Sexual Development

Sex Dev 2012;6:46–60
DOI: 10.1159/000332740

Gonadal and Sex Differentiation Abnormalities of Dogs and Cats

V.N. Meyers-Wallen

Baker Institute for Animal Health, College of Veterinary Medicine, Cornell University, Ithaca, N.Y., USA

Other recent reviews have discussed the molecular mechanisms of normal mammalian sex determination or their application in understanding abnormal sexual development in domesticated animals [Villagomez et al., 2009; Poth et al., 2010; Jakob and Lovell-Badge, 2011]. To focus the diagnostic plan on factors that normally control each step in sexual development, we previously categorized affected dogs and cats according to the first step in sexual development that was abnormal, being either errors in chromosomal sex, gonadal sex, or phenotypic sex [Meyers-Wallen, 2009]. A new method of categorizing disorders of sexual development (DSD) has been developed for humans, to develop a consensus of diagnostic terms [Pasterski et al., 2010]. The consensus terminology is amenable to incorporation of molecular diagnosis, which is increasingly important, and adoption of a common nomenclature should facilitate communication and collaboration between veterinarians, physicians, and researchers. Accordingly, cats and dogs are now described as having DSD rather than being described as intersex. This review updates canine and feline cases that have sufficient diagnostic evidence to consider them as potential models for human DSD, but does not attempt to reinterpret all cases reported. The disorders are categorized as sex chromosome DSD, XY DSD, or XX DSD (table 1), but previous terminology is included in the text.

Key Words
Cryptorchidism · Hermaphrodite · Hypospadias · Müllerian hypoplasia · Ovotesticular DSD · PMDS · Sex chromosome DSD · Testicular DSD · XY DSD · XX DSD

Abstract
The molecular steps in normal sexual development were largely discovered by studying patients and animal models with disorders of sexual development (DSD). Although several types of DSD have been reported in the cat and dog, which are often strikingly similar to human DSD, these have been infrequently utilized to contribute to our knowledge of mammalian sexual development. Canine and feline cases of DSD with sufficient evidence to be considered as potential models are summarized in this report. The consensus DSD terminology, and reference to previous terminology, is used to foster adoption of a common nomenclature that will facilitate communication and collaboration between veterinarians, physicians, and researchers. To efficiently utilize these unique resources as molecular tools continue to improve, it will be helpful to deposit samples from valuable cases into repositories where they are available to contribute to our understanding of sexual development, and thus improve human and animal health.
Sex Chromosome DSD

The normal chromosomal constitution of cats is 38,XX or 38,XY, while that of dogs is 78,XX or 78,XY. Several abnormalities in the number or structure of the sex chromosomes have been identified in cats and dogs. In general, however, sex chromosome DSDs are reported less frequently in these species than in human patients, as economic concerns influence the extent of diagnostic testing.

XXY and Variants

As in humans with Klinefelter syndrome, affected cats and dogs are phenotypic males that are sterile due to failure of spermatogenesis (fig. 1). There are many reports of 39,XXY cats and mosaic variants such as XY/XXY and XY/XYY [reviewed in Meyers-Wallen and Patterson, 1989]. The most comprehensive study discussed 25 cases [Centerwall and Benirschke, 1975] and another reported 14 cases [Leaman et al., 1999]. Most affected cats have been identified as unusual because they were phenotypic males having both black and orange in the hair coat (tortoiseshell or calico coat color). As the orange locus in the cat is X-linked [Grahn et al., 2005], and alleles at this locus are black or orange, a 38,XY male should have either orange or black coat color.

In the dog, there is no coat color linked to the X chromosome, and only four 79,XXY dogs have been reported [Clough et al., 1970; Nie et al., 1998; Goldschmidt et al., 2001; Reimann-Berg et al., 2008]. One of these developed a scrotal testis tumor at 5 years of age [Goldschmidt et al., 2001]. However, it is not known whether 79,XXY dogs with scrotal testes have an increased risk of testicular neoplasia.

Monosomy X and Variants

As in human Turner's syndrome, cats and dogs with monosomy X develop as phenotypic females. Three cases of feline 37,X have been reported, 2 of which died by 3 days of age [Norby et al., 1974; Long and Berepubo, 1980]. Normal ovarian histology was reported in one of these [Norby et al., 1974]. Gonadal dysgenesis was identified in the third cat, which presented at 2.5 years of age with primary anestrus and small stature [Johnston et al., 1983]. Unilateral gonadal dysgenesis was identified in a fourth cat, a mosaic variant (37,X/38,XX) that was pregnant at presentation [Thomsen et al., 1987].

There are few reports of canine X monosomy, all of which were phenotypic females, and some with small stature. However, all of these are likely mosaic variants. Two dogs presented with a history of persistent proestrus that failed to progress to estrus. The karyotype was reported as 77,X in the first case [Lofstedt et al., 1992] and 77,X/78,XX in the second [Mayenco-Aguirre et al., 1999]. Gonadal histology was similar in both dogs, in that no follicles or corpora lutea were identified. As signs of proestrus were present in both dogs, they were likely 77,X/78,XX mosaics. Two other dogs presented for failure to become pregnant after exhibiting apparently normal estrous cycles and breeding at the appropriate time [Switonski et al., 2007].

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Table 1. DSD in the cat and dog that are animal models or potential animal models for human DSD

Sex Abnormalities of Dogs and Cats

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Both were determined to be 78,XX/77,X mosaics in which the 77,X line was in low frequency. Another canine report of X monosomy [Smith et al., 1989] is discussed below (X/XY mixed gonadal dysgenesis).

XXX (and Variants)
As in humans, XXX cats and dogs are phenotypic females having variable ovarian development and presentation. One feline mosaic variant (37,X/39,XXX) had unilateral gonadal dysgenesis but was pregnant at presentation [Thomsen et al., 1987]. All 79,XXX dogs reported were phenotypic females, and most presented with primary anestrus [Johnston et al., 1985; Switonski et al., 2000; Goldschmidt et al., 2003]. However, 2 exhibited abnormal estrous cycles, including shortened interestrus intervals, persistent estrus, and anovulation [O’Connor et al., 2011]. Neither dog became pregnant when bred. Both ovaries in each dog were hypoplastic, in that normal follicles were absent. However, immature sex cords lined by granulosa cells were identified in 1 ovary of 1 of these dogs, confirming partial follicular development (fig. 2). Clinical signs of estrus in both dogs were most likely due to gonadal mosaicism (78,XX/79,XXX).

X/XY (Mixed Gonadal Dysgenesis)
Only 1 dog has been reported in this category, which had a 77,X karyotype and was small in stature [Smith et al., 1989]. The external genitalia were ambiguous and the primary gonadal cell type resembled Leydig cells. Therefore, 77,X/78,XY gonadal mosaicism is likely [Giger et al., 1989].

XX/XY (Chimerism, Ovotesticular DSD)
Several feline 38,XX/38,XY chimeras have been reported, usually because they were phenotypic males with both orange and black in the hair coat [reviewed in Meyers-Wallen and Patterson, 1989; Leaman et al., 1999]. Some of these developed a testis and an ovary [Biggers and McFeeley, 1966; Malouf et al., 1967], others developed ovotestes. In some cases fertility or spermatogenesis was documented [Moran et al., 1984; Kuiper et al., 2003].

While several dogs with XX/XY karyotypes have been reported, gonadal histology was not performed in most [reviewed in Poth et al., 2010]. Many of these were evaluated because they had ambiguous genitalia, as shown in a 78,XX/78,XY Fila Brasileiro (fig. 3; Meyers-Wallen [2001]). In comparison to littermates, the urogenital orifice was displaced caudally from the normal male position and cranially from the female position. Both gonads in this dog contained seminiferous tubules and many Leydig cells. Although a small rim of cuboidal epithelium was present at the cortical surface in 1 area, no oocytes were present. Immature epididymides were present, but deferent ducts were absent.
Disorders of Testicular Development

Complete or Partial Testicular Dysgenesis

This has not been reported in cats, but a few dogs with 78,XY karyotype and incompletely masculinized genitalia have been reported. Three cases have sufficient information to propose a diagnosis in this category. An SRY-positive poodle presented with ambiguous external genitalia, consisting of an enlarged clitoris protruding from the vulva [Meyers-Wallen et al., 1999]. The gonads, both undescended testes, were confirmed by histology to contain seminiferous tubules lined by Sertoli cells lacking germ cells. The testes were attached to the horns of a bicornuate uterus in which the endometrial glands were small in size and number. Since both androgen- and Müllerian inhibiting substance (MIS)-dependent masculinization were incomplete in this case, it is likely to be a disorder of testicular development, but the molecular etiology is unknown.

A second case reported was a 78,XY mixed breed dog with female external genitalia and no evidence of clitoral enlargement [Bigliardi et al., 2011]. The dog presented at 8 years of age with subcutaneous swellings lateral to the vulva, which contained gonads with Leydig cell and Sertoli cell tumors. Deferent ducts and Müllerian duct derivatives were apparently absent. The presence of bilateral testicular neoplasia precludes definitive judgment on the extent of testicular dysgenesis. SRY was present, and contained a single nucleotide polymorphism, the significance of which is unknown. Therefore this case is likely a disorder of testicular development or of androgen synthesis or action (see disorders of androgen synthesis or action below). The molecular etiology is unknown.

A final case was a 78,XY Labrador retriever that was SRY-positive and presented with an enlarged clitoris protruding from the vulva [Wernham and Jerram, 2006]. One testis was located in the subcutaneous skin near the vulva, and the other was in the abdomen. Histologic evaluation confirmed hypoplasia, as both testes contained seminiferous tubules without spermatogenesis and many Leydig cells in the interstitium. In addition, incompletely developed epididymides were adjacent to each testis, and deferent ducts were not found. No Müllerian duct derivatives were identified. Since only partial androgen-dependent masculinization, but complete MIS-dependent masculinization was confirmed in this case, it is likely a disorder of testicular development or of androgen synthesis or action. The molecular etiology is unknown.

Ovotesticular DSD

One case of feline ovotesticular DSD (XY sex reversal, true hermaphrodite) has been confirmed [Schlafer et al., 2011]. The 1-year-old mixed breed, phenotypically male cat presented with bilateral cryptorchidism (fig. 4). The gonotype was 38,XY and the SRY nucleotide sequence was the same as in a normal male control. Ovotestes, located at the caudal pole of the kidneys, were composed primarily of testis, with a thin cortical rim of ovarian tissue. A complete bicornuate uterus, oviducts, and fimbria were present. Epididymides were adjacent to each gonod, but deferent ducts were adjacent only to the cranial portion of the uterine horns. The causative mutation is unknown.

Two likely cases of canine ovotesticular DSD have been reported. The first was a 78,XY mixed breed [reviewed in Chaffaux and Cribiu, 1991] and the second a 78,XY Yorkshire terrier [Jurka et al., 2009]. The first had ambiguous genitalia, including an enlarged clitoris with a bone. One gonad was an ovary containing atretic follicles without oocytes. The other was a testis containing a Sertoli cell tumor and seminiferous tubules lacking germ cells.

Fig. 3. Sex chromosome DSD. Ambiguous external genitalia of a 78,XX/78,XY Fila Brasileiro dog. The prepuce is caudally displaced, being located closer to the anus and farther from the umbilicus (top of photograph) than in a normal male (reprinted with permission from International Veterinary Information Service, Ithaca, New York: Meyers-Wallen [2001]).
cells. In the second case, histologic confirmation of the gonads and a test for SRY were not performed.

**Disorders in Androgen Synthesis or Action**

**Complete Androgen Insensitivity Syndrome**

One case of feline complete androgen insensitivity syndrome has been reported in a 38,XY cat [Meyers-Wallen et al., 1989a]. The external genitalia were unambiguously female at 6 months of age when presented for routine ovariohysterectomy. The gonads were found at the caudal pole of the kidneys, and both Müllerian and Wolffian duct derivatives were absent. The vagina was blind-ended. The testes contained seminiferous tubules widely separated by interstitium containing abundant Leydig cells (fig. 5). Inability of the androgen receptor to bind tritiated dihydrotestosterone in fibroblasts cultured from the vulva was demonstrated in vitro.

**Partial Androgen Insensitivity Syndrome**

One case of canine partial androgen insensitivity syndrome was reported in a 78,XY mixed breed dog [Peter et al., 1993]. It was phenotypically female at 6 months of age, but scrotal-like swellings containing testes were later identified on each side of the vulva. A blind vaginal pouch was present. Gonadotropin-stimulated serum testosterone and dihydrotestosterone concentrations, and gonadal 5 alpha reductase enzyme activity were not significantly different from controls. Spermatogenesis was absent in both hypoplastic testes. A well-developed epididymis and partially developed deferent duct were adjacent to each testis. High affinity binding of tritiated dihydrotestosterone in vitro was undetectable in fibroblasts cultured from the vulva.
Persistent Müllerian Duct Syndrome

This category is etiologically divided into disorders in the synthesis or action of MIS, also known as anti-Müllerian hormone (AMH). Mutations in MIS or its type II receptor (MISRII/AMHR2) cause the same phenotype. Only a few cases have been reported of phenotypically male cats having internal Müllerian duct derivatives, and these lack critical diagnostic tests. Nevertheless, it is likely that some of these are feline persistent Müllerian duct syndromes (PMDS). For example, a complete uterus was identified in a bilaterally cryptorchid, phenotypically male cat [Schulman and Levine, 1989]. Clinical signs of stranguria and infection prompted surgical intervention during which a bicornuate uterus filled with purulent exudate was identified. With the advent of the feline genome, molecular diagnosis can be pursued in such cases.

Canine PMDS has been reported frequently in the miniature schnauzer breed, in which the causative mutation appears to be widely distributed [Brown et al., 1976; Marshall et al., 1982; Matsuu et al., 2009; Vegter et al., 2010; Breshears and Peters, 2011]. Early studies establishing a research model from this breed determined that it was inherited as a sex-limited, simple autosomal recessive trait [Meyers-Wallen et al., 1989b]. As fetal and neonatal testes of PMDS dogs produced biologically active MIS, a defect in the MIS receptor or its downstream signaling pathway was suspected as the cause [Meyers-Wallen et al., 1989b, 1993]. Subsequently, a single base pair substitution in MISRII was identified, which introduces a stop codon in exon 3 [Wu et al., 2009]. The homozygous mutation should terminate translation at 80 amino acids, eliminating much of the extracellular domain and the entire transmembrane and intracellular signaling domains of the receptor. A mutation test for the miniature schnauzer is available [Pujar and Meyers-Wallen, 2009]. Canine PMDS has also been reported in the basset hound in Europe and a mixed breed dog, in which the causative mutations are unknown [Nickel et al., 1992; Kuiper et al., 2004].

The phenotype in the miniature schnauzer model is strikingly similar to that of human PMDS patients. Externally, affected dogs are unambiguously male, except that approximately 50% are unilaterally or bilaterally cryptorchid. Internally, all Müllerian and Wolffian duct derivatives are present. Bilateral oviducts and epididymides are adjacent to the testes. The deferent ducts are included in the lateral walls of the uterus, and the cranial ends of each uterine horn are attached to the caudal pole of the ipsilateral testis (fig. 6). The cervix is present, and the cranial vagina terminates within the craniodorsal aspect of the prostate gland. Radiographic contrast studies of 3 affected dogs confirmed a patent connection between the cranial vagina and the prostatic urethra (fig. 7). Uterine infection (pyometra) and neoplasia in cryptorchid testes are well documented sequelae to PMDS in the miniature schnauzer [reviewed in Wu et al., 2009].

The canine model provides clinical insight for PMDS patients [Wu et al., 2009]. Most are diagnosed as children at the time of surgical correction for cryptorchidism, and others are identified as infertile adults. Notably, cryptor-
chidism and infertility are not consistently associated with canine PMDS. Fifty percent of affected dogs in the model pedigree had scrotal testes and appeared externally to be normal males. The remaining 50% were cryptorchid. We speculate that the close attachment of the testis to the uterine horn physically interferes with testis descent. PMDS dogs with at least 1 scrotal testis were fertile [Wu et al., 2009]. Therefore, more studies may be warranted to determine the proportion of PMDS patients who are neither cryptorchid nor infertile, and the frequency of secondary infections.

Isolated Hypospadias
Isolated hypospadias has been rarely reported in cats and dogs, and no molecular etiology has yet been identified in either species. Two reports in Himalayan cats described the severe phenotype [Bredal et al., 1997; King and Johnson, 2000]. The scrotum is bifurcated by a urethral canal that is open along the entire dorsal aspect, and the penis and prepuce are diverted dorsally. This phenotype has also been identified in a 38,XY domestic short hair cat in which normal stages of spermatogenesis were confirmed in testis histology (fig. 8).

Canine isolated hypospadias of varying severity has been reported (fig. 9). The location of the urethral orifice ranges from the glans penis (mild), to the penile shaft (moderate, Ndikuwera [2005]) to the perineum (severe, Ader and Hobson [1978]; Adelsberger and Smeak [2009]). The Boston terrier breed had the highest prevalence of isolated hypospadias in a survey of hospital cases in which affected purebred and mixed breed dogs were identified [Hayes and Wilson, 1986]. As it is likely familial in the Boston terrier, studies in this breed could serve as a model for humans. Hypospadias has also been reported in association with other canine abnormalities, such as cryptorchidism [Hayes and Wilson, 1986; Cassata et al., 2008], scrotal abnormalities [Jurka et al., 2009], anorectal defects [Hayes and Wilson, 1986; Cashmore and Ladlow, 2010], and XX DSD (below).

Cryptorchidism
Cryptorchidism can be associated with other DSD in cats or dogs, but particularly in dogs, it is usually reported as an isolated defect. The discussion below is limited to isolated cryptorchidism, in which XY males are phenotypically male, with the only exception being that 1 or both testes are undescended. The undescended testis may be located anywhere along the testis descent pathway, from the caudal pole of the kidney to the inguinal canal, or external to the canal but cranial to the scrotum [reviewed in Meyers-Wallen, 2009]. Thus, cryptorchidism is a term encompassing several phenotypic categories, likely reflecting a genetically complex control of testis descent.

As scrotal testes are not easily palpable in young kittens, the diagnosis of cryptorchidism is usually made in young males presented for neutering before 1 year of age. Feline cryptorchidism has been infrequently reported, and appears to be uncommon. In 1 hospital survey of 1,345 male cats admitted for neutering in a 10-year period, only 1.7% were cryptorchid [Millis et al., 1992]. In another study over 4.5 years, 1.3% of male cats presented were cryptorchid [Yates et al., 2003]. In both studies, most affected cats were unilateral cryptorchid. The prevalence in Persian cats was significantly greater than in other breeds [Millis et al., 1992]. The molecular etiology of feline cryptorchidism is unknown.

Canine testes are undescended at birth. At the end of gestation, the testis lies on the peritoneal side of the internal inguinal ring, but passes through the inguinal canal within 10 days after birth [Gier and Marion, 1969]. However, it is unclear when the canine testis becomes secured to the scrotum [reviewed in Meyers-Wallen, 2009]. Clini-
The diagnosis of canine cryptorchidism is warranted if the testes are undescended by 6–8 weeks of age, when pups are routinely examined for first vaccinations. In contrast to the cat, canine cryptorchidism is prevalent, ranging from 6.8% of males presented for neutering [Yates et al., 2003] to 1.4% of dogs at 6–12 months of age [Hayes et al., 1985]. It is also more prevalent in some breeds [Reif et al., 1979; Hayes et al., 1985; Yates et al., 2003]. In 1 study, inguinal cryptorchid testes were most common [Yates et al., 2003].

As in humans, late testis descent has been identified in dogs. In 1 study of cryptorchid dogs examined regularly until 1 year of age, late descent occurred in 24.6% of cryptorchid testes, with 63.3% of those being unilaterally cryptorchid [reviewed in Meyers-Wallen, 2009]. However, most that descended did so by 14 weeks of age and none descended after 6 months of age. In humans, late testis descent has been associated with heterozygous null insulin-like 3 (INSL3) mutations [Tomboc et al., 2000], but this has not been reported in dogs. An increased risk of neoplasia in undescended testes is well documented, estimated as 12.7/1,000 dog-years at risk [Reif et al., 1979; Hayes et al., 1985]. To prevent neoplasia and reduce the frequency of cryptorchidism in purebred dogs, affected dogs are usually neutered.

The molecular basis for the various types of canine cryptorchidism is unknown, but is likely to be polygenic and genetically heterogeneous between breeds. The genetic etiology of canine cryptorchidism is now being pursued with genome wide association studies [Zhao et al., 2010] and candidate gene studies [Arrighi et al., 2010]. In breeds where cryptorchidism has been associated with other DSD, such as PMDS in the miniature schnauzer...

Fig. 8. XY DSD, perineal hypospadias. External genitalia of a an affected and b a normal male cat, each in standing position with a catheter placed in the urethra. a The scrotum is bisected due to failure of closure of the prepuce and penile urethra, causing severe hypospadias. The urethra is open along the entire dorsal aspect, and the urethral orifice is directly ventral to the anus (photo courtesy of Peter Jezyk). b The normal cat scrotum is fused along the midline and lies dorsal to the penis and ventral to the anus. Hair surrounding the scrotum and prepuce is darkly pigmented in this cat. c Affected cat, representative testis histology in which all stages of spermatogenesis were identified.

Fig. 9. XY DSD, perineal hypospadias. The external genitalia of a mixed breed terrier dog, shown from the ventral aspect. The urethra and prepuce are open along the entire ventral aspect. The scrotum is bisected and the urinary orifice is located directly ventral to the anus. The penile shaft is diverted caudally (reprinted with permission from Journal of the American Animal Hospital Association: Ader and Hobson [1978]).
(above), affected dogs can be screened for those mutations to obtain a definitive diagnosis. As the mechanisms of testis descent are likely conserved in mammals, studies in canine models could be beneficial, increasing our knowledge of the genetic control of testis descent and hastening discovery of the causative mutations for cryptorchidism in humans and domestic animals.

**XX DSD**

**Ovotesticular DSD and Testicular DSD**

Several cases of canine XX sex reversal have been reported, with varying degrees of diagnostic certainty [reviewed in Meyers-Wallen and Patterson, 1986], but none has been reported in cats. After confirmation that the trait was inherited in the American Cocker Spaniel (ACS; Selden et al. [1978]), a research colony was subsequently established from that breed. Early studies in this pedigree documented that all affected dogs were 78,XX and had either bilateral testes (testicular DSD, XX male) or ovotestes (ovotesticular DSD, XX true hermaphrodite), and variable external phenotypes [Meyers-Wallen and Patterson, 1988]. Subsequent studies confirmed that affected dogs were SRY-negative, ruling out translocation as the cause [Meyers-Wallen et al., 1999].

Within the ACS research pedigree, approximately 10% of affected dogs had bilateral testes (XX males). Internally, these dogs had Wolffian duct derivatives and a complete uterus, but no oviducts [Meyers-Wallen and Patterson, 1988]. Deferent ducts were often identified in the lateral walls of the uterine horns. Externally, XX males were most frequently bilaterally cryptorchid, and had a caudally displaced penis and prepuce with mild hypospadias (fig. 10). The remainder of affected dogs (90%) usually had bilateral ovotestes, occasionally had an ovary and ovotestis, and rarely a testis paired with an ovotestis (XX true hermaphrodites; Meyers-Wallen and Patterson [1988]). Internally, an epididymis or oviduct, or both, were adjacent to ovotestes. A complete uterus was present. Externally, 15% had a prepuce-like vulva and 15% had an enlarged clitoris containing a bone (fig. 11). The remaining 70% of XX true hermaphrodites had an apparently normal vulva. However, a narrowed caudal vaginal lumen can be present in such dogs. Overall, the degree of phenotypic masculinization was correlated to the proportion of testis in each individual. Biologically active MIS was identified in neonatal testes and ovotestes from affected dogs [Meyers-Wallen et al., 1987]. Notably, the timing of MIS secretion in fetal gonads, as well as the amount of MIS secretion, was delayed [Meyers-Wallen et al., 1994]. This suggests a mechanism for regression of the cranial Müllerian ducts but persistence of the uterus.

Early breeding experiments in the ACS research model indicated the mode of inheritance was compatible with sex-limited autosomal recessive inheritance [Meyers-Wallen and Patterson, 1988]. Further histologic, cytogenetic and breeding studies in the ACS research pedigree indicated that most affected dogs were sterile. However, estrous cycles have occurred in affected true hermaphro-
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Androgen Excess

**Fetal Origin**

Only 1 case of adrenal enzyme deficiency (11-beta hydroxylase deficiency) has been identified in the cat, and none has been reported in the dog. The affected domestic shorthaired cat had normal male external genitalia when examined at 6 months of age except that it appeared to be bilaterally cryptorchid [Knighton, 2004]. A DSD was suspected because the cat had a calico hair coat. As discussed above (XXY, sex chromosome DSD) the feline orange coat color locus is X-linked, therefore males should have either orange or black hair, not both. Normal female internal genitalia were identified and removed during laparotomy. Histology confirmed the presence of Wolffian duct derivatives (epididymides and deferent ducts) as well as ovaries, oviducts and a complete bicornuate uterus. The karyotype was that of a normal female (38,XX). At 10 months of age, the cat was exhibiting polydipsia, polyuria, and male urinary marking behavior. Penile spines were present, which in the cat, are dependent upon sustained androgen stimulation [Aronson and Cooper, 1967]. Resting serum testosterone concentrations were within the normal range for a male cat. High resting serum ACTH concentrations and
low serum cortisol concentrations after ACTH stimulation suggested adrenal enzyme deficiency. Elevated serum progesterone, 17-hydroxyprogesterone, androstenedione, testosterone, deoxycorticosterone and 11-deoxycorticosterone concentrations indicated that a defect in 11-beta hydroxylase activity was likely. Subsequent to maintenance prednisone therapy, serum testosterone concentrations decreased and clinical signs ceased.

**Maternal Origin**

These disorders have not been reported in the cat; however, there are several reports in which canine female fetuses were masculinized by androgens or progesterone preparations administered to the dam during pregnancy. In veterinary practice, androgens have been used to suppress canine estrus. Mibolerone was licensed and marketed for this purpose for several years. In research trials where mibolerone was administered during gestation, the external genitalia of female offspring were masculinized [Sokolowski and Kasson, 1978]. Similar results have been observed in clinical practice [Medleau et al., 1983]. Testosterone has been used for estrus suppression in racing greyhounds, often over long periods. When administered during gestation in clinical practice, female offspring developed a prepuce [Olson et al., 1989]. Progestagens induce similar androgen effects in the canine fetus [Curtis and Grant, 1964].

**Other**

**Müllerian Agenesis/Hypoplasia**

In the human syndrome of MURCS (OMIM#601076), Müllerian duct aplasia/hypoplasia is highly associated with renal agenesis and/or ectopy, and cervicothoracic somite dysplasia, such that if one component is identified, the other anomalies should be investigated. Two case reports suggest that a similar syndrome may occur in cats, although cervicothoracic abnormalities were not reported. The diagnosis in both cats was segmental aplasia of the

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**Table 2. Canine breeds in which testicular or ovotesticular XX DSD has been identified**

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<tr>
<td>American pit bull terrier</td>
<td>Meyers-Wallen et al., 1999</td>
</tr>
<tr>
<td>American Staffordshire terrier</td>
<td>Meyers-Wallen, unpublished; Nowacka et al., 2005</td>
</tr>
<tr>
<td>Australian shepherd</td>
<td>Meyers-Wallen, unpublished</td>
</tr>
<tr>
<td>Basset hound</td>
<td>Hubler et al., 1999</td>
</tr>
<tr>
<td>Bernese mountain dog</td>
<td>Switonski et al., 2011</td>
</tr>
<tr>
<td>Beagle</td>
<td>Williams et al., 1997</td>
</tr>
<tr>
<td>Border collie</td>
<td>Meyers-Wallen et al., 1999</td>
</tr>
<tr>
<td>Brussels griffon</td>
<td>Meyers-Wallen, unpublished; Poth et al., 2010</td>
</tr>
<tr>
<td>Doberman pinscher</td>
<td>Meyers-Wallen et al., 1999</td>
</tr>
<tr>
<td>English cocker spaniel</td>
<td>Meyers-Wallen et al., 1999</td>
</tr>
<tr>
<td>French bulldog</td>
<td>Meyers-Wallen, unpublished; Campos et al., 2011</td>
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<tr>
<td>German pinscher</td>
<td>Meyers-Wallen, unpublished</td>
</tr>
<tr>
<td>German shepherd dog</td>
<td>Switonski et al., 2004</td>
</tr>
<tr>
<td>German shorthaired pointer</td>
<td>Meyers-Wallen et al., 1995b</td>
</tr>
<tr>
<td>Golden retriever</td>
<td>Meyers-Wallen, unpublished</td>
</tr>
<tr>
<td>Jack Russell terrier</td>
<td>Kuiper et al., 2005</td>
</tr>
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<td>Kerry blue terrier</td>
<td>Williamson, 1979</td>
</tr>
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<td>Mixed breed</td>
<td>DeLorenzi et al., 2008</td>
</tr>
<tr>
<td>Norwegian elkhound</td>
<td>Melniczek et al., 1999</td>
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<td>Podenco dog</td>
<td>Buijtels et al., 2009</td>
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<td>Pug</td>
<td>Stewart et al., 1972; Meyers-Wallen et al., 1999; Rota et al., 2010</td>
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<td>Soft coated wheaten terrier</td>
<td>Meyers-Wallen et al., 1999</td>
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<td>Tibetan terrier</td>
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<td>Walker hound</td>
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<td>Meyers-Wallen et al., 1999</td>
</tr>
<tr>
<td>Wheaten terrier</td>
<td>Meyers-Wallen, unpublished</td>
</tr>
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uterine horn with ipsilateral renal agenesis (domestic shorthaired cat, Chang et al. [2008]; Persian cat, Goo et al. [2009]). Furthermore, in a hospital survey of 53,258 cats and 32,660 dogs undergoing elective ovariohysterectomy, congenital uterine abnormalities were identified in 0.09% of female cats and 0.05% of female dogs [McIntyre et al., 2010]. These abnormalities included unicornuate uterus, segmental aplasia of 1 uterine horn and uterine horn hypoplasia. In 29.4% of cats and 50% of dogs with uterine abnormalities in which the kidneys were also evaluated, ipsilateral renal agenesis was present [McIntyre et al., 2010]. These findings suggest that further careful evaluation of such cases could establish feline and canine models of Müllerian agenesis/hypoplasia or MURCS.

Vaginal Atresia

Only 1 study of feline vaginal atresia has been reported [Nomura et al., 1997]. The cranial and caudal vagina were separated by connective tissue, suggesting failure of canalization between the Müllerian duct and urogenital sinus. No canine reports were identified.

Summary and Conclusions

Several types of DSD have been reported in the cat and dog, which are often strikingly similar to those in humans. In addition, cats and dogs share their owners’ environments and can act as sentinels for environmental influences on sexual development. Unfortunately, feline and canine models have been infrequently utilized to contribute to our knowledge of mammalian sexual development. Greater awareness on the part of veterinary clinicians and researchers can lead to better diagnostic tests and establishment of new models for further study. Since genome sequence is now available for both species, and methods to analyze these genomes are rapidly improving, it is possible to pursue the molecular etiology of feline and canine disorders. To efficiently utilize these unique resources as molecular tools continue to improve, it would be helpful to deposit genomic DNA and/or relevant tissue samples from confirmed cases into a repository where they are available to the research community. For example, the Cornell University College of Veterinary Medicine has established a DNA Bank and Biobank for this purpose (Castelhano et al. [2009]; www.vet.cornell.edu/research/DNABank/). Such a system facilitates collaboration between clinicians and researchers, allowing valuable case material to contribute to our understanding of sexual development long after the case has been reported. This could hasten progress in developing molecular diagnostic tests for humans and animals. The direct benefit to animals is the development of practical tests that can be used to reduce the number of affected cats and dogs produced, particularly in purebred populations.

Acknowledgements

We thank the many breeders and owners who have donated samples to further research in feline and canine DSD. Animal experimentation in original works by this author cited in this article was conducted in accordance with the guidelines established by the National Institutes of Health and were approved by the Institutional Animal Care and Use Committee at Cornell University. Original work cited in this article was supported in part by the National Institutes of Health (Grant No. HD19393 and HD40351 to V.N.M.-W.).


Sex Abnormalities of Dogs and Cats

Sex Dev 2012;6:46–60


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