



DISORDERS OF SEXUAL DEVELOPMENT IN THE CAT

Current state of knowledge and diagnostic approach

Robert A Foster

Phasing in of current terminology

A disorder of sexual development (DSD) in human medicine is any abnormality, anomaly, ambiguity or lesion that occurs because of a failure of development of the female or male reproductive systems. This terminology replaces the terms intersex, hermaphrodite, pseudohermaphrodite and sex reversal,^{1–4} and is increasingly being used in veterinary medicine and science.

Disorders of sexual development vary from major anomalies that affect fertility or clinical wellbeing to incidental and minor changes to structures.

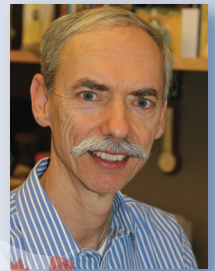
The original purpose of the DSD terminology in humans was to ensure consistency and to avoid the stigma of genital ambiguity and gender assignment in babies born with disorders of the external reproductive system. The classification allowed for all abnormalities of the reproductive tract to be categorized and defined in full. In this review, the broader approach is used to include all disorders, not just external sexual phenotypic ambiguity. Thus DSDs vary from major anomalies that affect fertility or clinical wellbeing to incidental and minor changes to structures.

'Intersex' conditions were always defined by sex chromosome type and arrangement, gonadal type and phenotype; this continues. In clinical veterinary medicine and science, access to sex chromosome analysis and gene identification is limited to research settings, so syndromes are often defined by gonadal and phenotypic sex only. The stigma and gender issues of humans are not a factor in cats.

SERIES OUTLINE
This article forms part of a series of evidence-based reviews on feline reproduction and reproductive problems, written by key opinion leaders. An outline of the series is included at: bit.ly/JFMSreproduction

Robert A Foster
BVSc, PhD, MANZCVS, DACVP
Department of Pathobiology,
Ontario Veterinary College,
University of Guelph,
Guelph, Ontario, N1G 2W1, Canada

Email: rfoster@uoguelph.ca



Practical relevance: Any congenital or developmental abnormality of any part of the male or female reproductive tract is a 'disorder of sexual development' (DSD). The tricolored male cat phenotype, cryptorchidism, gonadal hypoplasia and incidental abnormalities such as cystic remnants or embryonic ducts are well-known feline DSDs.

Clinical challenges: Full characterization of DSDs requires sex chromosome determination and identification of genes related to development of the gonads, internal tubular genitalia and external genitalia. Fortunately, affected cats are seen sporadically and the clinical effects are usually minimal.

Classification: The classification nomenclature has changed. In place of intersex, hermaphrodite, pseudohermaphrodite and sex reversal, the newer standard classification, based on sex chromosomes, designates sex chromosome DSD when there is an abnormality in the sex chromosomes, and XX (female) and XY (male) DSDs where there is not. Identification of the gonadal type (testes, ovaries, ovotestes or gonadal dysgenesis) and documentation of the internal and external genital components completes the classification.

Evidence base: The original basis of the DSD classification was a consensus reached in humans. It was quickly accepted in veterinary pathology, courtesy of its logic and ease of application, and it has subsequently begun to appear in peer-reviewed papers and clinical reviews. This article reviewing the various disorders in cats is based on application of the classification and draws on the feline peer-reviewed literature encompassing chromosome analysis and definition of reproductive abnormalities, syndromes and diseases.

Keywords: Disorder; sexual; development; intersex; ambiguity; anomalies

Summary box 1

Common clinical signs and lesions of disorders of sexual development (DSDs)

- ❖ Tricolored male cat
- ❖ Hypospadias
- ❖ Ambiguous external genitalia
- ❖ Female external genitalia but internal testes
- ❖ Anorchia, monorchia, cryptorchidism, testicular aplasia and hypoplasia
- ❖ Ovarian/periovarian cysts or cysts near the uterus
- ❖ Segmental absence of the uterus

Many of these clinical signs and lesions occur with different DSD classifications (see summary box 2). Note that ovarian hypoplasia or aplasia is also briefly discussed in the text, but is a very rare finding

Terms such as sex reversal, male feminization and persistent Müllerian duct syndrome are now only used in veterinary medicine and science when referring to historically defined clinical syndromes and will eventually be phased out.

The classification of DSDs into sex chromosomal, gonadal and phenotypic categories is now specific, accurate and more descriptive. It avoids the variation in the definitions of what constitutes intersex, hermaphroditism and pseudohermaphroditism. The classification begins with identifying the sex chromosomes and their make-up, such as XX, XY, X, or XXY. There are many different genes and gene products involved in normal sexual development in both males and females. *SRY* is the gene that is the sex-determining region of the Y chromosome which results in the development of a male, and *R-spondin1* (*RSPO1*) is an early gene in the development of a female. The convention in the scientific literature and adopted in this review is to use italics and uppercase for the gene with a human homologue; upper case and no italics is used for the protein product. *SRY* is the protein product of *SRY* and *RSPO1* is the product of *RSPO1*. Many publications now include the presence or absence of *SRY* in the classification, and eventually *RSPO1* could be a routine contributor to the classification.

The identification of individual disorders (summary box 1) does not usually allow the exact classification to be determined (summary box 2). A single individual disorder may occur with multiple classifications; for example, testicular hypoplasia is seen variously in cases of sex chromosome, XX and XY DSDs.

As yet, no veterinary diagnostic laboratory provides chromosomal analysis or gene

and/or protein identification for sexual development. When the various genes and protein products are identified and molecular tests become available, the classification system will expand to incorporate the genomics of sexual development.

There are many reviews, textbook chapters and conference proceedings devoted to feline DSDs.⁵⁻⁹ This article reviews the current state of knowledge and outlines a diagnostic approach when disorders are identified clinically either based on external genital development or changes observed at ovariohysterectomy or castration (see summary box 1).

Clinical signs and lesions of disorders of sexual development (DSDs)

The pathogenesis of any disease has three major components: 1) cause, 2) mechanisms and 3) lesions and/or clinical findings. A clinician identifies clinical findings and/or lesions of DSDs by evaluating the external genitalia during a physical examination, and the gonads and other components of the internal genitalia at neutering. To fully characterize a DSD, chromosomal and genomic information is required. The lack of access to such tests greatly restricts this part and thus this review will not include all of the differentiation genes that are known in cats. Gonadal and phenotypic components, including internal tubular genitalia, can be defined, however. This requires careful histopathological evaluation (and sometimes the expertise of a dedicated reproductive pathologist).

Summary box 2

Classification of disorders of sexual development (DSDs)

Sex chromosome DSDs

- ❖ Aneuploidy (monosomy, X₁; trisomy, XXY)
- ❖ Polyploidy (XX/XY)
- ❖ Mosaicism
- ❖ Chimerism

XX DSDs

- ❖ XX ovarian DSD
- ❖ XX testicular DSD
- ❖ XX ovotesticular DSD
- ❖ XX gonadal dysgenesis DSD

XY DSDs

- ❖ XY testicular DSD
- ❖ XY ovotesticular DSD
- ❖ XY ovarian DSD
- ❖ XY gonadal dysgenesis DSD

Fortunately, cats affected with DSDs are seen sporadically and the clinical effects are usually minimal (compared, say, with psychological effects in humans). Curiosity is often the major reason for attempting to fully define a disorder. The following discussion attempts to work backwards from the lesion or clinical findings to try to identify the underlying DSD. As with many diseases, there is a disconnect between what is seen clinically and the eventual classification or specific cause. Where there are direct correlations between the lesion or observation and the mechanisms and causes, these will be highlighted. A summary of the normal embryonic structures, their origin and the adult counterparts is provided in Table 1 for reference.

Tricolored male cat

Any male cat with three colors in the haircoat must have at least two X chromosomes; thus almost all have a sex chromosome DSD. The majority will have XXY trisomy, or will be a mosaic or chimera (see later discussion of 'Sex chromosome disorders of sexual development' for definitions). Some have other polypoidy. Their gonads can be testes or ovotestes and are usually hypoplastic. The external genitalia can be male, ambiguous with male and female components, and/or hypospadias may be present. Cryptorchidism is also common. These cats are rarely fertile.

Hypospadias

Cats with hypospadias have an opening of the urethra on the ventral surface of the penis. They typically also have a bifid scrotum – a divided scrotal sac, with the penis and its ventral opening between the scrota (Figure 1). Most cats with hypospadias have a sex chromosome DSD.

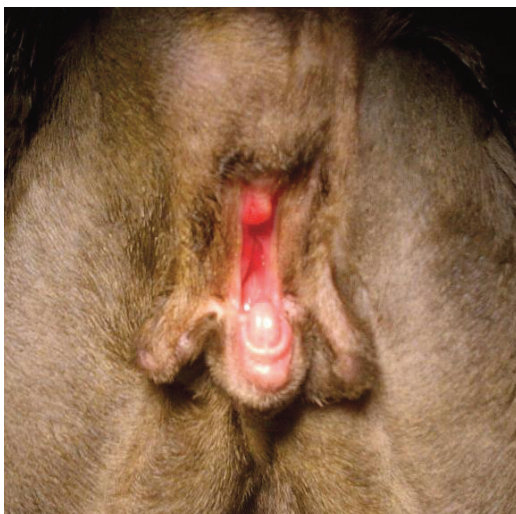


Figure 1 Cat with hypospadias and ambiguous genitalia. Courtesy of Jonathan Mitelman

Table 1 Normal embryonic structures, their origin, adult counterparts, and controlling gene and hormone			
Embryonic structure	Origin	Male genital structure	Female genital structure
Gonad	Retroperitoneal mesenchyme, peritoneal mesothelium, primitive adrenal tissue	Testis (<i>SRY</i>)	Ovary (<i>RSPO1</i>)
Mesonephric tubule	Mesonephros (transient second kidney)	Rete testis	Rete ovarii
Paramesonephric duct	Retroperitoneal mesenchyme, peritoneal mesothelium	* (anti-Müllerian hormone [Müllerian inhibitory substance])	Uterine tube Uterus Cervix Cranial vagina (<i>WNT4</i>)
Mesonephric duct	Retroperitoneal mesenchyme, peritoneal mesothelium	Epididymis Deferent duct Vesicular gland (<i>SRY</i> , <i>WNT4</i>)	*
Urogenital sinus	Peroneal tissues	Bulbourethral gland Penis Prepuce Scrotum (androgens and <i>INSL3</i>)	Caudal vagina Vestibule Vulva

Asterisk indicates regression
Genes and factors involved in sex determination are in parentheses. *SRY* inhibits female sexual development at multiple sites

Fortunately, cats with DSDs are seen sporadically and the clinical effects are usually minimal.



Ambiguous external genitalia

A cat with ambiguous external genitalia including penis and vulva could have a sex chromosome DSD or, less commonly, an XX (female) chromosome or XY (male) chromosome DSD.

Female external genitalia but internal testes

Most cats with a female phenotype including female genitalia, but with internal testes or ovotestes, are classified as having an XY testicular DSD. There is no testosterone production and no androgen receptor.

Anorchia, monorchia, cryptorchidism, testicular aplasia and hypoplasia

Anorchia, monorchia and cryptorchidism are terms that mean no testes, one testis or hidden testes, respectively. Cryptorchidism is the most common reproductive disease in the male cat; it is an XY chromosomal DSD. The terms anorchia and monorchia are often used incorrectly in clinical veterinary practice, and may convey a misleading message to clients. The hidden testis (or testes) or their remains are almost always found outside of the scrotum and either in the inguinal canal or within the abdomen. A specific diagnosis to indicate the cause, made after careful histological examination, is agenesis (testes did not begin development), aplasia (did not grow), extreme hypoplasia (too small to identify at surgery) or post-necrotic atrophy (testis became necrotic and scarred). Affected cats commonly have an XY testicular DSD.

Failure to find one or both testes in the scrotum presents a clinical challenge. If the results of hormone testing or the presence of penile spines indicate functional testicular tissue, the first condition to exclude is cryptorchidism. Surgery to remove the retained structure will hopefully reveal a testis and epididymis (Figure 2); this can usually be confirmed by histological examination. The main possibilities if a testis is absent from the scrotum are:

- ❖ Previous surgical removal
- ❖ Previous testicular necrosis
- ❖ Testicular agenesis, aplasia or extreme hypoplasia

Should there be testicular hypoplasia or aplasia, and an epididymis present in a cat that is not tricolored, this probably represents an XY testicular DSD.

Ovarian hypoplasia or aplasia

Female cats lacking an ovary or ovaries, or with ovaries that are smaller than normal, are a very rare finding and not fully described in the literature. Most are classified as having XX gonadal dysgenesis or an XX ovarian DSD; gonadal dysgenesis is where the gonad is too primitive to determine its type.

Ovarian/periovarian cysts or cysts near the uterus

There are a variety of retained embryonic ducts or tubules, and these may expand and develop into cysts within or near the ovary or uterus. Cysts are derived from either the paramesonephric (future female) or mesonephric (future male) ducts. These form from an embryonic duct that is an invagination of the celom, or the mesonephric (male) tubules that derive from the mesonephros. Such cysts are often an incidental finding and this is an XX ovarian DSD.

A retained, undescended or 'hidden' testis is the most common abnormality of the feline male reproductive tract.

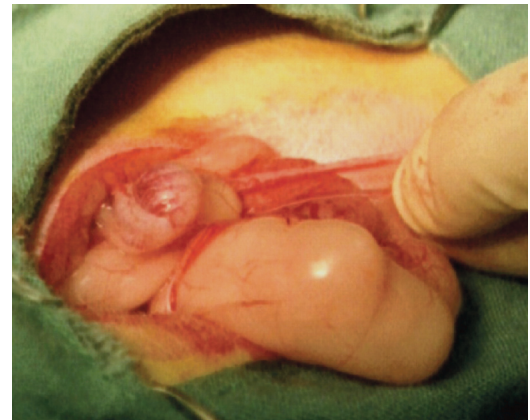


Figure 2 In cats with abdominal cryptorchidism, the retained testis is often found near the bladder.⁶ Courtesy of Susan Little

Segmental absence of the uterus

Phenotypically female cats with a partial absence of the uterus, diagnosed as segmental aplasia, are classified as having an XX ovarian DSD (Figure 3).

Classification of disorders of sexual development (DSDs)

The classification of DSDs begins with the sex chromosome composition. A normal cat has 38 chromosomes per cell; these 38 represent 19 matching pairs, 19 from each parent. A cell with 38 normal chromosomes is 'diploid'. Those cats with an abnormal composition of sex chromosomes have a sex chromosome DSD. Gonadal type is not part of the sex chromosome DSD classification.

Those animals with a congenital abnormality of the reproductive system and with a normal XX (female) or XY (male) chromosome complement have an XX DSD or XY DSD, respectively. Testing for *SRY* is most commonly reported in the literature; so, if available, the *SRY* status is included. Accordingly, there are XX *SRY*-positive, XX *SRY*-negative, XY *SRY*-positive and XY *SRY*-negative DSDs.

The next part of the classification concerns gonadal type. The main possibilities are testes, ovaries, ovotestes and gonadal dysgenesis. This determination is established histologically and accurate classification may require the input of a reproductive pathologist (see summary box 2).

As alluded to earlier, the sex chromosome composition and/or gonadal type cannot always be predicted by the clinical signs or

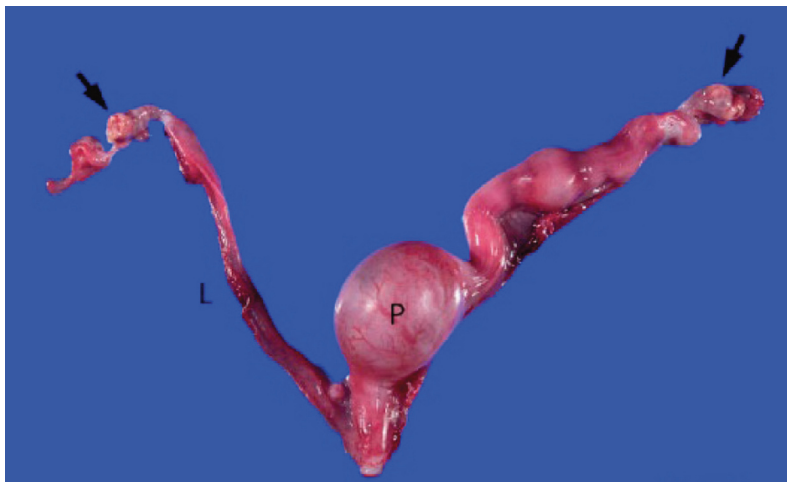


Figure 3 Reproductive tract of a cat with segmental aplasia of a uterine horn. Although one uterine horn may be hypoplastic or missing, the ipsilateral ovary is almost always present.⁶ In this case, the left uterine horn (L) is replaced by a solid cord of smooth muscle and vascularised loose connective tissue. Arrows denote corpora lutea within the ovaries. One site of placentation is prominent (P). Reproduced, with permission, from Brookshire et al (2017)¹⁰

The most well-known feline sex chromosomal disorder is the tortoiseshell/tricolor/calico male cat.



lesions. Similar clinical findings can occur with a variety of chromosome and gonadal types. Thus the information in summary boxes 1 and 2 may not always align with the actual lesions or changes present.

Sex chromosome disorders of sexual development

There are many sex chromosomal disorders identified in cats (see summary box 1) and the most studied and well known is the tortoiseshell/tricolor/calico male cat with DSD. Because the locus responsible for orange (or red) coat color (*O/o* locus) is located on the X chromosome, normal male cats (XY *SRY*-positive) can be either orange or not orange. A male cat with a tricolored coat almost certainly has two X chromosomes and an *SRY*; most are XXY.

There are many case reports of cats with sex chromosome abnormalities. The seminal paper – focusing on male tortoiseshell and calico cats – was published by Centerwall and Benirschke almost 50 years ago.⁵ Cats with abnormal numbers or arrangements of sex chromosomes are variously aneuploid, polyploid, mosaics or chimeras.

❖ **Aneuploidy** refers to an abnormal number of chromosomes. Aneuploid cats typically have one X chromosome only, thus have monosomy (analogous to Turner syndrome in humans),^{11,12} or alternatively XXY trisomy (analogous to Klinefelter syndrome in humans).^{5,13–18} Animals with X monosomy have ambiguous genitalia. Cats with XXY trisomy are usually tricolor males that often have cryptorchidism and/or testicular hypoplasia.

❖ **Polyploidy** describes two paired sets of the same chromosomes. This includes cats that are XXXY.^{5,14,16} These cats are usually male tricolored and many have testicular hypoplasia.

❖ **Mosaicism** is when there are two or more genetically different sets of cells, and 38,XX and 38,XY is the usual type.⁵ Other combinations include X/XY,¹⁹ XY/XXY and X/XX/XY/XXY.⁵ Cats are usually tricolor male with cryptorchidism and persistent paramesonephric ducts (uterus).

❖ **Chimerism** is when there are chromosomes from different individuals in one individual, with chromosomes being acquired from two zygotes. Feline chimeras are typically 38,XY/38,XY.^{5,18,20} They are usually tricolor male cats.

It is easy to miss the ovarian component of an ovotestis.



XX disorders of sexual development

Cats with an XX DSD can have ovaries, testes, ovotestes or gonadal dysgenesis. These disorders are categorized as XX ovarian, XX testicular, XX ovotesticular or XX gonadal dysgenesis DSDs, respectively. It is easy to miss the ovarian component of an ovotestis and reproductive pathologists make a concerted effort to identify ovarian tissue, especially if a DSD is suspected. Among XX DSDs, the most common are XX ovarian DSDs, and the lesions are aplasia, hypoplasia, segmental aplasia, embryonic duct and tubule remnants and duplications.

XX ovarian DSD and female phenotype

Cats with a normal diploid chromosomal complement and normal ovaries can have a wide variety of congenital abnormalities of their reproductive system. Some examples are described below.

❖ **Cystic rete ovarii** develop when the rete ovarii, primitive tubules derived from the remnants of mesonephric (future male) tubules of the early embryo, and which are located in the hilus of the ovary, become distended with fluid. The result is an ovary expanded by one or more cysts.²¹ Rete cysts, which are thin-walled epithelial structures that displace ovarian tissue peripherally, can be up to 2.5 cm in diameter.²²

❖ **Mesonephric tubule cysts** are incidental findings. Mesonephric tubules arise close to the ovary from the mesonephros (or transient second kidney; see Table 1) and give rise to cysts near the ovary, typically adjacent to the ovarian hilus and close to the rete ovarii.²²

❖ **Mesonephric and paramesonephric duct cysts** develop from remnants of these ducts. Paramesonephric (future female) and mesonephric (future male) ducts arise from division of a tube that develops on each side of the retroperitoneum. In normal females, the mesonephric duct regresses and disappears. In males, the paramesonephric duct regresses and disappears when anti-Müllerian hormone is produced by primitive sustentacular (Sertoli) cells in the embryonic testis. In females, remnants and their cysts of the mesonephric and paramesonephric ducts may occur along the pathway of the paramesonephric duct, which becomes the uterine tube, uterus and cranial portion of the vagina. Mesonephric duct remnants in the vagina, known in humans as Gartner's ducts, are reported in cats.²³

❖ **Paramesonephric duct cysts and uterine duplication** describes a structure or cyst with an endometrium that is found beside the uterine tube, uterus or cranial vagina. These structures and cysts are typically located at the mesometrial attachment of the uterus. Seldom is there complete uterine duplication.^{21,22} Just

like cysts of mesonephric tubules, these are usually incidental findings.

❖ **Segmental aplasia of the paramesonephric duct** is very common. A segment of the paramesonephric duct (future uterine tube, uterus or cranial vagina) fails to develop, the cause of which has not been established. The affected portion of the uterus is missing but the mesometrium remains. The missing portion is often one uterine horn (Figure 3),^{10,21,24–26} but there are reports of failure of the cervix and cranial vagina to form.^{21,27,28} Any remaining uterus cranial to the missing portion will be dilated and filled with fluid or inspissated contents.

XX ovarian DSD and male phenotype

Cats with an XX sex chromosome complement, ovaries and female tubular genitalia, but a male phenotype with a penis, prepuce and scrotum, are exceedingly rare.²⁹ They are only identified when laparotomy for removal of a cryptorchid testis results in the discovery of ovaries and female internal genitalia. The cause is deficiency of one of the enzymes responsible for cortisol formation, which leads to excessive testosterone production and congenital adrenal hyperplasia.

XX testicular DSD

For a cat to have an XX sex chromosome type and a testis and/or male tubular genitalia and evidence of male phenotype there must be an SRY gene or another gene that produces a product similar to SRY. There are two reports of phenotypic male cats, each with a penis and scrotum but with XX sex chromosomes. One was tricolored and XX SRY-negative (Figure 4),³⁰ and the other was XX and SRY-positive.¹²

XX ovotesticular DSD

XX ovotesticular DSD has not, to date, been reported in cats.

In clinical veterinary medicine, access to sex chromosome analysis and gene identification is limited to research settings, so syndromes are often defined by gonadal and phenotypic sex only.



XX gonadal dysgenesis DSD

Dysgenesis refers to altered development of the gonads, such that the structures are not identifiable as testis or ovary, yet there are gonadal components present (eg, sex cords, interstitial endocrine cells or stroma). Some of these structures are visible at surgery; others are not, but are microscopic. (Agenesis is when there is no development of any part of the gonad – this requires careful histological evaluation to confirm, and is so rare it is not given a separate category here.)

Cats with an XX chromosomal complement and no visible gonads on surgical exploration are exceedingly rare. Often reproductive pathologists are called upon to identify this abnormality, particularly when gonadal tissue appears either to be missing or minimal at ovariohysterectomy. Cats with these abnormalities are phenotypically normal females but have an immature uterus and vagina. They fail to cycle.

XY disorders of sexual development

Cats with an XY DSD can have testes, ovaries, ovotestes or gonadal dysgenesis. These disorders are categorized as XY testicular, XY ovarian, XY ovotesticular or XY gonadal dysgenesis DSDs, respectively. Just as for XX DSDs, it is easy to miss the ovarian component of an ovotestis and reproductive pathologists make a concerted effort to identify ovarian tissue, especially if a DSD is suspected. Among XY DSDs, the most common lesions are aplasia, hypoplasia, segmental aplasia, embryonic duct and tubule remnants and duplications.

XY testicular DSD

Normal tubular genitalia and normal scrotum ❖ **Congenital phimosis** and obstruction or partial obstruction of the preputial orifice or tip of the penis has been reported, and surgical correction described.³¹ In a prepubertal animal it may be difficult to determine whether phimosis, which is normal at this age due to the presence of the balanopreputial fold (see accompanying review on the tom in this series), is a congenital condition or if it will resolve as it typically does at puberty.

❖ **Diphallia** (a double penis) is a rare disorder and there is one report in a cat.¹⁶

❖ **Persistent penile frenulum** – retention of the attachment of the penis and prepuce – is a rarely reported disorder.¹⁶

❖ **Testicular hypoplasia and aplasia** (the latter referring to no testis present) can be challenging to distinguish, particularly in cases of extreme hypoplasia or even degeneration or necrosis. This requires a diligent search for any testicular tissue; to be thorough, all parts of the surgically removed tissue are examined



Figure 4 (a) Tortoiseshell cat documented as having an XX testicular (SRY-negative) DSD – the only such case reported to date. The cat had hypoplastic testes and a normal penis (b).³⁰ Images courtesy of Stefano Romagnoli

All retained testes are hypoplastic because internal temperatures are higher than in the scrotum. In extreme cases, there may be just a microscopic amount of testicular tissue.



histologically, preferably by a reproductive pathologist.

❖ **Testicular hypoplasia**, where the testis does not develop to its normal size at the expected time of puberty, is always accompanied by failure of the epididymis to acquire its normal size too. Most cases of hypoplasia are the result of cryptorchidism, but in the context of an XY testicular DSD, the testes have descended normally and thus hypoplasia is a primary condition.¹⁶ While hypoplasia is almost always observed as a failure of the prepubertal testis to enlarge to its normal size at puberty, there may be cases where even the prepubertal testis is smaller than normal.

Hypoplasia is best diagnosed clinically by identifying that the testis has not increased to its normal size at puberty. However, testicular size is seldom monitored in cats and so the presence of a small testis could indicate either hypoplasia (a potentially genetic or heritable condition – at least in other species) or atrophy (an acquired condition that results from degeneration of the seminiferous tubules).

Hypoplasia is variable in its degree. In production animals, testicular volume or scrotal circumference is measured and a certain size is deemed to be the minimum acceptable. Testes smaller than the minimum size at puberty usually have some degree of hypoplasia – in some, there are only mild changes but, in others, they are extreme. The literature suggests that many cats with testicular hypoplasia have chromosomal anomalies (see above discussion of ‘Sex chromosome disorders of sexual development’), so this must be excluded by sex chromosome analysis.

All retained testes are hypoplastic because internal temperatures are higher than in the scrotum. There is variation in the degree of hypoplasia in cryptorchid testes; at its extreme, there may be just a microscopic amount of testicular tissue present.

❖ **Spermatic granuloma of the epididymal head** is a rare XY DSD. Testicular fluid from the seminiferous tubules enters the tubules of the mediastinum testis, and then the rete testis, which becomes the efferent ductules. In turn, the efferent ductules, which are derived from the mesonephric tubules, connect to the single tube which is the epididymal duct (derived from the mesonephric duct). When one or more of the efferent ductules are blind-ending and do not connect with the epididymal duct, cystic dilation of efferent ductules, and sometimes

also the rete testes, occurs. This results in obstruction of outflow of rete testis fluid and an increase in pressure. Either cystic distension of the rete testis occurs or, after puberty, spermiostasis, spermatocele and then spermatic granulomas develop.^{22,23} These are all rare findings.

❖ **Aplasia and segmental aplasia of the mesonephric duct** refers to absence of part of the mesonephric duct, which gives rise to the epididymis and deferent duct. Usually the tail of the epididymis is missing. Reports in cats are scant: there is one documented case of a cat with a sex chromosome DSD that was XXY.¹⁵

❖ **Persistent paramesonephric ducts** describe failure of the paramesonephric (female) ducts to regress. These ducts, as discussed, give rise to the uterine tube, uterus and cranial vagina in females. This anomaly is the result of a deficiency in anti-Müllerian hormone or a lack of the hormone receptor. In dogs there is a well-recognized syndrome known as persistent Müllerian duct syndrome (named before the Müllerian duct was renamed the paramesonephric duct). An identical syndrome occurs in cats. The persistent paramesonephric (Müllerian) duct can be found parallel to the deferent duct and beside the epididymis. It is possible for pyometra to develop in these persistent paramesonephric ducts.³²

Normal tubular genitalia and external genitalia lacking scrotal testes

❖ **Cryptorchidism** (retained, undescended or ‘hidden’ testicle[s]) is the most common abnormality of the feline male reproductive tract.²⁵ In two studies cryptorchidism was reported to affect between 1.3 and 1.7% of male cats.^{33,34} In one of the studies,³³ there was no predisposition for abdominal vs inguinal cryptorchidism and, in the other, an increased likelihood of the inguinal form.³⁴ Left and right unilateral cryptorchidism occurred with equal prevalence. Most cases of cryptorchidism are in XY testicular males. Cryptorchidism is also a feature of sex chromosome DSDs.

Normally, the testes are within the scrotum at or soon after birth. Before puberty, the retained testis is identical to the descended testis in every way except for location. With the onset of puberty, there is no spermatogenesis in cryptorchid testes, so the histological appearance is identical to that of a prepubertal testis. In a postpubertal cat, cryptorchid testes are hypoplastic.

KEY POINTS

- ❖ Any congenital or developmental abnormality of any part of the male or female reproductive tract is a disorder of sexual development (DSD).
- ❖ Full characterization requires sex chromosome determination, identification of genes related to development of the gonads, and evaluation of both the internal tubular genitalia and external genitalia.
- ❖ The standard classification based on sex chromosomes is sex chromosome DSD when there is an abnormality in the sex chromosomes, and XX DSD and XY DSD when there is not.
- ❖ Identification of the gonadal type (testes, ovaries, ovotestes or gonadal dysgenesis) and listing of the internal and external genital components completes the classification.
- ❖ Cryptorchidism and incidental abnormalities such as cystic remnants of embryonic ducts are common DSDs.



Normal tubular genitalia and external genitalia, and an additional testis

❖ **Polyorchidism** (more than two testes) is reported only rarely in cats. There are single reports documenting three³⁵ and four³⁶ testes in individual cats. In both animals, the testes each had their own epididymis and deferent ducts that fused to form one duct.

Male or female tubular genitalia and hypospadias or ambiguous external genitalia

Male cats with hypospadias and/or a vulva and vagina are reported. (Previous terminology for those with a female phenotype and external genitalia was male feminization syndrome.) Many have a sex chromosome DSD. Some have normal male sex chromosomes³⁷ and, where examined, are also *SRY*-positive.^{38–42}

They may have a failure of expression of the androgen receptor.³⁹ The testes are usually cryptorchid or, if scrotal, are hypoplastic.⁴³

XY ovotesticular DSD

There is one report of a phenotypically male cat with penis and scrotum, and ovotestes in the location of the ovaries. This cat had both male and female tubular genitalia. It was 38,XY, *SRY*-positive.⁴⁴

XY ovarian DSD

This type of DSD is not well described in cats in the literature.

XY gonadal dysgenesis DSD

This type of DSD is not well described in cats in the literature.

Conflict of interest

The author declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author received no financial support for the research, authorship and/or publication of this article.

Ethical approval

This work did not involve the use of animals and therefore ethical approval was not specifically required for publication in *JFMS*.

Informed consent

This work did not involve the use of animals (including cadavers) and therefore informed consent was not required. No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

References

- 1 Houk CP, Hughes IA, Ahmed SF, et al; Writing Committee for the International Intersex Consensus Conference Participants. **Summary of consensus statement on intersex disorders and their management. International Intersex Consensus Conference.** *Pediatrics* 2006; 118: 753–757.
- 2 Lee PA, Houk CP, Ahmed SF, et al; International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. **Consensus statement on management of intersex disorders. International Consensus Conference on Intersex.** *Pediatrics* 2006; 118: e488–500.
- 3 Hughes IA. **Disorders of sex development: a new definition and classification.** *Best Pract Res Clin Endocrinol Metab* 2008; 22: 119–134.
- 4 Lee PA, Nordenström A, Houk CP, et al; Global DSD Update Consortium. **Global disorders of sex development update since 2006: perceptions, approach and care.** *Horm Res Paediatr* 2016; 85: 158–180.
- 5 Centerwall WR and Benirschke K. **Male tortoiseshell and calico (T-C) cats. Animal models of sex chromosome mosaics,**

- aneuploids, polyploids, and chimerics. *J Hered* 1973; 6: 272–278.
- 6 Little S. **Feline reproduction: problems and clinical challenges.** *J Feline Med Surg* 2011; 13: 508–515.
 - 7 Christensen BW. **Disorders of sexual development in dogs and cats.** *Vet Clin North Am Small Anim Pract* 2012; 42: 515–526.
 - 8 Meyers-Wallen VN. **Gonadal and sex differentiation abnormalities of dogs and cats.** *Sex Dev* 2012; 6: 46–60.
 - 9 Szczerbal I and Switonski M. **Genetic disorders of sex development in cats: an update.** *Anim Reprod Sci* 2020; 216. DOI: 10.1016/j.anireprosci.2020.106353.
 - 10 Brookshire WC, Shivley J, Woodruff K, et al. **Uterus unicornis and pregnancy in two feline littermates.** *JFMS Open Rep* 2017; 3. DOI: 10.1177/2055116917743614.
 - 11 Johnston SD, Buoen LC, Madl JE, et al. **X-chromosome monosomy (37,XO) in a Burmese cat with gonadal dysgenesis.** *J Am Vet Med Assoc* 1983; 182: 986–989.
 - 12 Szczerbal I, Stachowiak M, Dzimira S, et al. **The first case of 38,XX (SRY-positive) disorder of sex development in a cat.** *Mol Cytogenet* 2015; 8: 22. DOI: 10.1186/s13039-015-0128-5.
 - 13 Centerwall WR and Benirschke K. **An animal model for the XXY Klinefelter's syndrome in man: tortoiseshell and calico male cats.** *Am J Vet Res* 1975; 36: 1275–1280.
 - 14 Long SE, Gruffydd-Jones T and David M. **Male tortoiseshell cats: an examination of testicular histology and chromosome complement.** *Res Vet Sci* 1981; 30: 274–280.
 - 15 König H, Schärer V, Küpfer U, et al. **Testicular hypoplasia (lack of spermatogonia) and left-sided epididymal aplasia in a tricolored male cat with 39/XXY karyotype** [article in German]. *Dtsch Tierarztl Wochenschr* 1983; 90: 341–343.
 - 16 Axner E, Strom B, Linde-Forsberg C, et al. **Reproductive disorders in 10 domestic male cats.** *J Small Anim Pract* 1996; 37: 394–401.
 - 17 Pedersen AS, Berg LC, Almstrup K, et al. **A tortoiseshell male cat: chromosome analysis and histologic examination of the testis.** *Cytogenet Genome Res* 2014; 142: 107–111.
 - 18 Szczerbal I, Krzeminska P, Dzimira S, et al. **Disorders of sex development in cats with different complements of sex chromosomes.** *Reprod Domest Anim* 2018; 53: 1317–1322.
 - 19 Balogh O, Berger A, Pieńkowska-Schelling A, et al. **37,X/38,XY mosaicism in a cryptorchid Bengal cat with Müllerian duct remnants.** *Sex Dev* 2015; 9: 327–332.
 - 20 Bugno-Poniewierska M, Kij B, Witarski W, et al. **Fertile male tortoiseshell cat with true chimerism 38,XY/38,XY.** *Reprod Domest Anim* 2020; 55: 1139–1144.
 - 21 McEntee K. *Reproductive pathology of domestic mammals.* New York: Academic Press, 1990.
 - 22 Gelberg HB and McEntee K. **Cystic rete testis in a cat and fox.** *Vet Pathol* 1983; 20: 634–636.
 - 23 Shehata R. **Mesonephric remnants in the female genital system of the domestic cat. *Felis domestica*.** *Acta Anat (Basel)* 1974; 87: 301–310.
 - 24 Marcella KL, Ramirez M and Hammerslag KL. **Segmental aplasia of the uterine horn in a cat.** *J Am Vet Med Assoc* 1985; 186: 179–181.
 - 25 Memon M and Tibary A. **Canine and feline cryptorchidism.** In: Recent advances in small animal reproduction. Concannon PW, England G and Verstegen J (eds). International Veterinary Information Service (www.ivis.org).
 - 26 McIntyre RL, Levy JK, Roberts JF, et al. **Developmental uterine anomalies in cats and dogs undergoing elective ovariohysterectomy.** *J Am Vet Med Assoc* 2010, 237: 542–546.
 - 27 Batista-Arteaga M, Santana M, Espinosa-de-los-Monteros A, et al. **Exuberant mucometra associated with atresia of the cervix in a queen.** *Reprod Domest Anim* 2012, 47: e71–e74.
 - 28 Souther S, Baik NJ, Clapp K, et al. **A case of segmental aplasia of the uterus, cervix, and cranial vagina in a cat.** *Front Vet Sci* 2019; 6: 145. DOI: 10.3389/fvets.2019.00145.
 - 29 Bright SR and Mellanby RJ. **Congenital phimosis in a cat.** *J Feline Med Surg* 2004; 6: 367–370.
 - 30 De Lorenzi L, Banco B, Previdere C, et al. **Testicular XX (SRY-negative) disorder of sex development in cat.** *Sex Dev* 2017; 11: 210–216.
 - 31 Knighton EL. **Congenital adrenal hyperplasia secondary to 11beta-hydroxylase deficiency in a domestic cat.** *J Am Vet Med Assoc* 2004; 225: 238–241.
 - 32 Schulman J and Levine SH. **Pyometra involving uterus masculinus in a cat.** *J Am Vet Med Assoc* 1989; 194: 690–691.
 - 33 Millis DL, Hauptman JG and Johnson CA. **Cryptorchidism and monorchism in cats: 25 cases (1980–1989).** *J Am Vet Med Assoc* 1992; 200: 1128–1130.
 - 34 Yates D, Hayes G, Heffernan M, et al. **Incidence of cryptorchidism in dogs and cats.** *Vet Rec* 2003; 152: 502–504.
 - 35 Milwright RD and Smith KC. **Polyorchidism in a cat.** *Vet Rec* 1999; 145: 679–680.
 - 36 Roca-Ferrer J, Rodríguez E, Ramírez GA, et al. **A rare case of polyorchidism in a cat with four intra-abdominal testes.** *Reprod Domest Anim* 2015; 50: 172–176.
 - 37 King GJ and Johnson EH. **Hypospadias in a Himalayan cat.** *J Small Anim Pract* 2000; 41: 508–510.
 - 38 Bredal WP, Thoresen SI, Kvellestad A, et al. **Male pseudohermaphroditism in a cat.** *J Small Anim Pract* 1997; 38: 21–24.
 - 39 Hakala JE. **Reproductive tract anomalies in 2 male cats.** *Mod Vet Pract* 1984; 65: 629.
 - 40 Meyers-Wallen VN, Wilson JD, Griffin JE, et al. **Testicular feminization in a cat.** *J Am Vet Med Assoc* 1989; 195: 1456–1458.
 - 41 Vallefuooco R, Alleaume C, Jardel N, et al. **Type II atresia ani associated with rectovaginal fistula in a male pseudohermaphrodite kitten.** *Can Vet J* 2013; 54: 475–478.
 - 42 Nowacka-Woszuk J, Szczerbal I, Salamon S, et al. **Testicular disorder of sex development in four cats with a male karyotype (38,XY; SRY-positive).** *Anim Reprod Sci* 2014; 151: 42–48.
 - 43 Dzimira S, Nizanski W and Madej JA. **Morphological analysis of testicles in cats with disorders of sex development.** *Pol J Vet Sci* 2017; 20: 123–131.
 - 44 Schlafer DH, Valentine B, Fahnestock G, et al. **A case of SRY-positive 38,XY true hermaphroditism (XY sex reversal) in a cat.** *Vet Pathol* 2011; 48: 817–822.

Available online at jfms.com

Article reuse guidelines: sagepub.co.uk/journals-permissions

For reuse of images only, contact the author