THE IMPORTANCE OF CLINICAL GENETICS (Part I)

Urs Giger, PD, Dr. med. vet., FVH, Diplomate ACVIM & ECVIM
Charlotte Newton Sheppard Professor of Medicine
University of Pennsylvania, Philadelphia, Pennsylvania

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Recent developments in molecular and human genetics have increased interest in genetics. Clinical genetics is involved in the diagnosis, management, and control of hereditary disorders and has emerged as an important discipline in small animal practice for several reasons. Effective preventative measures reduced the frequency of infections, nutritional disturbances, and intoxications. Furthermore, life-saving advances in medicine and surgery have increased the chance of survival of companion animals and thus tend to raise the recognition of genetic defects. Inbreeding practices to preserve the desirable traits in certain breeds favor the occurrence of recessively inherited diseases. Technologic advances have allowed the recognition and characterization of the clinicopathologic, biochemical, and molecular basis of many hereditary diseases. Whereas in the past genetics had a large role of a few patients, specific genetic information is becoming critical in small animal practice for every patient. The many specific genetic disorders are covered under individual organ systems. This article on clinical genetics reviews the characteristic clinical features of hereditary diseases in small animals, the various modes of inheritance, diagnostic tests, and management and control of these diseases. The importance of genetic counseling is addressed, i.e., providing information for pet owners and breeders of animal afflicted with a hereditary disorder concerning the consequences of such a disorder and the ways in which it can be prevented in future generations. Furthermore, the recent completion of the human genome sequence and initiatives for a canine and feline sequence and availability of a partial canine genome sequence have greatly facilitated the research of single gene and complex inherited diseases. The recently introduced field of genomics is the study not just of single genes, but of the organization, functions, and interactions of all genes in the genome, including their interaction with environmental factors.

FREQUENCY

Because of the increased awareness of breeders, pet owners, and veterinarians of genetic defects and the improved diagnostic abilities in clinical practice, the number of reported hereditary diseases in small animals is rapidly growing. Originally, diseases with apparent clinical manifestations affecting the appearance and gait of an animal were recognized. Thus, it is not surprising that skeletal malformations, skin and eye abnormalities, as well as neuromuscular defects were more frequently reported than disorders involving internal organs. Furthermore, we recognize now that animals with recurrent or chronic infections or immune-mediated diseases may have a genetic defect that dysregulates their immune function. A variety of other genetic predispositions of certain animals, families, or breeds to develop disorders such as hip dysplasia, gastric torsion, and cancer have been clearly established.

At present, approximately 430 hereditary diseases in dogs and 170 disorders in cats have been adequately documented, and every year over a dozen new defects are being reported. These numbers are much higher than in food animals, where economic pressures rapidly eliminate and prevent investigation of diseased animals. In contrast, several thousand hereditary disorders have

been accumulated in the compendium known as Online Mendelian Inheritance in Man (OMIM) by Victor McKusicks. Thus, practically all diseases described in small animals have also been seen in humans and generally represent close homologues.

Although any genetic defect may occur in any animal, many have been documented only in one family or breed. In fact, in some breeds, the frequency of a particular disorder and the mutant allele may reach very high proportions. This may be due to a founder effect in which one or more of the founders of a small ancestral group was a carrier or even affected, or as observed in several smaller breeds where a popular sire was later determined to be a carrier of a mutant gene. Unfortunately, genetic disease frequencies are generally not available or are severely biased because of data collection. For instance, the prevalence of hip dysplasia may differ greatly depending on methods used to reach a diagnosis and whether a registry requires or only encourages recording of every examined animal. Large scale randomized screening programs and open registries with data on genetic diseases in certain breeds have rarely been established. In people, a disease occurrence of 1 in less than 500 individuals is rare and considered a high frequency disorder, whereas in companion animals many hereditary diseases appear to occur in 1-10% of certain breed populations.

Although many hereditary diseases occur rarely and often in only one breed, altogether they represent an important clinical problem. For the breeder and small animal practitioner, it can be a daunting, nearly impossible task to remember all these diseases. Recently, however, various resources have become available to obtain genetic information. In addition to the list of hereditary diseases and associated breeds is in the appendices of this book, there are other published lists organized by breed or disease. A list of genetic diseases in all species with references assembled by Frank W. Nicholas, known as *Mendelian Inheritance in Animals* (MIA), can be obtained online. The most comprehensive and updated searchable information, however, is Donald F. Patterson's *Canine Genetic Disease Information System*, available on disk and in book format. Similar efforts are in progress to have a complete data base on hereditary diseases in cats.

INHERITANCE

Genetic diseases are caused by chromosomal alterations or *gene mutations*. Disease-causing mutations are heritable changes in the sequence of genomic DNA that alter the production of the coded protein. The *genotype* refers to the animal's genetic makeup, reflected by its DNA sequence, whereas the *phenotype* relates to the clinical manifestation of specific gene(s) and environment, or both. The molecular genetic defect is now known for more than 40 hereditary disorders in small animals. Among the disorders caused entirely or partly by genetic factors, three main types are recognized: *chromosomal, single gene, and complex or multifactorial* disorders. For approximately half of the disorders suspected to be of a genetic nature, however, the mode of inheritance remains unknown.

These molecular genetic changes include *point mutations, deletions,* and *insertions* in the DNA sequence that result in a *missense* or *nonsense sequence* with an altered codon sequence. A codon is a three base sequence of DNA or RNA that specifies a single amino acid.

Chromosomal Disorders

The dog has 76 *autosomes* (38 pairs) and 2 *sex chromosomes* (78XX or 78XY), whereas the cat has 38XX or 38XY. The human genome project has also allowed major progress in canine and feline gene mapping. Through physical and genetic mapping strategies, genes can now be assigned to and localized along a chromosome, and new genes can be identified.

Chromosomal disorders are caused by an excess or deficiency of genes contained in a chromosome or chromosomal segment. Understandably, such defects may result in severe, often lethal clinical syndromes. Although alterations of autosomes have only rarely been reported in small animals - some had syndromes with multiple defects - they are common in infants and are often responsible for fetal losses. In contrast, abnormalities involving the X- and Y-chromosomes leading to sex development disorders are well recognized. The best example is the tricolored (calico, tortoiseshell) male cat with testicular hypoplasia and for instance an XXY chromosome set. However, not every sex developmental disorder is due to a defect in the sex chromosomes, e.g., XX-sex reversal reported in various canine breeds.

Single Gene Traits

The inheritance of a single gene defect is often called *Mendelian trait* and involves one mutant gene (allele) at a single locus. When an animal has a pair of identically mutant alleles, it is said to be *homozygous* (a homozygote), whereas when only one of the genes (alleles) is mutated, it is said to be *heterozygous* (a heterozygote) at that gene locus. The pattern of inheritance depends mainly on two factors: 1) whether the mutation is located on an autosome (autosomal) or on the X-chromosome (X-linked), and 2) whether the phenotype, the observable expression of a genotype as a disease trait, is dominant, i.e., expressed when only one chromosome of a pair carries the mutation, or recessive, i.e., expressed when both chromosomes of a pair carry the mutation. Thus, it is the phenotype rather than the mutant gene or protein that is dominant or recessive. Whereas in humans most diseases are dominantly inherited, recessive traits are favored by the common inbreeding practices in small animals.

Autosomal Recessive Inheritance

Autosomal recessive inherited traits are most common in small animals. The parents of affected animals must carry the mutant allele and are generally asymptomatic carriers (heterozygotes), therefore, called obligate carriers. Typically one fourth of males and females in a litter are equally likely expected to be affected. Phenotypically normal offspring may be in a ratio of 2:1 either carriers (heterozygotes) or free of the mutant allele ("clear," homozygous normal). Although the parents could also be affected, diseased animals generally are not used for breeding, unless they remain unrecognized, as they do not develop clinical signs until later in life (late onset diseases).

*X-Chromosomal Recessive Inheritanc***e**

In X-chromosomal recessively inherited disorders, males who are hemizygous for the X-chromosome typically are affected, whereas females are carriers. When heterozygous females (carriers) are mated to a normal male, half of their male offspring will be affected and half of their female offspring will be phenotypically normal carriers, whereas the other males and

females will be "clear." The mutant X-chromosomal gene is never passed on from the sire to a male offspring, but is transmitted by an affected male to its female offspring (*obligate carriers*). Affected females would occur only if a carrier female is mated with an affected male. Heterozygous females are usually unaffected, although some manifestations may occur because of X-chromosomal inactivation. In addition, an X-linked dominant trait may need to be considered, but has been reported only in Samoyeds with a specific glomerulonephropathy. X-linked disorders should not be confused with sex-limited disorders, such as diseases related to the primary and secondary sex organs. Finally, Y-chromosomal diseases have not been reported in animals.

Autosomal Dominant Inheritance

In autosomal dominant traits, the disease appears in every generation. An affected animal generally has one affected parent unless this animal has a new mutation in the gamete of a phenotypically normal parent or when the disease is variably expressed (nonpenetrant in parent). *Penetrance* refers to the likelihood that an animal carrying a particular mutation will exhibit an altered phenotype. Males and females are equally likely to transmit the disease to an offspring of either sex. Because affected animals are generally heterozygous, however, half of all offspring will be affected. Affected animals generally are not used in breeding programs. Furthermore, homozygous states of dominant traits are often lethal, and thus result in fetal loss or stillborns.

Mitochondrial Inheritance and Imprinting

Mitochondrial inheritance is a very rare and atypical Mendelian inheritance of disorders involving the mitochondrial DNA. Because all mitochondrial DNA is transmitted from the ova, all offspring from an affected female, but none from an affected male, will be diseased. In humans several neuromuscular diseases are known to be associated with mutations in mitochondrial DNA, and in dogs some myopathies may be caused by a mitochondrial defect.

Imprinting is another non-Mendelian mechanism for single gene disorders, by which the effects of certain genes depends on whether they are inherited through the maternal or paternal parent. In companion animals this phenomenon has not yet been documented.

Complex or Multifactorial Inheritance

A number of developmental disorders resulting in congenital malformations are caused by complex or multifactorial inheritance, as well as other disorders in adult animals. Rather than having one single gene error, several major and minor gene defects (polygenic) in the genetic information together with certain environmental factors can produce or predispose to a serious illness. Hip- and other dysplasias as well as certain congenital heart defects (conotruncal defect) are examples, and the degree to which a trait (e.g., hip dysplasia) is genetically determined may greatly vary between breeds (heritability).

Thus, the hereditary nature of a particular disease may be suggested or established by a certain familial occurrence, breed predilection, breeding studies, an established mode of inheritance and/or an identified gene defect.

