Inherited Disorders in Sexual Development

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Normal Sexual Development

Normal mammalian sexual development depends on the successful completion of a series of steps that are under genetic control. For simplicity, this series is described in three key steps: establishment of chromosomal sex, gonadal sex, and phenotypic sex.

Chromosomal sex is normally determined at fertilization. The zygote has either an XX or an XY chromosome constitution that is maintained by mitosis in all cell types as the embryo develops. The early embryo is sexually indifferent in that the genital morphology is similar and the gonads are undifferentiated in XX and XY embryos.

Gonadal sex is determined by genetic sex, which normally corresponds to chromosomal sex. A testis-determining gene on the Y chromosome, Sry, encodes a protein that initiates testis differentiation (Koopman et al. 1991). Sox9, an autosomal gene, is involved in the testis differentiation pathway. Two normal Sox9 alleles are necessary for testis development in XY males having Sry (Foster et al. 1994). Sox9 expression in embryonic gonads is consistent with a role in Sertoli cell differentiation (Morais da Silva et al. 1996). Normal XX individuals, lacking the Sry gene, do not develop testes. The gonadal expression pattern of the X-linked Dax1 gene (Bardoni et al. 1994) is consistent with a role in ovarian differentiation, although it also has a role in adrenal, hypothalamic, and pituitary development (Swain et al. 1996). Of interest, other genes that are important in development of the indifferent gonads are also necessary for renal (WT1; Bruening et al. 1992) and adrenal development (SF1; Luo et al. 1994). Thus the study of abnormal gonadal differentiation is revealing developmental gene pathways that are shared by different organ systems.

Phenotypic sex is determined by the presence or absence of a testis, since gonadectomy of XX or XY embryos prior to gonadal differentiation results in development of a female phenotype (Jost et al. 1973). This led to the conclusions that ovarian hormones are not necessary for female embryonic differentiation, and the default phenotypic plan is female. Phenotypic masculinization depends on the presence of a testis and its hormonal secretions, which divert the phenotypic plan from female to male. Sertoli cells secrete Mullerian inhibiting substance (MIS), also known as anti-Mullerian hormone (Amh), which causes regression of the Mullerian duct system. Leydig cells secrete testosterone which promotes Wolffian duct differentiation (epididymis and vas deferens). In other target organs, testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5-alpha reductase. The prostate and external genitalia develop in response to DHT. The action of both androgens is mediated through binding to the intranuclear androgen receptor. Male external genitalia are completed by descent of the testes. However, the control of testicular descent is incompletely understood and may differ between species.

Inherited Disorders of Sexual Development

In this article, defects are classified according to the first step at which development differs from normal as errors in chromosomal sex, gonadal sex, or phenotypic sex (Table 1).

Abnormalities of Chromosomal Sex

The primary defect in these animals is an abnormality in the number or structure of the sex chromosomes, such as monosomy or trisomy. In general, these defects occur through random errors in meiosis or mitosis and may not be transmitted further.
than the single affected animal in the pedigree. The XXY syndrome (Klinefelter’s syndrome in humans) has been reported in several mammals. It is most often recognized in male cats that have a calico or tortoise-shell coat. Similarly, animals with XO and XXX chromosome constitutions, and chimeras and mosasics have also been described (reviewed in Meyers-Wallen 1993).

### Abnormalities of Gonadal Sex

In these disorders, the chromosomal and gonadal sex of the individual do not agree. Affected individuals are termed sex reversed. Animals with XY sex reversal fail to develop testes, and may have hypoplastic ovaries or streak gonads. Since a functional testis is absent, a female phenotype results, and these individuals are termed XY females. For example, XY sex-reversed horses are usually presented as mares that fail to cycle and are sterile. This is likely to be an inherited defect, but the etiologic mutation is unknown. Some human XY females have SRY mutations, but others have a normal SRY. There are at least two autosomal loci that have been linked to human XY sex reversal (Goodfellow and Lovell-Badge 1993).

Individuals with XX sex reversal have a normal female karyotype but develop varying amounts of testicular tissue. When both gonads are composed entirely of testis, they are termed XX males. More commonly, the gonads contain both ovarian and testicular tissue, and these are XX true hermaphrodites. It has been demonstrated that translocation of the SRY gene from the Y to the X chromosome is responsible for most human XX males. However, 20% of human XX males have neither the SRY gene nor any other Y chromosome sequence (Goodfellow and Lovell-Badge 1993). Sry-negative XX sex reversal syndromes in goats (Hamerton et al. 1969), pigs (Sittman et al. 1980), and purebred dogs (Meyers-Wallen and Patterson 1988; Meyers-Wallen et al. 1995a,b) are inherited as simple autosomal recessive traits. Isolated cases of XX sex reversal have been reported in the Pasa Fino horse (Meyers-Wallen et al. 1997) and the llama (Lopez et al. 1998; Wilker et al. 1994).

### Abnormalities of Phenotypic Sex

In disorders of this category, chromosomal and gonadal sex agree, but the internal or external genitalia are ambiguous to some degree. Affected individuals are either male or female pseudohermaphrodites.

Female pseudohermaphrodites are XX and have ovaries, but also exhibit androgen-dependent masculinization of the genitalia. There is frequently a history of an androgen or progestagen administration to the dam during gestation of the affected animal (reviewed in Meyers-Wallen 1993). Adrenogenital syndromes, a well-characterized cause of female pseudohermaphroditism in humans, has not been described to our knowledge in domestic animals. These are inherited defects in the steroid enzyme pathway that impair cortisol production.

Male pseudohermaphrodites are XY, have bilateral testes, and have genitalia that are female to some degree. Two etiologically distinct categories are recognized: failure of Mullerian duct regression and failure of androgen-dependent masculinization.

**Failure of Mullerian duct regression.** Persistent Mullerian duct syndrome (PMDS), in which the Mullerian ducts fail to regress, has been reported in the miniature schnauzer, bassett hound, and the cat (reviewed in Meyers-Wallen 1993). Affected miniature schnauzers have oviducts, uterine horns, uterine body, cervix, and cranial vagina, as well as male internal and external genitalia. Approximately 50% are cryptorchid. In this breed, PMDS is inherited as a simple autosomal recessive trait with expression limited to XY males. Affected embryos produce MIS throughout the critical period for Mullerian duct regression (Meyers-Wallen et al. 1993), which is supportive of a receptor defect.

**Failure of androgen-dependent masculinization.** The phenotype in these disorders can vary from severe (complete failure) to mild (incomplete failure). Affected individuals are XY and have bilateral testes. The Mullerian ducts regress normally, but structures dependent upon androgens for masculinization fail to develop, or develop incompletely. In humans, there are a number of different defects that produce a similar phenotype, which are of three broad categories.

The first group includes defects in the hypotalamic-pituitary-testis axis, such as abnormal gonadotropin secretion or abnormal steroid synthesis, which result in insufficient testosterone secretion. Hypospadias, an abnormality in the location of the urinary orifice, may be an example in dogs. This defect results from incomplete masculinization of the urogenital sinus in formation of the male urethra. It has been...
reported as a familial defect in purebred dogs such as the Boston terrier (Hayes and Wilson 1986). Teratogen-induced hypospadias has been reported in other species. Although hypospadias may be initiated by many factors, the common pathophysiology may be inadequate embryonic or fetal androgen production.

The second group of defects caused by a failure of androgen-dependent masculinization in humans is characterized by 5-alpha reductase deficiency. The resultant DHT deficiency produces incomplete masculinization of the urogenital sinus, genital tubercle, and genital swellings. Testosterone one-dependent structures masculinize normally. This has not been reported to our knowledge in domestic animals.

The third group of human defects is due to target organ insensitivity to androgens (androgen resistance or testicular feminization [Tfm] syndromes). These are caused by quantitative or qualitative defects in the androgen receptor and are X-linked inherited disorders in mammals. Affected individuals are XY and have bilateral testes and normal Mullerian duct regression. In animals having a nonfunctioning androgen receptor, Wolffian duct derivatives are absent, and the external genitalia are female, as described in the cat and the horse. These are examples of the complete form of androgen resistance. The phenotypic spectrum in humans ranges from the incomplete to complete forms. Affected humans can be normal but infertile males, individuals with ambiguous genitalia, or phenotypic females with complete androgen resistance.

**Miscellaneous male pseudohermaphroditism.** Cryptorchidism is included here because the mechanism of abnormal testis descent is incompletely understood. While cryptorchidism can be associated with other defects in sexual development, it also occurs as an isolated defect. As an isolated defect, cryptorchidism is the most common disorder of sexual development in dogs, occurring in as many as 13% of dogs presented to small animal clinics (Dunn et al. 1968). It is likely that some forms of canine cryptorchidism are inherited, since there is a high frequency in some breeds and within some families of breeds, and the frequency increases with inbreeding. In Angora goats, it has been proposed that cryptorchidism is inherited as a single locus, sex-limited, autosomal recessive trait. In swine, it has been reported as a sex-limited autosomal trait involving at least two gene loci.

**References**


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