

Are there specific genetic defects affecting the male reproductive tract? What are the underlying mechanisms?

Turner's and Klinefelter's syndromes, genetic loci, GnRH/LH/FSH, steroid biosynthesis and androgen insensitivity

T.R. Brown

Normal development and function of the male reproductive tract begins in the zygote where the X and Y chromosomes establish the genetic sex and direct the sequential evolution of gonadal and phenotypic sex in the fetus (Chapter 16). Under normal circumstances, gonadal and phenotypic sex agrees with chromosomal sex; however, abnormalities of sexual phenotype and function can arise from various defects during development. Beyond the sex chromosomes, disorders of male sex differentiation, development and function can result from single gene mutations. The analysis of these disorders has been highly informative in defining the genetic and molecular determinants of sex development and reproductive function (Fig. 1).

Gonadal disorders

True hermaphroditism

The clinical designation of true hermaphroditism is predicated upon the presence of both testicular and ovarian tissue. Subjects have a testis or ovary present in combination with a contralateral ovotestis containing both ovarian and testicular tissue (50%), or have a testis on one side and ovary on the other (30%), or bilateral ovotestes, or even bilateral ovary and testis combinations (20%). Functional oocytes may be present within the ovarian tissue whereas spermatogenesis is impaired within the undescended testicular tissue. The extent of functional testicular tissue will determine the internal duct structures. Secretion of Mullerian inhibiting substance (MIS) by Sertoli cells causes variable degrees of bilateral Mullerian duct regression, whereas local secretion of testosterone by Leydig cells is necessary for ipsilateral development of the Wolffian ducts. If a uterus is present on one side, an associated fallopian tube is often present. Approximately half of subjects develop a uterus, but the cervix may be absent. The external genitalia are usually ambiguous, although relatively normal male or female phenotypic appearance is possible. Hypospadias (abnormally placed urinary opening), cryptorchidism (undescended testis) or an inguinal hernia containing a gonad or Mullerian remnant may also be present. A majority of true hermaphrodites are raised as males due to the external appearance of

the genitalia, even though over 50% of subjects have a 46XX karyotype. Other karyotypes, such as 46XY, 46XX/XY chimerism or various forms of mosaicism may be present. Many 46XX true hermaphrodites do not possess the SRY gene suggesting that the etiology in these subjects differs from that of 46XX males who have a translocation of the Y chromosomal SRY (sex determining region of the Y chromosome) gene locus.

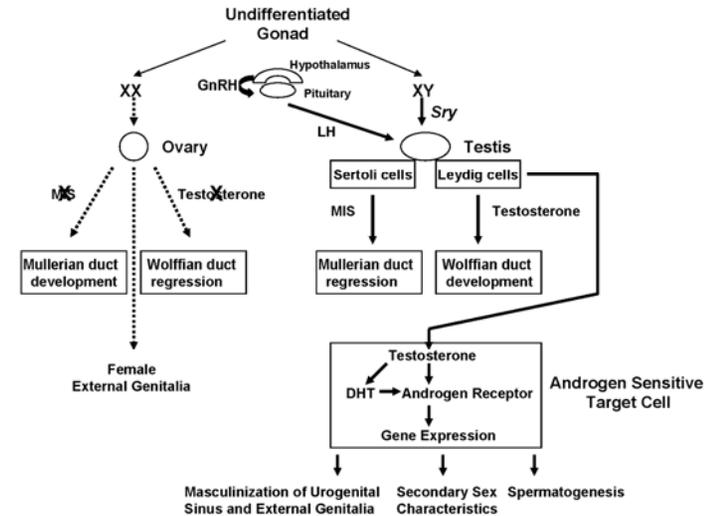


FIG. 1. Determinants of human sex differentiation and development. The undifferentiated gonad in the fetus develops into a testis when the chromosomal sex is XY due to the presence of the sex determining region of the Y chromosome, Sry, gene. If the chromosomal sex is XX, the undifferentiated gonad evolves into the ovary. Initially under the control of placental hCG, fetal testicular Leydig cells synthesize and secrete testosterone necessary for development of the Wolffian ducts. Sertoli cells in the fetal testis produce Mullerian Inhibiting Substance (MIS) which causes regression of the Mullerian ducts in the male. Subsequent to placental hCG, GnRH is synthesized and secreted by the hypothalamus to stimulate the synthesis and secretion of LH by the anterior pituitary gland to provoke testosterone biosynthesis and secretion by Leydig cells in the testis during the later fetal, immediate postnatal and pubertal stages of development. By contrast to the fetal testis, the fetal ovary produces neither gonadal steroids (e.g. estradiol) nor MIS. In target cells, testosterone, or its more potent 5 α -reduced metabolite, dihydrotestosterone (DHT), bind to the androgen receptor and promote masculinization of the urogenital sinus and external genitalia in the fetus, as well as the pubertal expression of secondary sex characteristics and the initiation and maintenance of spermatogenesis.

Klinefelter syndrome

Seminiferous tubular dysgenesis due to 47XXY aneuploidy in subjects with Klinefelter syndrome represents the most common cause of testicular failure, with a reported incidence of 1:500 males. Other sex chromosome aneuploidies, 48XXYY, 48XXXYY and 49XXXXYY, also occur but with much reduced frequencies and are also males. 47XXY males may present with a variety of subtle, age-related clinical signs including hypospadias, small phallus or cryptorchidism in infancy; language delay, learning disabilities or behavioral problems in adolescence; followed by delayed or incomplete pubertal development with eunuchoid body habitus, gynecomastia (breast enlargement) and small testes with infertility due to progressively decreasing numbers of spermatogonia. At puberty, gonadotropin (luteinizing hormone, LH and follicle stimulating hormone, FSH) levels increase but testosterone concentrations remain relatively suppressed in accordance with the degree of testicular failure. Gynecomastia arises from the decreased testosterone:estradiol ratio. Despite impairment of seminiferous tubular function, intratesticular sperm retrieval and intracytoplasmic sperm injection for fertilization of eggs has been used successfully for a few subjects.

Turner syndrome

The diagnosis of Turner syndrome is based upon the characteristics of short stature, gonadal dysgenesis leading to premature ovarian failure and infertility, typical dysmorphic features (epicanthal folds, high arched palate, low nuchal hair line, webbed neck, shield-like chest, pigmented nevi and inverted nipples), and abnormalities in the kidneys and heart. The karyotype is complete or partial absence of one of the X chromosomes (45X), although frequently accompanied by cell line mosaicism (45X/46XX). The presence of dysgenic gonad(s) and Y chromosome material increases the probability for development of gonadoblastomas. Hormone replacement therapy is necessary to promote normal female sex characteristics and to prevent cardiovascular complications and osteoporosis in affected subjects. Oocyte donation is an option for assisted reproduction.

XX males

Subjects with an apparent 46XX karyotype but male phenotype are the result of translocation of a portion of the Y chromosome containing the testis determining SRY gene most often to the X chromosome. Subjects may have undescended testes (15%) and hypospadias (10%) and usually have small testes that may be soft early in life but become firm with increasing age. Testicular histology reveals no spermatogonia, a decrease in the diameter of the seminiferous tubules and Leydig cell hyperplasia, similar to that in Klinefelter syndrome. By comparison, 46XX males are shorter than those

with 47XXY karyotype. Testosterone production is low whereas gonadotropin levels are elevated.

XY gonadal dysgenesis

Gonadal dysgenesis may be of the “pure” or “mixed” form where the former refers to the presence of aplastic or “streak” gonads on both sides and the latter to a unilateral streak gonad on one side and testicular tissue, usually within a dysgenic testis on the other side. The pure form may occur in subjects with a 46XY karyotype, whereas the mixed form commonly involves chromosomal mosaicism (45X/46XY) but also occurs in 46XY subjects with variable degrees of functional testicular tissue in each of the gonads. The etiology may be deletion of the Y chromosome or deletion/mutation of the SRY gene, or other genes associated with testicular development such as SOX9, SF1, or WT1.

Genetic lesions in the hypothalamic-pituitary-gonadal axis

GnRH synthesis and release

Gonadotropin releasing hormone (GnRH) neurons originate in the olfactory placode and migrate with olfactory neurons to the olfactory bulb and finally to the fetal hypothalamus, a position that enables their secretory product, GnRH, to access the hypophysial portal circulation and reach the anterior pituitary. If this migratory process is disturbed, the outcome is hypogonadotropic hypogonadism (combination of low gonadotropin and gonadal steroid levels) with anosmia (lack of smell), referred to as Kallmann syndrome (KS), with a frequency of 1:8000 in boys. This syndrome is genetically heterogeneous with X-linked, autosomal dominant and autosomal recessive forms. The autosomal forms comprise 85% of the cases. Two genes can cause this condition: KAL1, encoding anosmin-1, is mutated in some X-linked forms of KS whereas KAL2, encoding the fibroblast growth factor receptor 1 (FGFR1), is mutated in some autosomal dominant cases. Other candidate genes implicated in KS are chromodomain helicase DNA binding protein 7 (CHD7) and G-protein coupled receptor prokinectin receptor-2 (PROKR2). Adult men with KS do not develop male secondary sex characteristics in the absence of androgen replacement and remain azoospermic unless treated with GnRH or gonadotropins; androgen therapy alone does not initiate spermatogenesis in these men.

A breakthrough in understanding the regulation of GnRH synthesis and secretion was the recent discovery that GPR54, a G-protein coupled receptor and its ligand, kisspeptin, trigger puberty in humans and experimental animals (Chapter 18). Kisspeptin is expressed in the arcuate nucleus and GPR54 in GnRH neurons. Subjects with inactivating mutations in GPR54

present with hypogonadotropic hypogonadism due to absence of GnRH synthesis and release. These subjects lack pubertal development but respond to exogenous administration of GnRH. In rare cases, congenital deficiency of leptin or its receptor can lead to severe early onset obesity and hypogonadotropic hypogonadism due to GnRH deficiency. Leptin regulation of gonadotropin secretion is likely due to its role in the release of neurotransmitters, such as neuropeptide Y, that affects GnRH secretion.

Although the GnRH gene is a natural candidate for mutations leading to hypogonadotropic hypogonadism, such mutations have not been detected. By contrast, inactivating mutations of its receptor, GnRHR, have been reported. Mutations of the GnRHR gene in males cause delayed puberty, decreased libido, poor masculinization and reduced testis size with asthenoteratozoospermia. GnRH mutations cause reduced ligand binding and/or reduced second messenger (inositol triphosphate) response to GnRH stimulation. In affected subjects, the gonadotropin levels are low with normal frequency of low amplitude peaks and responses to GnRH stimulation are variable.

Gonadotropins and their receptors

Mutations in gonadotropin subunits would be expected to directly impair fertility and reproduction, and thus would likely be eliminated from the gene pool. Hence, only a few sporadic cases of such mutations have been described. In addition to inactivating mutations, polymorphisms in these genes are suggested to be causative or contributing factors to mild disturbances of male reproductive function. The common α -subunit is shared by the three gonadotrophins, luteinizing hormone (LH), human chorionic gonadotrophin (hCG) and follicle stimulating hormone (FSH), as well as by thyroid-stimulating hormone (TSH). Therefore, inactivating mutations of this gene would have significant consequences with respect to male hypogonadism, hypothyroidism and pseudohermaphroditism. In females, pregnancy would be seriously compromised by the absence of hCG during gestation. Consequently, no mutations in the α -subunit gene have been detected in humans. Rare inactivating mutations of the LH β subunit gene have been reported in men. These men are masculinized at birth presumably due to normal activity of hCG during pregnancy, but lack sexual maturation at puberty in the absence of pituitary LH and postnatal stimulation of Leydig cell testosterone biosynthesis.

LH receptor (LHR) gene mutations occur in humans; a phenotype is observed when both alleles are inactivated due to homozygous or compound heterozygous mutations. The inactivating mutations may be complete or partial. With mutations of LHR, the testis is devoid of trophic stimulus and the Leydig cells fail to develop resulting in a condition referred to as Leydig cell

hypoplasia or agenesis. Testes have Sertoli cells and occasional immature germ cells. Subjects fail to masculinize due to the absence of fetal testicular androgens as well as impaired postnatal androgen biosynthesis in response to hCG/LH. In severe cases of Leydig cell hypoplasia, subjects have female external genitalia, low testosterone and high LH levels, normal FSH concentrations and absence of secondary sex characteristics, but do not have breast development at puberty. The low testosterone levels and absence of breast development distinguish these subjects from those with complete androgen insensitivity (as discussed below). In cases of partial LHR inactivation, testicular androgen production is sufficient to stimulate partial masculinization of the external genitalia represented by cryptorchidism, small phallus and/or hypospadias, thus resembling partial forms of androgen insensitivity syndrome. Gain of function mutations associated with constitutive activation of LHR have also been described in subjects with early onset familial male-limited precocious puberty, also termed testotoxicosis due to the chronologically abnormal elevation of testosterone production. Early onset of puberty causes short stature in adult age and the residual psychological impact of inappropriately early pubertal development, whereas testicular function and fertility are otherwise normal.

Interestingly, the FSH receptor (FSHR) and LHR genes are both located on chromosome 2p. Loss of function mutations in FSHR cause phenotypes in homozygous and compound heterozygous forms. Fewer FSHR than LHR mutations are known probably because the phenotypes associated with the former are less clinically striking. Although FSH action was presumed to be essential for Sertoli cell proliferation and function and for regulation of spermatogenesis, FSHR mutations in men have been reported to reduce testicular volume and lower sperm counts, but do not cause azoospermia. These findings suggest that normal androgen production in these men suffices to initiate and maintain spermatogenesis at a qualitatively and quantitatively reduced level that obviates a requirement for FSH bioactivity.

Disorders of androgen biosynthesis

Androgens and estrogens are made from cholesterol by a series of well-defined enzymatic steps (Chapter 5) (Fig. 2). Defects in these enzymes affect androgen biosynthesis by Leydig cells and virilization of the male fetus but do not interfere with regression of the Mullerian ducts. The enzymatic defects may be of variable severity, partial or complete, and may present in the newborn period as degrees of sexual ambiguity ranging from complete feminization to mild hypospadias or they may only become apparent at puberty. Severe defects in these enzymes that affect mineralocorticoid and glucocorticoid biosynthesis may present life-threatening circumstances in the newborn.

androgen receptor gene that prevent normal expression of androgen-responsive genes. In complete AIS, the phenotype of the external genitalia is female despite normal to elevated levels of testosterone and DHT. In the infant, inguinal or labial testes may be palpable, although they are most often discovered during exploration for an apparent inguinal hernia. The vagina is short due regression of the Mullerian ducts following secretion of MIS by testicular Sertoli cells. High testosterone levels result from elevated gonadotropins at puberty due to the lack of negative feedback at the hypothalamic-pituitary axis. However, peripheral aromatization of testosterone leads to high levels of estradiol that promotes breast development when unopposed by androgen action. Axillary and pubic hair is scant. If the diagnosis is not made in the infant, the clinical presentation may be primary amenorrhea and infertility at the expected time of puberty. The increased incidence of testicular tumors in the undescended testes during the third decade of life recommends orchiectomy followed by estrogen therapy. By comparison, partial AIS presents as highly variable degrees of genital virilization ranging from slightly virilized female genitalia to hypospadias, undescended testes and adolescent gynecomastia to micropenis or even isolated infertility. These subjects may present with ambiguous genitalia during the neonatal period with a hormonal profile of elevated testosterone and LH, characteristic of androgen insensitivity. Further diagnostic testing with androgen stimulation but inadequate penile growth in response to androgen is indicative of androgen insensitivity. Marked ambiguity and biochemical evidence of demonstrable androgen insensitivity may dictate a female sex of rearing as the partial defect may allow some masculinization in response to the pubertal rise in testosterone that is accompanied by gynecomastia. Prepubertal gonadectomy will prevent the latter circumstances. Recently, abnormal expansion of the trinucleotide repeat region encoding the polyglutamine sequence in the aminoterminal of the androgen receptor has been determined as the cause of spinal bulbar muscular atrophy in young men who may initially present with apparent hypogonadism. Additional studies have suggested that polymorphism of the glutamine repeat region may also influence male fertility.

Suggested reading

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