous strain of pointer dogs was more fearful than a stable strain from 2 months of age to maturity in dogs whose rearing environment and handling had been the same.^{20,21} Overall and Dunham²² noted that of dogs identified with obsessive-compulsive disorder (OCD) for whom familial information was available, multiple relatives were also affected. Breed task affected the form of the OCD for many breeds: German shepherds almost always spun and chased their tail. Breeding for different personality criteria may result in extremes of the selected behavior or unintended covariance with other undesired traits (ie, a focused working dog who also has OCD). A survey of the common behavior problems seen in military working dogs showed that aggression represented more than 30% of the behavioral complaints, with 25% involving repetitive behaviors.²³ Problems with object/reward release and overactivity were also significant.

A genetic association has been identified for Doberman pinschers exhibiting one form of OCD, flank sucking,²⁴ and an association has been suggested for Border collies and profound noise reactivity.²⁵ Overall and colleagues²⁶ assessed more than 1300 adult dogs of one breed at 12 to 18 months of age using an ethogram, and identified dogs who consistently withdrew when approached by humans. More than 800 offspring of these dogs were examined at 5 weeks of age, and the distribution of behaviors was similar to that in the adult populations; dogs who consistently withdrew from humans were readily identified, suggesting a heritable component to the fearful condition.

Hilliard and Burghardt²⁷ noted that the age at which they identified unsuccessful dogs differed from that at which they identified successful ones, and that these ages were not independent of breed. As a result, if dogs were sent to be raised by a foster family/puppy walker family, Belgian Malinois were returned to the colony for training at an earlier age (9 months) than were German shepherds (12 months).

Analyses of the records of training centers in England, the United States, and Australia have shown that dogs fail, not because of an inability to learn guide dog tasks, but because competing responses interfere with the dog's performance.²⁸⁻³¹ Reasons cited for failure were fearfulness, distractibility, and aggressive behaviors.

In one Japanese guide dog program, 80.6% of successful dogs had low scores for distractibility in a factor analysis, whereas 28.2% of failed dogs had high scores.³² Distracted dogs performed less well in a sample of 33 Belgian military working dogs.³³ Distractibility was significantly related to failure in another program,³⁴ and showed a weak genetic relationship with the serotonin transporter protein haplotype, suggesting a potentially testable and measurable mechanism for some attribute of success. Some measure of distractibility/anxiety/uncertainty may ultimately allow performance to be assayed early. Heart rate combined with behavioral scores at 3 months help to identify distractible dogs.³² Four behavioral responses associated with distractibility, restlessness, and anxiety predicted low suitability as a guide dog.³⁵ Earlier predictability of success in working dogs was found to be associated with 3 assessments: activity and vocalization (birth–7 weeks), fear of social and environmental stimuli (2 months), and absence of later fear of the environment (15 months).¹⁷

What Makes an Assessment "Good"?

Assessment of behavior must minimally meet 3 quality requirements^{14,36,37}: standardization, reliability, and validity of selection procedures. These assessments represent a scientific standard that allows evaluation of how believable and consistent the data are, and whether similar data can be collected from other groups and compared in a meaningful way across groups.

- Tests must be standardized: when this criterion is met, the only source of variability is the animal being tested.
- The test must be reliable: if the same test is given to the same animal twice, the outcome should have a statistically significant and strong positive correlation. For this to happen, the test must also be sensitive so true behavioral differences can be assessed objectively, with only small variation in assessment among the assessors.
- A tests should be valid; it must measure what the evaluator is truly evaluating.

All of these requirements have been problematic, but the one that has been evaluated least often is validity.

Validity refers to how well a test measures and reports on the behaviors the test intends to measure. Validity assessment can be tricky for behavior, because what

something is labeled may adversely affect its ability to be measured.^{38,39} For example, not all fearful animals are fearful in the same way or for the same reason. In a comparison of specific behaviors exhibited by dogs subjected to an established temperament test, De Meester and colleagues⁴⁰ found that fearfulness on one subtest did not predict either the presence of fearfulness or how it appeared on another, related subtest. Contextually characteristic responses of the individual dogs were more important than was the subtest in determining the form of the fear.

Not all dogs that exhibit behaviors associated with an agonistic response are problematically aggressive: distinguishing normal agonistic/aggressive behavior from pathologic aggressive behavior requires a discrete assessment of context and excellent definitions of behaviors and conditions.⁴¹ Studies that do not do this may not only label breeds or groups of dogs as aggressive^{42–44} but also lose any phenotypic information that helps with further assessments of canine behavior or selection of breeding stock. The better subgroups of fear or problematic aggression can be characterized, the more likely genetic associations for undesirable traits within the breed or breeding program can be identified. Well-characterized trait subgroups may contain useful and easily recognizable phenotypes for identifying genetic regions associated with an enhanced risk of developing a problematic condition.²⁴

Predictive ability (external validity) of behavioral tests for puppies varies greatly, and not just because of the test³⁷; it depends on the complexity of the desired characteristics the test is intended to evaluate. If these desired behaviors are well defined and closely related to the test content, predictive ability can be as high as 91.7% for aptitude for police dogs.⁴⁵ If less of an association is present between the ultimate tasks that the test hopes to predict and the test battery, no predictive ability may be possible, as Rooney and Bradshaw⁴⁶ found for specialist search dogs. Predictive validity is enhanced when measures are specific and accurate.

Failure to identify specific behaviors that are well defined and closely related to the test content may be the single most worrisome aspect of most canine evaluations, especially if the concept of drive is involved.

The characteristics of drive involve:

- The definition from the craft of dog selection that is most often considered to be the propensity of a dog to exhibit a particular pattern of behaviors when faced with particular stimuli.
- That it is triggered by particular stimuli and expressed in a typical and predictable way associated with the particular stimulus.
- That it is enhanced or diminished through experience (eg, training, environment) but cannot be created or eliminated.

Assessments of drive are not quantified or standardized: one person's moderate-drive dog may be another's high-drive dog, and these tests usually lack an external referent that will assure the 3 aspects of validity are met: accuracy, specificity, and scientific validity. At best, tests assessing drive measure clusters or correlates of traits of interest, but they seldom measure any trait in a manner that would be useful to geneticists who require a useful phenotype.

When scores are used to assess behavior, the only way to assess whether dogs with lower scores perform worse than those with higher scores is to follow the dogs across time. Given that behaviors may change with development, tests hoping to identify behaviors that are valid and may be heritable should be evaluated for the sensitivity and specificity of the test. The *sensitivity* of a test is the probability that positive dogs test positively. The *specificity* of the test is the probability that negative dogs test negatively. The positive predictive value (PPV) of the test is the number of true positives,

compared with the total number of positives; the negative predictive value (NPV) of the test is the number of true-negatives compared with the number identified as negative.

Van der Borg and colleagues⁴⁷ and De Meester and colleagues⁴⁰ used the Socially Acceptable Behavior (SAB) test to evaluate dogs for aggressive behavior to humans. The external referent is the actual bite to a human. The tests used were scored based on specific behaviors and their frequencies during timed intervals. Van der Borg and colleagues⁴⁷ found a sensitivity, specificity, and accuracy for the test of 0.33, 0.81, and 0.64, respectively, for 479 tests. The low sensitivity of the test was attributed to the decision to classify dogs as aggressive if they bit only once, coupled with the weak ability of the test to detect some types of aggression. The PPV of the test was approximately 0.30, but the NPV was approximately 0.85, meaning that aggression during the test did not predict aggression later, but lack of aggression during the test more often predicted lack of aggression later. De Meester and colleagues⁴⁰ compared subtests with the entire test and likewise found a low PPV (aggression by the dog during the test was not helpful for determining behavior later). When predictability and/or sensitivity fail, one aspect of test validity is missing. The small sample of studies using validity criteria seem to support convergent validity of behavioral assessments in adult dogs, but evidence for discriminant validity (when a measure does not correlate with other measures with which it should not be associated) is generally lacking.⁴⁸ This fact could be why so many tests of sheltered animals fail to identify types of behaviors that later appear,^{49–52} and why investigators should focus on following dogs over time to assay the extent to which the evaluation procedures were truly valid and indicative of behaviors that may be worthy of future genetic study.

This discussion about measuring behavior shows why behaviors or phenotypes for accurate genetic assessment are so difficult to identify. The next section discusses the effect of these measures on heritability assessments.

IS BEHAVIOR HERITABLE?

When the question is asked whether behavior is heritable, 3 questions are really being asked: is this a behavior that contributes to the individual's fitness (for animals under natural selection); is this a behavior that could be enhanced or minimized through selective breeding within this group/breed (artificial selection and quantitative genetics); and is this a behavior that is transmitted by an identifiable region of the genomic code that in some way contributes to the mechanism of the behavior (molecular genetics)? This article focuses only on quantitative and molecular genetics. In fact, some of the changes in canine traits that were selected would be selected against if dogs would evolve merely under natural selection (eg, breeds that can only deliver puppies through Caesarian sections, behaviors such as severe compulsive behavior and extreme aggression or fearfulness).

Quantitative Approaches to Behavior

In quantitative genetics, heritability (h^2) is the proportion of the total phenotypic variance (V_P) that is attributable only to the additive genetic variance (V_A), and not to the variance from effects of dam or environment ($h^2 = V_A/V_P$).⁵³ V_A is available to be acted on by differential selection (eg, breeding for tighter hips or more milk fat). Heritability estimates pertain only to the population studied, not to the individual or any specific genetic region associated with any behavior or trait. Heritability estimates will not identify whether a certain dog has certain genes, and therefore cannot provide tests for genetic markers, but they can help change the frequency of a condition in a population of dogs. For example, through breeding only dogs with the tightest 20% of

hips, hip laxity of a group of interbreeding Labrador retrievers could be greatly decreased over a decade without any knowledge of which genes are involved in sculpting hip dimensions. Behavior can be selected in the same manner, and most heritability focus on behavior has been on personality/temperament. Svartberg and Forkman^{54–57} were the first to use the term *personality* in canine temperament studies when they identified 5 stable personality factors: playfulness, curiosity/fearlessness, sociability, aggressiveness, and chase-proneness, from a sample of 15,000 dogs of 164 breeds. Sociability, playfulness, curiosity/fearlessness, and chase-proneness were further found to correlate with each other: the more playful dogs were also more sociable, less fearful, and more interested in chasing.

Approximately 30% to 50% of the personality differences observed between humans are thought to be affected by genes.^{58,59} Similar heritability estimates have been obtained for various personality traits in animals.^{60–63} Because so much variation in behavior exists across breeds, dogs may provide one of the easiest routes to understanding the genetic component for behavior.⁶⁴

Several studies have investigated the heritability of behavioral traits in dogs. Although heritability estimates calculated for any trait in one population (eg, boldness in Swedish Rottweilers) cannot be used as heritability estimates in another population (eg, Finnish golden retrievers), estimates for the same behavioral trait in different breeds should provide valuable information on the general heritability of particular traits, if the traits are evaluated in the same way.⁶⁵ This last condition is not usually met, and therefore caution is urged in overinterpreting breed and study comparisons.

Heritability values vary from 0 (no genetic variation) to 1 (all differences in a trait reflect genetic variation). Generally, heritability estimates larger than 0.40 are considered to be high, indicating that selective breeding can have a large effect on altering the proportion of the trait in the population. Heritability estimates of 0.20 to 0.40 are considered moderate, and estimates less than 0.20 are low and suggest that only a small proportion of the variation observed is of genetic origin in the population studied. In general, heritability estimates for behavior are usually lower than for morphologic traits,⁶⁶ and it should be considered that the extent to which this is true may be because of the failure to define clear, quantifiable behavioral measures, and therefore these estimates should be evaluated discretely within tests that can be validated. It is also important to remember that low h^2 values means that a small proportion of the observed differences in a particular population are caused by variation in genotypes, and not (necessarily) that the trait is not heritable.

Some heritability studies have evaluated personality traits important for working dogs, such as boldness, fear, general aggression, sociability, and reactivity to guns/sound sensitivity.^{67–69} Heritabilities for boldness (or courage) in German shepherds have varied from low (0.05)⁷⁰ to moderate (0.27)⁶² values. Fearfulness seems to have higher heritabilities in the breeds examined, with h^2 estimates from 0.46 and 0.58 in Labrador retrievers in training as guide dogs.^{31,71} Similarly, reactivity to guns may have high h^2 estimates (0.56 in Labrador retrievers; 0.21 for German shepherds).⁶⁹

Breeds and dogs within breeds vary in their reaction toward humans. Reactions can range from neutral to aggressive to extremely open/friendly. This sociability/amicability toward humans has a large h^2 in German shepherds (0.32) but an extremely low h^2 in Labrador retrievers (0.03),⁶⁹ suggesting that selection could change population norms in these shepherds but not in the retrievers. Is it possible that this retriever population is already the result of sustained selection (ie, all Labradors have a “friendly genotype,” which results in no genetic variation for that trait)? Yes, but in the absence of continuous measures h^2 analysis, and discrete behavioral analyses, one should assume nothing.

Aggressiveness has been long known to have a strong genetic component, and aggressive and nonaggressive mouse strains have been bred for decades.⁷² Similarly contrived dog breeds do not exist, but in a study investigating aggressiveness in golden retrievers, reactions to humans and dogs both had high heritabilities (0.77 toward humans; 0.81 toward dogs).⁷³ Aggressive responses to humans did not correlate with aggressive responses to dogs, suggesting that if the assessment was equally sensitive, these responses had different genetic backgrounds.⁷³ Heritability of dominance aggression (also called *impulse control aggression/conflict aggression*) in English cocker spaniels was calculated separately for dam (mother) and sire (father). Dam heritability was greater than that of the sire (0.46 vs 0.20),⁷⁴ but the higher heritability in dams includes both maternal genetic and maternal environmental factors in the calculation. Although diagnoses should not be considered phenotypes, they can identify patterns of behavior that can be quantified, and may help create subsequent assessments that can be validated.

Given the ongoing effort in selective breeding and the number of breeds involved, one would expect various aspects of hunting behavior to have high heritability. Liinama and colleagues⁷⁵ found h^2 values of 0.06 to 0.13 for different hunting behaviors of the Finnish hound. Similarly, studies investigating heritability for different aspects of hunting behaviors (eg, speed, style, eagerness, cooperation, independence) have found low h^2 values (0.06–0.28 for German short-haired pointers, German wired-haired pointers, and Brittany spaniels; 0.18–0.29 for English setters⁷⁶). However, in flat-coated retrievers in Sweden, Lindberg and colleagues⁷⁷ tested litters dogs of the same age, at the same time, and found high h^2 values for hunting excitement (0.48), willingness to retrieve (0.28), and independence (0.18). Heritability of herding behavior in Border collies was as high as 0.30 (average over 17 traits), indicating a strong genetic component for herding.^{78,79} However, the h^2 estimates for the flat-coated retrievers and Border collies was based on actual behavioral testing, and not on questionnaires soliciting people's opinions (as was the case for the aggressive assessment in golden retrievers), and therefore may be the result of more repeatable and reliable behavioral measures. When questionnaires are used, they must be validated to ensure that the variance being studied is not that of human opinion or misperception; this is seldom done.

If behavior is clearly heritable, why do most studies of behavior find only very low heritabilities? Several possible explanations exist.

1. The test in which heritability is calculated may not measure the trait it is supposed to measure; instead, it may actually measure the owner's ability to train the dog (Courreau and Langlois⁸⁰ provide examples of heritability for heeling and jumping).
2. Hunting and working tests include a huge amount of noise in the data and do not test for interrater and intrarater reliability, which can be affected by factors such as opinion, bias, and lack of agreed terms. The use of several judges and testing places, and testing dogs at different times of year make measuring behaviors and estimating the genetic component more difficult.⁷⁵ Studies in which heritability values have been derived from properly standardized tests using only a few well-trained judges show much larger heritabilities for behavior.^{67,68,78,79} The use of well-defined and/or objective criteria is a further improvement.^{78,79}
3. The traits for which the heritability is calculated may have been split into pieces that are too numerous, and they correlate with each other. Reanalyzing existing data with some kind of factor analysis may reveal more reliable and independent personality components with larger heritabilities.^{63,68,77}

4. Traits may be under strong genetic control, but the particular population studied may have no genetic variation; this also results in low heritability values.

To summarize, several behavioral traits in dogs seem to have a large genetic component because the behavior appears frequently in the pedigree (Fig. 3), but heritability studies may not identify these behaviors as having high heritability. This problem is largely because of the difficulty in capturing or evaluating the behavior's genetic component. Large heritability values observed for traits such as fear, activity, and noise sensitivity mean that most of the variation observed in these traits is caused by variation in the genotypes (ie, behavior is inherited in large degree from parent to offspring), and that selective breeding for these traits is possible in dogs. When these studies are used with molecular studies, problems with identifying and testing behaviors may be explained. For now, the primary use of heritability studies in canine behavior continues to be for purpose-bred dog groups (eg, service dogs) to make breeding decisions based on the direction in which breeders wish to encourage change in the population. Heritability studies are also useful for breeds or breeding groups if breeders decide that the dogs have a problem with a genetic basis and the breeders are going to use heritability to define the population that should be bred to minimize that problem (eg, the original example of hip laxity). These uses only work well when the assessments used are objective, repeatable, and reliable, and the data are recorded and used to make decisions. These constraints do not characterize the population of dogs from which average pets come, but should encourage the cooperation of breeders to realize that they have it in their power to improve the behavioral and welfare needs of pet dogs.

Molecular Approaches to Behavior

Methods to study genes behind complex traits

Molecular approaches in genetics seek to identify the genetic architecture of a trait or condition. Once a genetic basis/pattern has been established for a trait/condition, 2 types of methodologies can be used to map the putative genes: linkage and association studies. Gene association studies investigate whether statistically significant

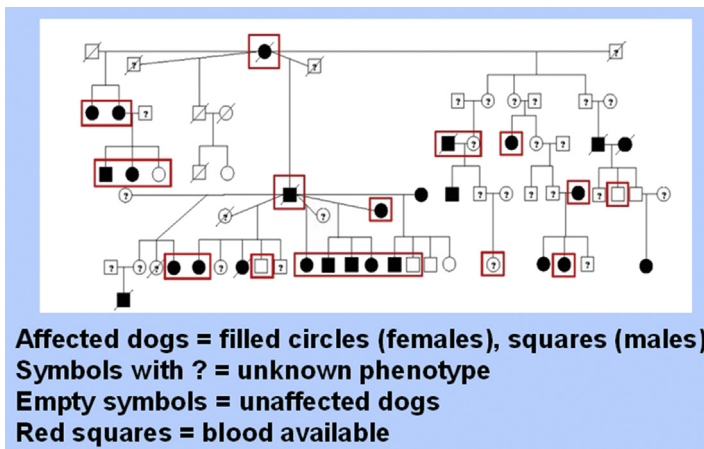


Fig. 3. Border collie pedigree for noise reactivity/phobia. (From Overall KL. Manual of clinical behavioral medicine for dogs and cats. St Louis (MO): Elsevier; 2013; with permission.)

differences in the allele frequencies exist between individuals with different phenotypes,⁸¹ whereas linkage studies examine whether specific genetic markers cosegregate with trait/disease alleles.⁸² Association studies are most likely more effective in complex traits (such as behavior) to which numerous genes are expected to contribute, each with a relatively small effect, whereas linkage analysis is effective in identifying rare and highly penetrant variants.^{83,84} Association analysis can use both related and unrelated individuals, whereas linkage analysis is performed using a pedigree structure.

Candidate gene studies (a form of association study) mostly use a case-control study design, meaning that dogs are matched (and preferably unrelated, at least at the grandparental level) so that for every dog with the condition, one is without. Candidate genes are chosen based on the function of the proteins for which the genes code, and therefore are hypothesis-driven. Candidate gene studies are cheap to perform, but they are vulnerable to population stratification—systematic ancestry differences between cases and controls—which is common in dog breeds. Underlying population structure may produce false-positive associations in candidate gene studies in which observed association is actually the result of different allele frequencies or cryptic relatedness, and not the result of a genetic disease effect.⁸⁵ To ensure this is not a risk, candidate gene allele frequencies should be compared against the phenotype within one breed, and in some cases, within one breeding line, because breeds often have distinct conformation/show and working lines (eg, German shepherd, Border collies). Regardless, it is worth remembering that complex traits such as behavioral traits are most likely controlled by many loci, and by their interaction with each other and the environment. These considerations limit the usefulness of candidate gene studies in behavioral genetics.

Genome-wide association (GWA) studies have become increasingly popular, and the publication of the expanded canine genome (7.5x, Boxer) has made them possible.⁴ GWA studies investigate the association between common genetic variations and some phenotype. GWA studies are non-hypothesis-driven. These studies require a dense marker set that captures a substantial proportion of the common genetic variation across the genome. They also need a large sample size.⁸⁶ Single nucleotide polymorphisms (SNPs) are the most prevalent class of genetic variation used in human and canine GWA studies.⁸⁷ Copy number variations (deletions or multiple copies of sections of genome) are also frequently used as markers in association studies.^{88,89} SNPs that are in proximity to each other are more often inherited together, which is referred as *linkage disequilibrium* (LD). In dogs, the average length of LD is 2 Mb, whereas in humans it is 0.28 Mb.^{4,90,91} When combined with the large genetic homogeneity within breeds, this average LD means that many fewer individuals are needed in dog GWA studies than in human GWA studies. But, because of the longer LD blocks, accuracy in dogs is typically not as good as it is in humans. GWA studies investigating canine complex traits have successfully identified several affecting loci.⁹² With sufficient sample size and detailed phenotyping, GWA studies should be able to find several loci that affect complex traits, such as behavior.

Whole-genome sequencing or next-generation sequencing (NGS) are now widely used in human genetics⁹³ and have also been used for dogs.^{94,95} Whole-genome sequencing means simply sequencing the complete genome, whereas targeted NGS means sequencing certain area of interest. In the future, these methods will most likely increase the success of genetic studies in dogs, including those for behavior, because they provide the largest cover of genetic variants, which lowers costs.

GENETIC MARKERS AND CANINE STUDIES

Candidate Genes and Neurochemistry

Takeuchi and colleagues⁹⁶ used key word analysis of trainer observations in a factor analysis and found a significant association between the factor activity level and degree of polymorphism in genes associated with glutamate transporters and the catechol-O-methyltransferase (COMT) gene. COMT is important in dopamine metabolism, and glutamate has been implicated in impulsivity in aggression and neurocytotoxic events, such as stroke and seizures.

In a study of the dopamine D4 receptor (DRD4) in 96 unrelated German shepherds, Héjjas and colleagues⁹⁷ found significant associations between the exons ($P = 0.002$) and introns ($P = 0.003$) of the variable number of tandem repeats (VNTR) in the DRD4 gene and the social impulsivity phenotype of their Greeting Test. The phenotype was derived from a coded score that rated how a dog behaved during a staged human approach: 0 = the dog was not friendly; 1 = the dog was friendly but did not follow the person testing the dog; and 2 = the dog followed the person testing the dog when the person walked away. Higher scores were thought to indicate increased interest in novel social companions, which some authors characterize as social impulsivity. Although one could argue with this definition of impulsivity, this test was sufficient to characterize behavioral differences associated with the long (Q) and short form (P) polymorphisms of the DRD4 intron 2 VNTR and the DRD4 exon 3 VNTR. The scores for P/P (1.36 ± 0.58 ; $n = 50$), P/Q (0.84 ± 0.64 ; $n = 32$), and Q/Q genotypes (1.43 ± 0.51 ; $n = 14$) differed ($P = 0.006$), indicating that there was an association between the behaviors captured by the score and variability in gene expression. Similar patterns were shown for the DRD4 exon 3 VNTR. Whether these techniques will be valuable for screening or breeding pet and/or working dogs will depend on how variable the population of available dogs is and whether these behavioral assessments are representative of behavioral profiles useful for work or desired in pets. The population of German shepherds from which these dogs were sampled had the following genotype frequencies for the DRD4 intron 2 VNTR: 48.3% for P/P; 39.3% for P/Q; and 12.4% for Q/Q. Equivalent frequencies for Belgian Malinois, Belgian Tervuerens, Belgian Groenendael, and Siberian Huskies were, respectively, 30.0%, 14.9%, 29.5%, and 3.0% for P/P; 52.0%, 48.5%, 45.7%, and 5.1% for P/Q; and 18.0%, 36.6%, 24.8%, and 91.1% for Q/Q. Whether variation in genotype frequencies is functionally important for any dogs is unknown, but the question is especially relevant for working dogs.

Distractibility that was significantly related to failure³⁴ showed a weak genetic relationship with the serotonin transporter protein haplotype, suggesting a potentially testable and measurable mechanism for some attribute of success as a working dog. Whether these findings have any direct applicability for pet dogs, better characterization of any dog's behavior will provide clients with clearer expectations about their dog's behavioral style and needs, and may lead to more humane handling/training and better relationships.

The Special Case of Gene Mapping and Olfaction in Dogs

Olfactory receptors (ORs) are found on ciliated membranes of olfactory sensory neurons in the olfactory mucosa. Efficient odor discrimination requires that ORs bind with odorants and that this process trigger a signal transduction pathway that allows information to be processed and acted on via connections in the olfactory bulb and brain cortex. If dogs vary in odorant detection ability, are those who are more skilled

more efficient in initiating the signal transduction cascade, or do they have different alleles encoding ORs with greater odorant affinity⁹⁶? No simple answer to this question exists.

OR genes are members of the G protein-coupled receptor (GPCR) superfamily, which contains approximately 1300 genes in dogs⁹⁸ and is one of the largest gene families in mammals.^{99,100} Intracellular and extracellular loops of GPCRs are polymorphic in all species studied, including dogs.¹⁰¹ These polymorphisms are believed to play a large role in odor discrimination and, because of the large number of OR genes, the initial processing of information associated with the ability to discriminate odors has been thought to depend on the selective binding affinity of the ORs. However, ORs show only moderate affinity for scent molecules/odorants, and therefore binding affinity may also depend on the concentration of a particular odorant,¹⁰² as has been confirmed for *Drosophila*, in which large concentration differences are treated like different odors.¹⁰³ Perception of odor relies on 3 stages of processing in the brain after OR binding: memory of odor quality, memory of odor intensity, and the range of intensities and qualities over which the odor is generalized.

Using 38 cloned OR genes belonging to the same canine OR gene family, Benbernou and colleagues¹⁰⁴ found considerable cross-receptor reactivity, suggesting that the number of combinations possible for the estimated 1000 receptors is sufficient to convey a portrait of the olfactory world to the dog in a manner that uniquely identifies the odors they encounter.

Assumptions made about breed superiority in olfactory skills have not been borne out by attempts to study the putative genes involved.^{105–107} OR genes seem to be highly polymorphic across and within breeds.^{101,102,107,108} Robin and colleagues¹⁰⁸ examined DNA sequences of 48 dogs from 6 breeds, of which 4 have been asserted to have strong olfactory detection skills (German shepherds, Belgian Malinois, English springer spaniel, Labrador retriever) and 2 have been asserted to have weak olfactory detection skills (greyhound, Pekinese). All sampled dogs were unrelated at least at the grandparental level, and every effort was made to sample dogs from diverse international sources. The number of SNPs differed among breeds, but their distribution did not. The number of OR genes without polymorphism differed markedly across breeds: German shepherds, greyhounds, and Labrador retrievers had, respectively, 24, 21, and 10 genes with no polymorphism. A total of 193 of 732 SNPs were restricted to a single breed, and their breed distribution varied significantly, with 10 private SNPs for German shepherds, 26 for Belgian Malinois, 47 for English springer spaniels, 18 for greyhounds, 8 for Labrador retrievers, and 84 for Pekinese. A total of 199 SNPs were common to all breeds, 79 were common to 3 breeds, and 50 were common to 2 breeds. These results suggest that the 199 SNPs that all breeds had in common likely arose before the separation of these 6 breeds, and that most of the private SNPs arose after these breeds developed. Comparison at the breed level found that the most polymorphic breed was the English springer spaniel (N value = 594), and the least polymorphic was the German shepherd (N value = 926), yet both of these breeds are favored as detection dogs.

These data strongly suggest that there has been no strong selection for more variable OR genes or proteins. Dogs with particularly acute olfactory detection capabilities may perform so well because they are particularly good at processing and acting on olfactory information, rather than at detecting it. If so, aspects of communication between the dog and handler may be more important for the success of detection dogs than has previously been believed.^{109–112} Oddly, the modern view of relationships in the pet population is that good communication between dog and human is essential.

WHAT OTHER GENETIC ISSUES CAN AFFECT BEHAVIOR? EPIGENETICS IN BRIEF

Epigenetic changes are those changes in gene expression that are caused by mechanisms other than alterations in the underlying genetic sequence. Many epigenetic effects have been shown to be heritable. Some of the most common epigenetic effects involve methylation: tagging a CH₃ group onto a region of the DNA that affects how or whether it is transcribed.

For example, prenatal exposure to maternal stress causes epigenetic methylation of glucocorticoid receptor promoter regions, which leads to hyperreactivity in rodents and human beings.^{113–115} Behavioral differences may not be present only in the first generation of offspring, they can also be apparent in the second generation, although none of these offspring experienced maternal stress themselves. In rodents, hippocampal expression of the glucocorticoid receptor gene and behavioral responses to stress are modulated by the amount of care mothers give their young in the first few days of life.¹¹⁶ These processes also likely occur in dogs and cats and are known to affect task learning, which can be enhanced when stress and distress are mitigated. These effects may be responsible for the findings in one study that showed that canine puppies raised with their mothers and siblings through 56 days (8 weeks) developed fewer behavior problems and were less reactive than puppies adopted at 30 to 40 days, all other aspects being equal.¹¹⁷ Similarly, early separation from the mother and lower-quality maternal care seems to be associated with frequent tail chasing in several breeds.¹¹⁸ Raising puppies with their siblings and dam through at least 56 days, a time when most brain myelination is complete but when neuronal remodeling should be rapidly ongoing, may provide mitigation of potential epigenetic effects caused by acute neurodevelopmental stress.

Geneticists who study behavioral development have a strong sense that epigenetic effects may be extremely important for determining early genetic trajectories. Quick, inexpensive, and easy-to-use tools to test for these effects do not yet exist, but because so many of these effects are associated with prenatal, perinatal, and postnatal stress, the best advice veterinarians could give is to provide as excellent, stable, and enriched physical, nutritional, and behavioral environments as possible. The data to date also suggest that dogs and cats subject to stressors may be more at risk for becoming more reactive regardless, and should receive remedial intervention as soon as possible. These animals may include strays, shelter dogs/cats, feral dogs/cats, dogs/cats whose mothers were ill or malnourished or undernourished, puppies/kittens experiencing dystocia, or those experiencing less-than-optimal social and/or nutritional environments (puppy mills/farms, commercial catteries). Possible interventions may include diet, supplements, medication, and behavior modification that prompts learning of more appropriate responses.

FUTURE DIRECTIONS

Tables 1 and **2** contain lists of somatic conditions that can be confirmed/identified by genetic testing for cats and dogs, respectively (online resources in which updates can be found are listed in the [Appendix](#)). A quick look at these lists shows that genetic tests are restricted to conditions that are easily recognizable and that interfere in a clear, measurable way with physiologic or neurologic function. This characterization is a challenge in behavior, but progress can be made.

Gene discovery for behavioral traits in humans and other animal has not been as straightforward as for simple Mendelian traits. Although knowledge of the genetics of complex traits will increase hugely in a decade, the process to gain that

Dermatologic conditions	Rex coat Alopecia
Ocular conditions	Retinal degeneration
Neurologic conditions	Deafness in white cats Cerebellar degeneration Feline hereditary neuroaxonal dystrophy Lysosomal storage diseases
Musculoskeletal conditions	Muscular dystrophy Dwarfism and chondrodystrophic disorders Polydactyly Split foot Short bent tail Curled ears
Cardiovascular conditions	Hypertrophic cardiomyopathy in Maine coon cats, only
Hematologic/immunologic conditions	Neonatal isoerythrolysis Inherited hyperchylomicronemia Bleeding disorders

Data from International Cat Care. Available at: <http://www.icatcare.org/advice/cat-breeds/inherited-disorders-cats>. Accessed January 2, 2014.

knowledge may not get much simpler. The hope is that the roles of epigenetics, gene–gene interactions, and gene–environment interactions will become clearer, if the pattern in human psychiatric genetics is a model. After decades of work, efforts to understand the genetics of human anxiety are making progress, and one is reminded that genes do not follow diagnostic manuals. Several neuropsychiatric disorders seem to share predisposing loci,¹¹⁹ and a similar result should be expected for canine behavioral genetics. A highly significant association between canine compulsive disorder and a neuronal adhesion protein, CDH2, on chromosome 7 has now been identified in Doberman pinschers.²⁴ This genetic locus was the first identified for any OCD in animals, but its role in the mechanism of the pathology remains unclear.

In the next decade, several novel loci associated with behavioral traits are likely to be discovered in dogs. However, potential gene discovery for conditions such as OCD, or noise phobia in one breed, does not necessarily mean that the puzzle is solved and a genetic test will be available for every breed. These conditions likely involve several genes, which may (at least partly) be breed-specific or breed group-specific (eg, herding dogs), as seems to be the case in heritable eye diseases and epilepsy in dogs.^{120,121} In the future, potential gene tests may at most offer information on the risk for the allele carrier to develop, for example, noise phobia.

The challenge of behavioral genetics in all species is to characterize phenotypes sufficiently well that genetic studies illuminate both the risk of the condition and some of the mechanisms causing behavioral suffering. When this stage is reached, and it will be, therapies can be targeted that address specific malfunctions.

Until then, veterinarians are best advised to offer functional counseling about behavioral problems that involves advice to clients to understand normal, recognize any deviations from it, seek help from veterinarians and behavior specialists early, do not breed affected individuals, and, if the condition is common in the breed line (at least once every generation), seek genetic counseling and consider revision of all breeding

Table 2 Sample single-gene tests commercially available for specific disease conditions in dogs, among the more than 145 diseases listed as heritable		
Genetic Trait	Disease Condition	Breeds Affected
GRM1 gene mutation	Neonatal ataxia	Coton de Tulear
CMR1 & CMR2: BEST1 gene mutations	Canine multifocal retinopathy	Australian shepherd, bull mastiff, bulldog, Cane Corso, Coton de Tulear, English bulldog, English mastiff
CNM gene: recessive trait	Centronuclear myopathy	Labrador retriever
CT gene: autosomal recessive gene	Copper toxicosis	Bedlington terrier
CN gene: autosomal recessive gene	Canine cyclic neutropenia (gray collie syndrome)	Collie
Cyst gene: autosomal recessive trait	Renal cysteine calculi	Newfoundlands
DCM: gene mutation	Dilated cardiomyopathy	Doberman pinscher
Factor VII deficiency: autosomal recessive	Mild to moderate hemorrhage	Alaskan Klee Kai, beagle, giant Schnauzer, Scottish deerhound
PN: autosomal recessive mutation	Greyhound polyneuropathy	Greyhound
Hem B: mutant X chromosome	Hemophilia B	Bull terrier, Lhasa Apso
HSF4 mutation	Hereditary cataract	Boston terrier, French bulldog, Staffordshire bull terrier
HN: X-linked dominant trait	Hereditary nephritis	Samoyed
HU: autosomal recessive trait	Hyperuricosuria	American Staffordshire, Australian shepherd, Black Russian terrier, bulldog, Dalmatian, GSD, giant Schnauzer, Parson Russell terrier, large Munsterlander, pit bull terrier, South African Boerboel, Weimaraner
L-2-hydroxyglutaric aciduria: recessive mutation	L-2-hydroxyglutaric aciduria	Staffordshire bull terrier

Abbreviations: BEST, bestrophin; CMR 1 and 2, canine multifocal retinopathy 1 and 2; GRM 1, metabotropic glutamate receptor 1.

Data from the CIDD Database. Available at: <http://ic.uepi.ca/cidd/disorder/overview>. Accessed January 2, 2014.

decisions. For some breeds this will be difficult, because inbreeding has so greatly constrained the gene pool,¹²² but if we are interested in the welfare of the animals who share our lives, we must invest in choosing to select for behaviors that do not cause animals suffering or distress, and in the tools that will help us identify these behaviors.

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APPENDIX: ONLINE RESOURCES

Canine Inherited Disorders Database	University of Prince Edward Island	http://ic.upei.ca/cidd/
Online Mendelian Inheritance in Animals	The University of Sydney	http://omia.angis.org.au/home
LIDA	The University of Sydney	www.sydney.edu.au/vetscience/lida
Inherited Diseases in Dogs	University of Cambridge	http://server.vet.cam.ac.uk
Orthopedic Foundation for Animals	Orthopedic Foundation for Animals	http://www.offa.org
American Kennel Club Canine Health Foundation	American Kennel Club Canine Health Foundation (AKC CHF)	http://www.akcchf.org
Fabcats	International Cat Care (formerly Feline Advisory Bureau)	http://www.fabcats.org/breeders/inherited_disorders

Data from Slutsky J, Raj K, Yuhnke S, et al. A web resource on DNA tests for canine and feline hereditary diseases. *Vet J* 2013;197(2):187.