Inherited Abnormalities of Sexual Development in Dogs and Cats (13-Sep-2001)

V. N. Meyers-Wallen

Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA.

Overview of Normal Sexual Development
The purpose of this review is to briefly describe inherited disorders resulting in ambiguous sexual morphology that have been reported in the dog and cat. An understanding of normal development is helpful in formulating a diagnostic plan and reaching a definitive diagnosis. Normal mammalian sexual development occurs in three steps, with each step depending upon successful completion of the previous step:

1. Establishment of chromosomal sex,
2. Development of gonadal sex, and
3. Development of phenotypic sex.

At fertilization, sex chromosome constitution and genetic sex are established. Early XX and XY zygotes develop similarly, that is, they are sexually indifferent, until the onset of gonadal sex determination. The mesonephros gives rise to the urogenital ridge, containing the mesonephros, indifferent gonad, and Wolffian (mesonephric) and Mullerian (paramesonephric) ducts. The Wilms' tumor-associated gene (Wt-1) and steroidogenic factor 1 gene (Sf-1) are important at this stage in maintaining the indifferent gonad [1] (Fig. 1). The morphology of the external genitalia at the indifferent stage more closely resembles a female phenotype rather than that of a male.

Figure 1. Summary of genes known to have a role in mammalian sex determination and differentiation. (Included with permission from: Parker KL, Schimmer BP and Schedl A. Genes essential for early events in gonadal development. Cell Mol Life Sci 1999; 55:831-838). - To view this image in full size go to the IVIS website at www.ivis.org . -

Gonadal sex determination is the process whereby the indifferent gonad is induced to become either a testis or an ovary. We are just beginning to understand the genetic control of testis determination through studies of mice and humans, but know very little concerning genetic control of ovarian differentiation. A model that is consistent with present data is that the indifferent gonad is programmed to become an ovary. It is only diverted from this path by early exposure to testis induction signals that are under genetic control.
Two genes that are important in mammalian testis determination are Sry (sex determining region on the Y chromosome) and Sox9 [2]. Both genes encode proteins that are members of the high mobility group (HMG) of non-histone proteins that associate with DNA. Sry encodes the testis-determining factor (formerly referred to as Tdf), in mammals and is the only Y-linked gene that is necessary and sufficient to initiate testis development. Sox9 is an autosomal gene that is involved in testis determination in several vertebrates. Case studies of humans and mice with Sox9 mutations indicate that two normal Sox9 alleles are required for normal testis determination (Fig. 1).
Dax-1 is an X-linked gene. When there is a duplication in this region of the human X chromosome, the testis fails to develop in XY individuals despite the presence of a normal SRY gene (Fig. 1). The mechanism for Dax-1 interference in testis determination is under investigation [3]. There are likely to be other genes, presently unknown, that contribute to differentiation of the testis and ovary.
Development of phenotypic sex is the final step in prenatal sexual development. Again, the female pathway is the "default" program in that the indifferent phenotype will develop as female in the absence of masculinizing signals. Differentiation of internal ducts, accessory sex organs, and external genitalia occurs in response to the presence or absence of two testis hormones, testosterone and Mullerian Inhibiting Substance (MIS) or Anti-Mullerian hormone (AMh). Mullerian ducts regress in response to MIS. Testosterone is directly responsible for masculinization of the Wolffian ducts. Through the action

of 5 alpha reductase in the external genitalia, testosterone is converted to dihydrotestosterone (DHT), and masculinizes these structures (Fig. 1). Testosterone and DHT exert their effects via the androgen receptor (AR), and MIS via the MIS receptor (MIS-R).

Sertoli cell secretion of MIS marks the beginning of the functional embryonic testis (Fig. 1).Present evidence indicates that Sf1, Wt-1, and Sox9 synergistically stimulate transcription of the MIS gene in testes [1]. Sf1 stimulates expression of steroidogenic enzymes, such that testosterone secretion from Leydig cells begins soon after testis differentiation. Testis descent in the dog normally occurs postnatally, at approximately day 10 [4]. The genetic and endocrine mechanisms for canine testis descent are poorly understood at present (see cryptorchidism below).

Diagnostic Plan

Intersex is a general, nonspecific term meaning that ambiguous genitalia are present, but does not indicate the nature or etiology of the abnormality. Since these disorders can be caused by an error at any of the three steps of sexual development (above), intersex is not a very useful term. To reach a definitive diagnosis it is helpful to categorize these disorders by the first step that differs from normal. Thus they are categorized here as either abnormalities of chromosomal sex, abnormalities of gonadal sex, or abnormalities of phenotypic sex, as shown by examples in Table 1.

Table 1. Main features of selected disorders of sexual development. Examples are disorders reported in dogs and cats. (Adapted with permission from: Meyers-Wallen VN. CVT Update: Inherited Disorders of the Reproductive Tract in Dogs and Cats. In: Bonagura ed. Current Veterinary Therapy XIII. 2000; 905 p.)						
Abnormality of :	**Karyotype**	**Gonad**	**Mullerian duct derivatives**	**Wolffian duct derivatives**	**External genitalia**	**Diagnosis**
Chromosomal sex	XXY	testis	none	epididymis vas deferens	male	XXY syndrome
	XO	streak gonad	uterus oviduct vagina	none	female	XO syndrome
	XX/XY	ovary/ ovotestis/ testis	varies		female/ ambiguous/ male	Chimera
Gonadal sex	XX	testis/ ovotestis	uterus +/- oviduct	+/- epididymis and vas deferens	male/ ambiguous/ female	XX sex reversal XX male or XX true hermaphrodite
Phenotypic sex Female Pseudohermaphrodite	XX	ovary	uterus oviduct	+/- epididymis	ambiguous or male	Exogenous androgen/progestagen
Male Pseudohermaphrodite	XY	testis	uterus oviduct	normal epididymis vas deferens	normal male except +/- cryptorchid	Persistent Mullerian duct syndrome
Male Pseudohermaphrodite	XY	testis	none	none/ +/- epididymis & vas deferens	female/ ambiguous	Complete or Incomplete Tfm

The diagnostic plan for these disorders usually involves:

1. karyotype to determine sex chromosome constitution (XX or XY) and polymerase chain reaction (PCR) to determine the presence or absence of the Sry gene,
2. histology to determine whether testes, ovaries, or ovotestes are present, and
3. gross and histologic examination of the internal and external genitalia. When possible, it is preferable to define the disorder by genetic etiology. In the future for example, it is likely that definitive diagnosis will be confirmed by finding specific gene mutations in the DNA of affected individuals.

Abnormalities of Chromosomal Sex
Animals with these disorders have an abnormality in the number or structure of the sex chromosomes which usually can be detected by karyotype of blood lymphocytes or skin fibroblasts. Those with sex chromosome trisomy or monosomy (XXY, XXX, or XO), generally have underdeveloped genitalia and are sterile, but have unambiguously male (XXY) or female (XXX or XO) external genitalia. The XXY and XO syndromes have been well described in humans as the Klinefelter and Turner syndromes, respectively. Both syndromes have been reported in dogs and cats [5,6], and the XXX syndrome has been reported in dogs [7]. Many tortoiseshell and calico male cats have been reported with the XXY syndrome [5].
Chimeras are individuals composed of two or more cell populations, each arising from different individuals. Mosaics are also individuals composed of two or more cell populations, but the cells originate within the same individual. The gonadal sex of chimeras and mosaics depends upon the proportion of XX cells and XY cells present in the indifferent gonad at the time of gonadal sex determination and the ability of those cells to form a functional testis or ovary. The type of gonad formed then determines the phenotypic sex. Several examples in dogs and or cats have been reported [8]. An example is shown in Fig. 2.

Figure 2. Incomplete masculinization of the external genitalia in a canine chimera (78 XX / 78XY). Although a prepuce-like structure has developed, the urogenital orifice location is displaced caudally from the normal male position and cranially from the normal female position. The attendant is pointing to the umbilicus. (Property of V.N. Meyers-Wallen). - To view this image in full size go to the IVIS website at www.ivis.org . -

Trisomy, monosomy, and mosaicism can result from chromosomal nondisjunction during meiosis or mitosis, while chimerism may result from fusion of zygotes. It is unusual, but not impossible, to find more than one affected individual with such disorders within a family.

Abnormalities of Gonadal Sex: Sex Reversal

XX Sex Reversal -
These dogs invariably have a 78,XX chromosome constitution and some testicular tissue in one or both gonads. They are either XX true hermaphrodites, having at least one ovotestis, or XX males, having bilateral testes. The degree of phenotypic masculinization is related to the amount of testicular tissue present. XX true hermaphrodites can have normal female external genitalia, or an enlarged clitoris resembling a penis with a bone (*os clitoris*), or any phenotype in between these extremes (Table 2). XX males generally have a caudally-displaced prepuce, a penis with hypospadias, and are bilaterally cryptorchid. Internal genitalia in all affected dogs includes a complete bicornuate uterus, but oviducts and epididymides may or may not be present.

Table 2. Range of phenotypic variation observed in dogs affected with Sry-negative XX sex reversal in a family of research dogs derived from the American cocker spaniel. Adapted from: Meyers-Wallen [22].

90% of affected dogs were XX true hermaphrodites, of these:

- 15% had clitoral enlargement
- 15% had an abnormally shaped vulva
- 70% had normal female external genitalia

10% of affected dogs were XX males, of these:

- all had a caudally displaced prepuce
- all were bilaterally cryptorchid

XX sex reversal has been reported in 16 breeds, has been shown to be an inherited disorder in the American cocker spaniel, and is a familial trait in at least 6 of the 16 breeds in which it has been reported [5,9-11] (Table 3).

Table 3. Dog breeds in which XX sex reversal (XXSR) has been reported [5,9-11]	
American cocker spaniel	XXSR is inherited as an autosomal recessive trait
Beagle German shorthaired pointer	Inheritance is consistent with autosomal recessive inheritance
English cocker spaniel Kerry blue terrier Norwegian elk hound Pug Weimaraner	Mode of inheritance has not been studied in detail and XXSR is considered to be a familial trait
Afghan hound American pit bull terrier Basset hound Border collie Doberman pinscher Soft coated wheaten terrier Vizsla Walker hound	Mode of inheritance of XXSR has not been studied in breeds without annotation

Thus, several individuals may occur within a family. Diagnosis of XX sex reversal depends upon confirmation of an 78,XX chromosome constitution and the presence of at least one ovotestis or testis. Diagnostic tests should include a molecular test for the presence or absence of Sry, since Sry-negative XX sex reversal is the type that has been documented in purebred dogs and is likely to be inherited [10-13]. This form of XX sex reversal is inherited as an autosomal recessive trait in the American cocker spaniel [14], but the etiologic gene is unknown. In genetic counseling one should note that both parents of an affected American cocker spaniel are carriers. Most of the male and female siblings of the affected dog are expected to be carriers. No more than 25% of the siblings, on average, are expected to be noncarriers. Sry-positive XX sex reversal is caused by a different genetic mechanism and has not been described in dogs or cats. For example in humans, translocation of the SRY gene from the Y to a different chromosome has resulted in SRY-positive XX sex reversal.

Abnormalities of Phenotypic Sex: Pseudohermaphroditism
In pseudohermaphrodites, the chromosome constitution and gonadal sex are in agreement, yet the internal or external genitalia are ambiguous. Affected individuals are either male or female pseudohermaphrodites.
Canine female pseudohermaphrodites are 78,XX and have bilateral ovaries. Mullerian duct derivatives develop normally, forming oviducts, uterus, and cranial vagina. Androgen-responsive organs are masculinized during development [5]. Masculinization ranges from mild clitoral enlargement to nearly normal male external genitalia with an internal prostate. Iatrogenic causes include androgen or progestagen administration during gestation. Presenting signs include proestral bleeding, urinary incontinence, or uterine infection (Fig. 3). Ovariohysterectomy with gonadal histopathology for diagnostic purposes is recommended. To prevent this disorder, steroid administration should be avoided during gestation, particularly during the period that canine internal and external genitalia normally develop (days 34 - 46, counting from the serum LH peak (d0) of the dam [15,16]).

Figure 3. Radiographic study of a canine female pseudohermaphrodite presented for ambiguous external genitalia and urinary incontinence. Contrast was introduced retrograde into the urinary orifice within a caudally displaced, prepuce-like structure. Contrast fills the urethra, narrowed caudal vagina (CdV), distended cranial vagina (CrV), uterine body and horns, and urinary bladder (UB). Uterine horns are visible as thin lines of contrast (arrow head), cranial to the distended vagina and dorsal to the urinary bladder. In response to androgens, the female urogenital sinus formed a male urethra rather than a vestibule and caudal vagina. However the cranial vagina communicates with the urethra via a narrowed portion (arrow) of the caudal vagina, resulting in urine pooling and incontinence. (Photo courtesy of Mary Louise Martin). - To view this image in full size go to the IVIS website at www.ivis.org . -

Canine male pseudohermaphrodites are 78,XY and have bilateral testes, yet have female internal or external genitalia to some degree. This definition EXCLUDES XX males, in which chromosomal and gonadal sex do not agree (see XX sex reversal above). Two categories of male pseudohermaphroditism are recognized: 1) failure of Mullerian duct regression and 2) failure

of androgen-dependent masculinization.

Failure of Mullerian duct regression - Persistent Mullerian Duct Syndrome (PMDS) has been reported in the miniature schnauzer and the basset hound. An intersex condition that may be PMDS has also been reported in a Persian cat [5]. Affected dogs have bilateral oviducts, a complete uterus with cervix, and a cranial portion of the vagina (Fig. 4a and Fig. 4b).
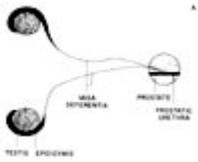

Figure 4a. - To view this image in full size go to the IVIS website at www.ivis.org . -
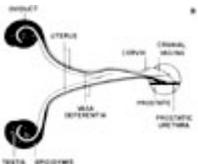

Figure 4b. - To view this image in full size go to the IVIS website at www.ivis.org . -

Figure 4a and 4b. Diagram of (A) male dog gentalia and (B) a male dog with Persistent Mullerian Duct Syndrome (PMDS). All Mullerian duct derivatives are present in the PMDS male in addition to male genitalia. (Adapted with permission from: Meyers-Wallen VN, Donahoe PK, Ueno S, Manganaro TF, Patterson DF. Mullerian Inhibiting Substance is present in testes of dogs with Persistent Mullerian Duct Syndrome. Biol Reprod 1989; 41:881-888).

Bilateral scrotal testes or unilateral or bilateral cryptorchidism may be present. These dogs may present with pyometra, urinary tract infection, prostate infection, or Sertoli cell tumor. Diagnosis is confirmed by presence of a 78,XY chromosome constitution, bilateral testes, and the presence of all Mullerian duct derivatives. Notably, androgen-dependent masculinization is that of a normal male. Treatment is limited to castration and hysterectomy. The defect is inherited as an autosomal recessive trait in miniature schnauzers [17], so females and males can be carriers. Homozygous affected dogs that have a descended testis are usually fertile and will transmit the trait to all offspring, producing either carriers or affected dogs.
Failure of androgen-dependent masculinization - Male pseudohermaphrodites with defects in androgen-dependent masculinization are 78,XY and have bilateral testes. Regression of the Mullerian duct system occurs as in normal males. However, structures requiring androgens for masculinization fail to develop normally. Inherited defects of this type generally affect both prenatal and postnatal male development. Failure of masculinization can range from mild, where some masculinization occurs, to severe, where no masculinization occurs (complete failure).
These phenotypes can be caused by defects in:

1. luteinizing hormone (LH) or LH receptors,
2. androgen production,
3. conversion of testosterone (T) to dihydrotestosterone (DHT) by 5-alpha-reductase, or
4. the androgen receptor.

Defects in LH, LH receptors, androgen production, and 5-alpha-reductase have not been documented in the dog or cat. Androgen resistance and androgen insensitivity refer to those syndromes where androgen production is normal but masculinization fails to occur due to defects in the 5-alpha-reductase enzyme or the androgen receptor. The term testicular feminization (Tfm) is reserved for androgen receptor defects. In the Tfm syndromes, both T- and DHT-dependent masculinization can be affected, resulting in either complete or partial failure of masculinization.
Androgen receptor defects -
Testicular Feminization Syndromes (Tfm) are caused by mutations in the X-linked androgen receptor gene. Although testosterone production and conversion to dihydrotestosterone are normal, the target organs are unable to respond appropriately. There is either complete or partial failure of androgen-dependent masculinization, depending upon whether the androgen receptor is nonfunctional or partially functional. In the future, it should be possible to diagnose these disorders by testing for mutations in the canine or feline androgen receptor gene. Castration is the recommended treatment for affected dogs and cats. Mothers of affected males are carriers, as are some female siblings. Male siblings having normal male genitalia can be used in a breeding program.
When the androgen receptor is completely nonfunctional, androgen-dependent masculinization is entirely absent, and the diagnosis is complete Tfm. Affected males often present as females that fail to cycle and are sterile. Mullerian duct

derivatives are absent as in normal males, since their regression is not dependent upon androgens. A defect of this type has been reported in a domestic shorthaired cat [18]. Bilateral abdominal testes were present, but there were no epididymides, vasa deferentia, or uterus, and the external genitalia were female (Fig. 5).
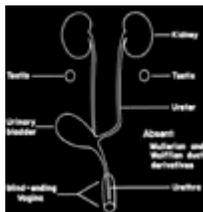

Figure 5. Diagram of the internal genitalia of a domestic shorthaired cat affected with testicular feminization (Tfm) syndrome. Androgen-dependent characteristics, such as Wolffian duct derivatives, are absent due to a nonfunctinal androgen receptor. Mullerian duct derivatives are absent, as expected in a male, since Mullerian duct regression is dependent upon MIS and not androgens. (Adapted with permission from: Meyers-Wallen VN, Wilson JD, Griffin JE, Fisher S, Moorhead PH, Goldschmidt MH, Haskins ME, Patterson DF. JAVMA 1989; 195:631-634). - To view this image in full size go to the IVIS website at www.ivis.org . -

When the androgen receptor has partial function, the diagnosis is incomplete Tfm. The spectrum caused by these defects ranges from individuals with ambiguous genitalia to phenotypic males that are infertile. This has been reported in a mixed breed dog [19] and may occur in cats, but has not been well documented.

Additional Abnormalities of Phenotypic Sex

Hypospadias - Hypospadias is an abnormality in location of the urinary orifice resulting from incomplete masculinization of the urogenital sinus during formation of the male urethra (Fig. 6). The cause of this disorder is unknown, but could be teratogens or inherited traits that affect androgen production or binding. It has been reported as a familial defect in some dog breeds [5]. If hypospadias is accompanied by scrotal abnormalities or retention of Mullerian duct derivatives, inherited defects such as XX sex reversal should be considered in the differential diagnosis. Although dogs with mild hypospadias may be able to breed normally, they are not recommended as breeding stock.

Figure 6. Hypospadias in a Shetland sheep dog. The catheterized urinary orifice (arrow) is located on the ventral shaft of the penis. This results from incomplete masculinization of the urogenital sinus during formation of the male urethra. (Property of V.N. Meyers-Wallen). - To view this image in full size go to the IVIS website at www.ivis.org . -

Cryptorchidism - Cryptorchidism can occur in association with other defects in sexual development, as mentioned above. However in this section we refer to isolated cryptorchidism, where cryptorchidism occurs as the only abnormality in the male reproductive system. It is included here somewhat arbitrarily since the underlying mechanisms for abnormal testis descent are incompletely understood.

Isolated cryptorchidism is the most common disorder of the reproductive tract reported in dogs [5,20]. Canine testes normally descend by 10 days after birth [4], although they are not easily palpable at this age. However, both testes should certainly be palpable within the scrotum by 6 - 8 weeks of age, and the diagnosis of cryptorchidism is warranted if they are not. Dogs with bilateral cryptorchidism are sterile, while those with unilateral cryptorchidism can be fertile. However, the recommended treatment for both is bilateral castration because 1) there is an increased risk of Sertoli cell tumor in cryptorchid testes, and 2) isolated cryptorchidism is clearly a familial trait in several breeds, and is very likely to be inherited (Table 4).

Table 4. Dog breeds reported to have a high prevalence of cryptorchidism [23].

● Boxer	● Miniature schnauzer
● Cairn terrier	● Pekingese
● Chihuahua	● Pomeranian
● English bulldog	● Shetland sheepdog
● Maltese	● Toy poodle
● Miniature dachshund	● Yorkshire terrier
● Miniature poodle	

Although the genetics of cryptorchidism in dogs is incompletely characterized, there is enough data to aid in genetic counseling. Inheritance of isolated cryptorchidism as a sex-limited recessive trait is consistent with available data. Using this model, the first recommendation is that affected dogs be removed from the breeding population. The second recommendation is that both the father and mother of affected dogs should be considered to be carriers. Some full siblings of the affected dog will also be carriers. In other species in which cryptorchidism occurs as a recessive trait, a reduction in the frequency of affected animals was obtained in a few generations by removing carrier parents and affected males from the breeding population. This is probably the minimum program that should be pursued in dogs.

Although medical regimens have been suggested to induce testicular descent in cryptorchid dogs, there are no published reports to confirm that these are more successful than no treatment at all. If the testes descend several months after birth, this is delayed descent which has been documented in lines of dogs that have a high incidence of cryptorchidism [20]. Thus dogs with late descent may be a variant of the cryptorchid phenotype, and could still transmit genes for this defect to their offspring.

When the genetic causes of cryptorchidism are discovered, it should be possible to identify carriers of this trait with certainty. Recent experiments in mice indicate that androgen is necessary for degeneration of the cranial suspensory ligament of the embryonic testis while Insl3, an insulin-like hormone secreted by Leydig cells, is necessary for gubernacular development independent of androgens [21]. Mice that are homozygous for Insl3 deletions are bilaterally cryptorchid, but have no other reproductive tract abnormalities. It is possible that Insl3 mutations are responsible for this condition in dogs, but it is also possible that the genetic control of testicular descent in dogs may differ from that in mice.

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