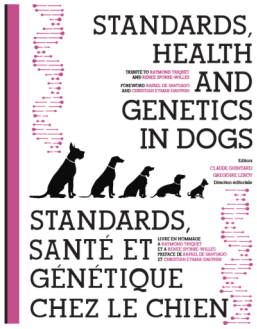

Standards, Health and Genetics in Dogs

CHAPTER II - Genetic testing in dogs

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Abstract - Over the past 15 years, the advent of powerful tools for exploring the canine genome has led to the discovery of a growing number of genes and mutations involved in canine diseases or traits of interest. To date, more than 670 canine inherited traits have been identified, more than 200 of which have been elucidated at the molecular level (gene and mutation identified). These mutation discoveries result in screening and diagnostic DNA tests for inherited diseases, but also in DNA tests for desirable traits such as coat colour or texture. In order to put these tests to good use, it is essential to understand the specificities of canine and feline inherited diseases, which determine the fields of application for these tests and the interpretation of their results.

The first part of this chapter presents the genetic characteristics of the canine species and the basics of canine genetics. The second part addresses the use of screening and diagnostic tests for inherited diseases, with a focus on genetic counselling and the parameters that determine the interpretation of test results. The third part concentrates on the search for informations on canine inherited diseases and the tests available. The final part presents tests for aesthetic characteristics such as coat colour.

Keywords: DNA, Screening, Dog DNA testing, Diagnosis, Susceptibility, Inherited disease, Colour, Coat.

I - THE CANINE GENOME AND INHERITANCE PATTERNS OF GENETIC TRAITS

1) Domestication and inherited disorders

Purebred dogs as we know them are the result of intensive selection by humans over the last few hundred years. However, the common history of the canine and human species goes back much further. Descended from domesticated wolves long before Neolithic times, a period of extensive domestication of crops and animals (Vigne, 2011; Meyer & Purugganan, 2013), dogs have accompanied human beings for thousands of years (Wayne & Ostrander, 2007).

The creation of dog breeds therefore appears recent on the scale of the evolution of the canine species. Each breed is the result of a small number of founder individuals chosen for their specific characteristics, whether behavioural (an aptitude for guarding houses or herds, or for hunting, for example), morphological (size, shape of head, ears or tail, coat colour and texture), or both. Careful selection of their offspring and inbreeding then resulted in the creation of canine breeds with very homogeneous individuals, whereas the various breeds differ greatly from one another (take, for example, the Pyrenean Mountain Dog and the Miniature Poodle). **Selection and inbreeding have permanently fixed the desired traits within each breed, but have also resulted in the unintentional fixation of undesirable traits such as inherited diseases,** morphological abnormalities and various predispositions (Wayne & Ostrander, 2007).

More than 400 dog breeds are currently recognised. Each breed is unique and has its own specific characteristics, but also its burden of inherited diseases, whether simple (caused by a single mutation) or complex (caused by multiple mutations and environmental factors). The OMIA database currently lists about 500 canine inherited diseases (*Online Mendelian Inheritance in Animals*: *http://omia.angis.org.au*). Each breed is affected by a certain number of inherited diseases and these are very often specific to one or a group of breeds. This breed specificity in canine inherited disorders is explained by the fact that each breed was created from a small number of sires and dams and that cross-breeding is forbidden. Thus, if a mutation was part of the gene pool of the initial breeding stock, or subsequently appeared in one of the breeding dogs, it will be transmitted vertically. This situation, in which a single mutation is transmitted within a line or a breed, is called the founder effect. This means that all affected individuals within a breed have the same causal mutation. However, mutations may also be present in several similar breeds. In this case, there are two possibilities: either the mutation was present before the creation of the related breeds, or the mutation was introduced to one breed from another following cross-breeding.

2) Canine genetics

A dog's genetic information is contained in its chromosomes, which are found in the cell nucleus. The canine species has 78 chromosomes divided into pairs. Each pair has a paternal and a maternal chromosome. There are 38 pairs of chromosomes known as autosomes, which include all the chromosomes except for the sex chromosomes, and a pair of sex chromosomes known as X and Y. Male dogs have 76 autosomes + a pair of XY sex chromosomes, and female dogs have 76 autosomes + an XX pair. The complete set of a dog's chromosomes, contained in the nucleus of its cells, is known as its genome.

Each chromosome is made up of a DNA (deoxyribonucleic acid) molecule and contains structural and functional units known as genes. In simple terms, a gene is a DNA sequence that enables the synthesis of a protein. Each gene has a specific and invariable position on a chromosome, known as its locus. The same gene may be found in different forms known as alleles. These variations result in the differences observed between individuals. The maternal and paternal chromosomes in a pair have the same genes, but not necessarily the same alleles. Thus, an individual may have two different alleles of the same gene.

A dog is homozygous if it has the same allele on both the paternal and maternal chromosomes.
A dog with two different alleles is heterozygous.

The genotype is the combination of alleles in all of a dog's genes or its combination of alleles for a given gene depending on whether we refer to the definition of the term genotype in the broad sense or in the strict sense (figure a).

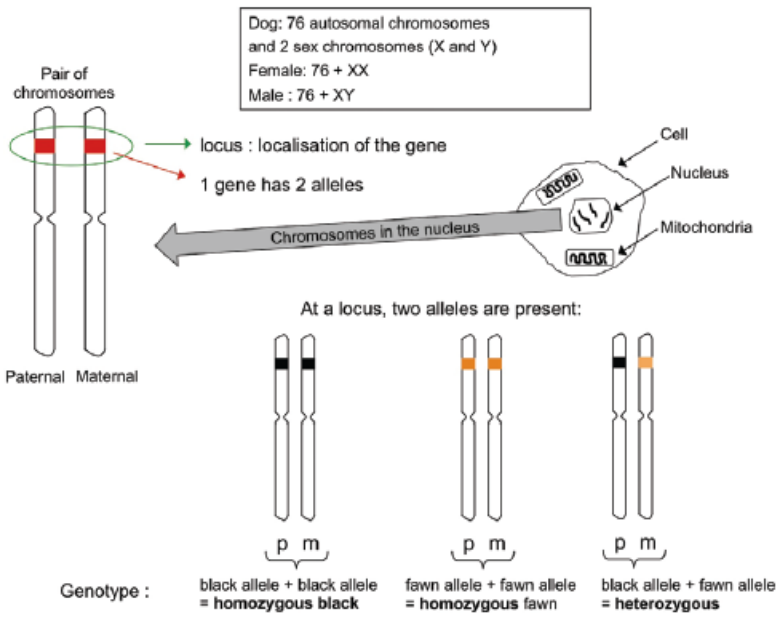
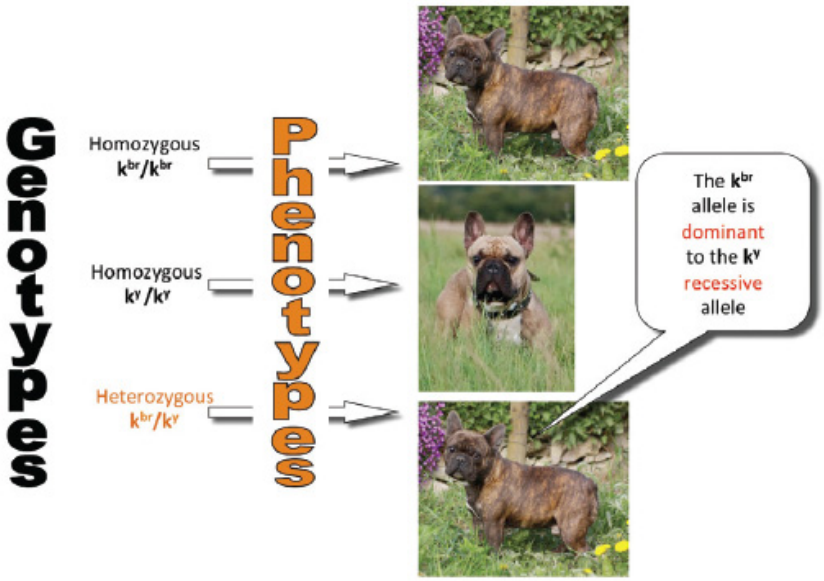


Fig a. Canine genetics

If a dog has two different alleles, generally only the expression of the dominant allele shows. The other allele, whose expression does not show, is then referred to as recessive. In the rare event that the expression of both alleles shows, then they are both referred to as codominant. For example: in dogs, at the *K* locus (*BlacK*) lies a gene responsible for the fawn or brindle coat colour. This locus contains several alleles, including the *kbr* allele, which determines a brindle coat, and the *ky* allele, which is recessive to *kbr* and gives a fawn coat. Thus, a *kbr/kbr* dog (*kbr* homozygous), but also a *kbr/ky* dog (heterozygous), will have a brindle coat, whereas only a *ky/ky* dog (*ky* homozygous) will be fawn (figure b) .



The translation of genotype (the individual's genome) into phenotype (the individual's aspect) is not direct. The action of numerous environmental parameters may modify the results of gene expression.

Fig b. Dominant or recessive

3) Inheritance patterns

Modes of disease and trait inheritance can be divided into simple modes (the trait is controlled by a single gene) and complex modes (the trait is controlled by multiple genes as well as environmental factors). There are five simple modes: autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant, and Y-linked. Polygenic or multifactorial inheritance is a complex mode. Finally, it should be noted that there is also a purely maternal mode of inheritance: the mitochondrial mode.

- Autosomal recessive traits

Autosomal recessive inheritance is characterised by males and females being affected with equal frequency, equivalent disease transmission by males and females, and the presence of healthy carriers. Autosomal recessive diseases require the presence of two copies of the mutant allele in order to be expressed. This is the most commonly encountered mode of inheritance for simple (monogenic = caused by a single gene) genetic diseases in dogs. Affected individuals generally have unaffected parents (healthy carriers). A higher frequency of the disease is also seen in the case of inbreeding. If two healthy carrier animals are mated, statistically a quarter of the litter will be affected (figure a).

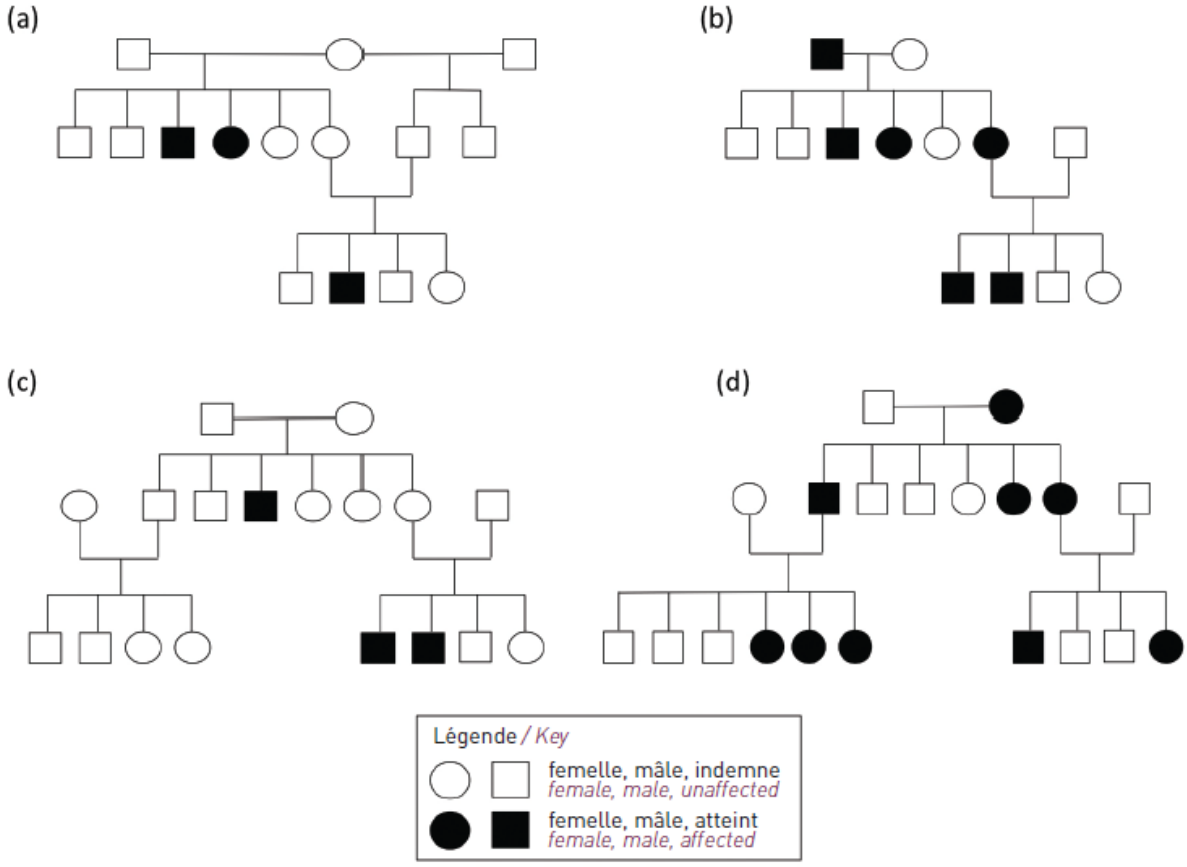


Fig c. Modes de transmission / *Inheritance pattern*

The difficulty with autosomal recessive diseases lies in the fact that the parents of the individuals concerned are often asymptomatic since they are very often healthy carriers. It is therefore only possible to predict the birth of affected puppies if the genotype of both parents is known (are they homozygous for the normal allele or heterozygous healthy carriers?).

- Autosomal dominant traits

Autosomal dominant inheritance is characterised by males and females being affected with equal frequency, equivalent disease transmission by males and females, and the absence of healthy carriers (except in the case of incomplete penetrance, see below). Thus, one of the parents of the affected individual is also affected. An individual produced by mating an affected dog with an unaffected dog has a 50% chance of being unaffected and therefore a 50% risk of being affected (figure b).

It should be noted that most autosomal dominant diseases show incomplete penetrance. This means that not all individuals carrying the mutant allele responsible for the disease systematically present the symptoms of the disease. These individuals do not express their genotype, but they pass on the mutation to their offspring. Consequently, sometimes just under half of the litter is affected and, in some cases, both parents of affected individuals may be unaffected.

- X-linked recessive traits

X-linked inheritance differs from autosomal modes in that the causal mutation of the disease is carried by the X sex chromosome. Thus, males (which only have one X chromosome) and females (which have two X chromosomes) are not equal when it comes to the disease.

X-linked recessive diseases or traits are determined by a causal gene carried by the X chromosome whose responsible allele is recessive. Thus, for a female to be affected, she must have two copies of the mutant allele, whereas a single copy is sufficient in males. X-linked recessive diseases therefore affect males far more frequently than females.

Affected males generally have unaffected parents, with the mother thus being a healthy carrier. No transmission is observed between males within a family. Male puppies from a healthy-carrier female have a 50% risk of being affected. The very few affected females are the result of mating an affected male with a healthy-carrier female (figure c).

- X-linked dominant traits

X-linked dominant diseases or traits are determined by a causal gene carried by the X chromosome whose responsible allele is dominant. Both males and females carrying a mutated X chromosome (their only X for males, one of two for females) are affected. There are no healthy carriers. X-linked dominant diseases affect males and females, but females are affected more frequently than males. An affected male will pass on the disease to all of his female offspring, whereas an affected female will only pass it on to half of her offspring, whether male or female (figure d).

- Y-linked traits

Only males have a Y sex chromosome. Y-linked diseases and traits are therefore only passed on by males and only males can express them. This mode of inheritance has not yet been observed in dogs.

- Complex traits

Some inherited diseases and traits are referred to as polygenic or complex: they are determined by multiple genes. Usually the number of these genes is unknown, as is their respective influence in the genetic determinism of the disease. The disease therefore sporadically occurs within litters and there is no way to predict the percentage of puppies affected, knowing the clinical status of the parents. **Complex traits are heavily influenced by environmental parameters (which may be very difficult to identify) that interact with the genes concerned.** Canine hip dysplasia is an example of a complex trait: several genes determine the genetic component of the disease, which is known to be inherited, but environmental factors also interact: food and physical exercise, for example.

- Mitochondrial (maternal) traits

Mitochondrial diseases or traits are passed on in a purely maternal manner. They are determined by a causal gene carried by mitochondrial DNA. Mitochondrial DNA is not found in the cell nucleus in the form of chromosomes, but inside small cellular organelles called mitochondria. During fertilisation, only the mother’s mitochondria are transmitted to the embryo. This is why mitochondrial DNA mutations are only passed on by mothers. This mode of inheritance is rare.

II - USE OF SCREENING AND DIAGNOSTIC TESTS

DNA tests can be used for the diagnosis of inherited diseases. In this case, genetic testing is a complementary examination like any other (x-rays, biochemical tests), helping to reach a diagnosis. For example, it can be used to rule out an inherited disease from the different possible diagnoses and to subsequently prescribe the use of sometimes costly further examinations that would not have been indicated in the first line (such as scans or magnetic resonance imaging - MRI).

However, the principal use of genetic tests is screening. DNA tests are used to screen affected individuals before symptoms appear, in the case of dominant diseases showing incomplete penetrance and late-onset diseases whatever their mode of inheritance. Screening thus enables better veterinarian monitoring of dogs and, where necessary and available, the initiation of early treatment. Screening also helps to avoid at-risk matings and the birth of affected or predisposed puppies.

Moreover, genetic testing can be used to screen healthy carrier individuals in the case of recessive diseases. It thus helps to avoid at-risk matings and the birth of puppies that will develop the symptoms of the disease caused by the mutation.

1) Samples and authentication

In order to diagnose or screen an inherited disease or a trait of interest (coat colour, for example), different types of samples can be used, but buccal swabs are the preferred option. They are simple, quick, painless and provide good quality DNA in sufficient quantities for one or several genetic tests (figure d).

Fig d. Frottis buccal / *Cheek swab sample*

In addition, they can be kept at room temperature and can be easily sent by standard post. Blood samples (whole blood on EDTA), which provide larger quantities of DNA, are generally preferred for research protocols or when the test is complex and requires a large quantity of DNA (rare cases). It is also possible to use DNA from semen, hair (with roots), biopsies or anatomopathological samples preserved in a fixative or embedded in paraffin.

To carry out a disease test in France, the veterinarian authenticates the sample before sending it to the laboratory: he/she verifies the identity of the dog (microchip or tattoo) and carries out the buccal swab (or

blood sample). Thus, the genetic certificate, drawn up by the laboratory conducting the test, can serve as a guarantee during the sale of a puppy or the exchange of sires and dams between breeders. The document certifies the genetic status of the dog for the causal mutation screened. In France, the test result may also be indicated on the dog's genealogical papers. The result of the test is confidential and valid for life.

2) Direct and indirect tests

There are two major categories of DNA tests that differ in terms of the method used to determine the status of a dog for an inherited disease. If the gene and the causal mutation have been identified, the DNA test is direct: the laboratory will directly test for the presence of the mutation in the dog's genome and determine whether it is present in zero, one or two copies.

When the causal mutation of a disease has not been identified, but the chromosomal region containing this mutation has been determined, an indirect DNA test (linkage test) can be conducted using genetic markers. These genetic markers are benchmarks, whose specific location on chromosomes has been identified, and which in this particular case flanked the causal mutation of the disease. The laboratory will then genotype the dog, not for the mutation (as yet unknown), but for markers close to this mutation. A dog's status can thus be determined indirectly. Indirect tests using markers rather than direct detection of the mutation are subject to high rates of false positives and false negatives. Moreover, they are often a complex, lengthy process and generally require DNA analysis of not only the dog to be tested, but also its parents. This type of test remains confidential and most of the canine tests currently available throughout the world are direct ones.

3) Genotype-phenotype correlation

In order to ensure an accurate, balanced interpretation of the result of a DNA test, one fundamental datum is needed: the genotype-phenotype correlation. This correlation between the genetic status (genotype) and the clinical status (phenotype) is specific to each mutation and indicates the probability of a genetically affected individual developing the symptoms of the disease in question. For many diseases, the genotype-phenotype correlation is close to 100%, and any mutated individual will therefore develop the symptoms of the disease over the course of its life (although the age of symptom onset may vary from one individual to another). The DNA tests for these types of mutations are true screening and diagnostic tests. By contrast, for mutations characterised by a weak genotype-phenotype correlation, the corresponding DNA tests are predisposition tests rather than actual screening tests (Mellersh *et al.,* 2009). Indeed, if the genotype-phenotype correlation is weak, a genetically affected dog may well remain healthy throughout its life, while a dog that does not carry the mutation could develop the symptoms of the disease (due to another causal mutation, to environmental factors, or to both).

4) Genetic counselling

As indicated, the result of the DNA test is confidential and valid for life. However, a genetic test is often only valid for a given breed. Indeed, many canine inherited diseases are breed-specific and the mutations identified in one breed cannot be transposed to another, even very similar one. This situation is explained by the founder effect (see paragraph I, part 1). A DNA test can therefore only be used for a single breed, or for a breed group. Some tests have an even more restricted field of application, since they concern only part of a breed. For example, the DNA test for dilated cardiomyopathy (DCM) in Doberman Pinschers, available in the United States *(www.ncstatevets.org/genetics/dobermanpinscherdcm)*, is relevant for dogs bred in the US but not for dogs bred in Europe, since the causal mutation of DCM in European Doberman Pinschers is different (Meurs *et al.,* 2012; Owczarek-Lipska *et al.,* 2013).

Furthermore, **a genetic test detects a mutation, not a disease: it is therefore only valid for a given genetic disease, caused by a given mutation. It does not indicate the status of a dog concerning the other acquired (or inherited) forms of the same disease.** For example, there are inherited cataracts and acquired (non-inherited) cataracts. A dog tested as genetically unaffected by an inherited cataract may be affected by an acquired cataract.

Moreover, if the genotype-phenotype correlation is weak (see part 3 of this paragraph), the result of the test should be interpreted with caution. It is a predisposition test, and a positive result (affected animal) should be interpreted as a risk factor.

Finally, a test may be inaccurate, especially if it is an indirect one (see part 2 of this paragraph). Consequently, there may be false positives and false negatives. It should be noted that the majority of DNA tests currently available for dogs are direct tests, whose sensitivity and specificity are almost 100%. Several general rules of genetic counselling can nevertheless be set down, taking into account the mode of inheritance. **These rules must be adjusted according to the specific situation of the dog, its line, its population of origin, the severity of the symptoms and the frequency of the causal mutation in the breed.**

Thus, in general, whatever the mode of inheritance for the disease in question, it is advisable to remove any homozygous mutated dogs (with two copies of the deleterious allele) from breeding schemes.

- *Autosomal recessive disease*

For autosomal recessive diseases, heterozygous individuals (healthy carriers) may be used for breeding. In some cases, it is even necessary to use them in order to avoid reducing the genetic diversity of the breed. Indeed, some mutations responsible for inherited diseases are very common in certain breeds (Abitbol *et al.,* 2010; Grall *et al.,* 2012). These heterozygous individuals will be bred with healthy homozygous dogs, and their offspring will be genetically tested. Good quality, healthy homozygous dogs in the progeny can be used for breeding.

- *Autosomal dominant diseases*

It is advisable to remove heterozygous dogs (with one copy of the deleterious allele) from breeding. If penetrance is complete, these dogs will present symptoms of the disease. If penetrance is incomplete, they may be unaffected. These heterozygous dogs, whether affected or healthy, will transmit the mutation to 50% of their offspring, which may present symptoms.

In some extremely rare cases, a heterozygous dog may be used for breeding. It will then be mated with a healthy homozygous individual. All of their offspring will need to be genetically tested and only healthy homozygous puppies will be later used for breeding, in order to perpetuate the line. This type of breeding can be envisaged in the case of a breed with a small population, when the causal mutation is frequent and the sire or dam is of great value, or if the goal is to save a line.

- *X-linked recessive disease*

In the case of X-linked recessive diseases, it is advisable to remove affected individuals from breeding (males and rare females), as well as healthy carrier females (which have given birth to an affected male). However, mating an affected male with a healthy homozygous female may be envisaged if the sire is of very high value or if the goal is to save a line. The progeny will be 100% healthy-carrier females, which should not be used for breeding, and 100% unaffected males, which may be used in order to perpetuate the line.

- *X-linked dominant disease*

There are no healthy carriers for X-linked dominant diseases. Moreover, these diseases are very uncommon in dogs, and it is therefore advisable to remove any affected individuals from breeding.

- *Multifactorial disease*

At present there are two predisposition DNA tests available for multifactorial diseases: one for hip dysplasia in Labrador Retrievers (*www.bioiberica.com*) and one for histiocytic sarcoma in Bernese Mountain Dogs (*www.antagene.com*). These tests are based on genetic markers that have been identified as being associated with a risk of developing or passing on the disease in question. Interpreting the results of these tests is complex. They should be used bearing in mind that they are predisposition tests and not screening or diagnostic tests.

For the hip dysplasia test, the result can be interpreted for a given individual: non-predisposed dog that can be used for breeding; or predisposed dog that should not be used for breeding and should be monitored by a veterinarian within the framework of personalised veterinary care.

For the histiocytic sarcoma test, the result should not be interpreted for a given individual. The test is a selection tool and not a predictive test of the occurrence of the cancer. The test is intended to be a tool to assist breeders and to help them manage their breeding schemes, in order to reduce the incidence of histiocytic sarcoma in the Bernese Mountain Dog breed.

5) Genetic diversity

A growing number of DNA tests are launched every year for dogs, reflecting the extraordinary dynamism of canine genetics. For some breeds, no less than nine DNA tests are available (Labrador Retriever breed, for example). Screening of breeding stocks is becoming costly for breeders and the management of mating can be a real headache for breeders and breed clubs. It should be kept in mind that inherited disease control, which aims to avoid the birth of affected or predisposed dogs and to eliminate causal mutations, should not be detrimental to the qualities of each breed. **Genetic diseases should be eliminated progressively, within the framework of a global breed management policy.** Positive selection efforts by breeders are critical. In all cases, inherited disease control plans should also aim to preserve the qualities of each breed and their genetic diversity.

III - DISEASE TESTS AVAILABLE

Every year, new DNA tests for canine diseases are launched. To date (September 2016), 678 inherited traits (diseases and traits of interest) have been identified for dogs (*http://omia.angis.org.au/home/*). This growing number of identified inherited traits for the canine species means that it is impossible to know them all and it is now becoming necessary to ensure rapid access to information on diseases and the DNA tests available from laboratories. Several databases, accessible on the internet, list useful information for veterinarians, breeders or dog owners, but at present, none contain all of the data needed to determine whether a test exists and for the correct interpretation of test results. The OMIA database contains information on inherited diseases and traits of interest for numerous animal species, and in particular for dogs, but there is no mention of the availability of DNA tests. Likewise, the IDID (*www.vet.cam.ac.uk/idid/*) and CIDD (*http://discoveryspace.upei.ca/cidd/*) databases, which present canine inherited diseases by breed and/or by type of organ affected, do not say whether a DNA test is available. It is therefore necessary to consult the PennGenn database, which lists the DNA tests available throughout the world for canine inherited disorders (*http://research.vet.upenn.edu/penngen*). It should be noted that the main animal genetic laboratories in the world present lists of tests breed by breed,

sometimes with information sheets, and that some French initiatives are working to create French language databases for canine inherited diseases.

IV - COAT COLOUR AND TEXTURE TESTS

Progress in canine genetics has benefited the field of inherited diseases, but also that of traits of interest. There are now a great many aesthetic inherited characteristics that can be identified through DNA tests. These characteristics include numerous coat colours or patterns, coat texture and also tail length. The different traits covered by DNA tests on the market are listed in table 1.

CONCLUSION

When a DNA test is available for an inherited disease, it helps to effectively control this disease. DNA tests make it possible to establish control plans at the level of lines or breeds, with the goal of avoiding the birth of affected dogs and reducing the frequency of (or even eliminating) the causal mutation in the line or breed in question. The procedures for setting up a control plan for an inherited disease depend on a number of factors, including the severity of symptoms, the mode of disease inheritance, the sensitivity and specificity of the DNA test, the breed population and the frequency of the causal mutation. **Each selection programme against an inherited disease must therefore be specific and adapted to a particular breed, disease and situation.** In addition to disease control, this programme must also be aimed at preserving the intrinsic qualities of the breed and its genetic diversity.

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Table 1: Canine phenotypic traits with an available DNA test

Locus	Gene	Alleles*	Phenotype
Brown (B)	*TYRP1*	B	Black eumelanin
		b	Brown eumelanin
Extension (E)	*MC1R*	E^M	Melanistic face mask
		E^G	Grizzle & domino
		E	Wild-type allele (eumelanin production)
		e	Only pheomelanin (red/yellow/cream)
Agouti (A)	*ASP*	a^y	Fawn/sable: yellow to red with some dorsal black tipped hairs
		a^w	Wild-type banded hairs of yellow and black (wolf type)
		a^t	Black-and-tan
		a	Black (recessive black)
BlacK (K)	*CBD103*	K^B	Dominant black (eumelanin)
		k^{br}	Brindle
		k^y	Fawn
Dilution (D)	*MLPH*	D	Full colour
		d	Dilution
Merle (M)	*SILV*	M	Merle pattern
		m	Wild-type allele
Harlequin (H)	*PSMB7*	H	Harlequin pattern
		h	Wild-type allele
Spotting (S)	*MITF*	S	No (or minimal) white spotting
		S^p	White spotting
Dobermann OCA (OCA)	*SLC45A2*	OCA	Full colour
		oca	Albino (OCA: oculocutaneous albinism)
German Shepherd "panda white spotting"	*KIT*	P	"Panda" white spotting
		p	Self
Natural Bobtail	*T*	BT	Bobbed tail (short tail)
		bt	Full length tail
Hair length (L)	*FGF5*	L	Short hair
		l	Long hair
Curl (C)	*KRT71*	C	Straight coat
		c	Curly coat
Furnishing & improper coat	*RSP02*	W	Furnishing
		w	No furnishing

Sources: Schmutz & Berryere 2007; www.vgl.ucdavis.edu.