DISORDERS OF SEXUAL DIFFERENTIATION

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KEYWORDS

• Sexual differentiation • Genotype • Phenotype • Intersex disorders • Hermaphroditism

ABSTRACT

The term, *disorders of sexual differentiation*, broadly represents a disjunction between genotype and phenotype. Phenotype in turn can refer to external or internal genital development. Disorders of sexual differentiation are determined at conception insofar as (1) the abnormal genotype is the aberrant genetic product of fertilization at the chromosomal level or (2) the abnormal phenotype results from postfertilization errors in function at the gene level, somewhere along the pathway of transcription and translation. In either event, the error is genetic, whether or not sporadic or inherited, even if the pathways have yet to be fully elucidated for a given disorder.

OVERVIEW

Also known as intersex disorders, disorders of sexual differentiation broadly represent a disjunction between genotype and phenotype. Phenotype in turn can refer to external or internal genital development. Disorders of sexual differentiation are determined at conception insofar as (1) the abnormal genotype is the aberrant product of fertilization at the chromosomal level or (2) the abnormal phenotype results from postfertilization errors in function at the gene level, somewhere along the pathway of transcription and translation. In either event, the error is genetic, whether or not sporadic or inherited, even if the pathways have yet to be fully elucidated for a given disorder.

Traditionally, sexual differentiation disorders have been classified by phenotype, because cataloguing aberrant external appearances, and later internal anomalies, long preceded identification and classification of their genetic substrates. In this vein, a bit of terminology warrants clarification in the context of genotype/phenotype correlations.

Male pseudohermaphroditism refers to a genetic male who appears as a phenotypic female. This disorder indicates an error in testosterone influence on external (and internal) genital, although not gonadal, development.

Female pseudohermaphroditism refers to a genetic female who appears as a phenotypic male. This disorder indicates erroneous conversion of estrogens to androgens. Internal genitalia, including gonads, are female.

In general, patients with undervirilization or disorders with an SRY-bearing Y chromosome are susceptible to gonadal neoplasia. This tumor susceptibility seems to be the consequence of germ cell maturation delay, which may in turn be (1) directly gene related or (2) due to functional alterations in maturation associated with undescended (intra-abdominal or inguinal) gonads. At baseline, the odds ratio for testicular neoplasia in undescended gonads in otherwise normal males varies from 1.6 to 17.1 in published series, and it increases with increasing age. Additive molecular factors associated with certain disorders of sexual differentiation increase the likelihood of germ cell neoplasia up to approximately 30% in the highest risk groups. The rarity of these patient groups limits comparison between and among them of published statistics regarding relative risks of developing germ cell and other tumors.

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BACKGROUND EMBRYOLOGY

Gonadal development begins in the fourth postconceptual week, during which time germ cells arise from the endodermal lining of the yolk sac, from whence they migrate along the yolk sac, midgut, and dorsal mesentery, and subsequently populate the urogenital ridge. Mitotic divisions over the next two weeks populate the genital ridge with precursor gametes, whereas failure of migration or gametal mitosis results in the absence of gonadal development. At week 7, the gonad begins to differentiate into a testis in the presence of a Y chromosome or into an ovary with two X chromosomes. As a rule, only those germ cells that successfully complete migration to the gonadal ridge survive and differentiate. Others undergo apoptosis, except perhaps for those that escape programmed cell death; these may be the precursors to germ cells tumors that arise along the embryonic germ cell migratory path.

In the presence of germ cells, the coelomic epithelium lining the genital ridge differentiates into germinal epithelium, ultimately giving rise to sex cords. From this juncture, gonads are committed to gender fate; signal failure at this stage results in true hermaphroditism.

In the genetic male, sex cord cells proliferate. Germ cells differentiating into spermatogonia are surrounded by sex cord cells that differentiate into Sertoli cells via sex cord–germ cell contact signaling.

In the genetic female, ovarian differentiation lags testicular differentiation by approximately two weeks. Sex cord cells proliferate, as in the male, but as germ cells differentiate into oocytes, the surrounding sex cord cells differentiate into granulosa cells, also by sex cord–germ cell contact signaling.

Concomitant with germ cell and sex cord differentiation, and surface coelomic commitment to germinal epithelium, subepithelial mesenchyme differentiates in the male to interstitial Leydig cells and in the female to theca cells.

Testicular descent from the abdomen into the scrotal sac is androgen dependent, requiring fetal gonadotropins and a functional hypothalamic-pituitary-testicular axis. Sertoli cell–derived Müllerian Inhibiting Substance (MIS) may also participate in testicular descent through hormonal influence on the gubernaculum, an embryonic subperitoneal fibrous cord that tethers the testis to the scrotal sac. Failure of testicular descent in several XY sexual differentiation disorders is thus a likely consequence of aberrant hormone-dependent signaling.[1,2]

INTERNAL GENITALIA

Internal genital development is distinct from gonadal and external genital development in that Internal anlage of male (Wolffian) and female (Müllerian) derivatives develop simultaneously in early embryonic life, normally with subsequent regression of one duct system to embryonic remnants. By contrast, gonadal and external development begins along a single bipotential pathway, differentiating rather than regressing under normal circumstances to a gender-specific phenotype.

Sexual differentiation of the internal genitalia into a male phenotype is dependent on testicular secretory products. Failure of appropriate signaling or signal recognition results in female internal genitalia. In the male, MIS is secreted by Sertoli cells under the influence of sex-determining region of the Y chromosome (*SRY*), a protein encoded by the *SRY* gene located on the short arm of the Y chromosome. MIS induces regression of female, or Müllerian duct, derivatives. Testosterone, secreted by Leydig cells under the control of placental human chorionic gonadotropin, induces differentiation of Wolffian duct derivatives into epididymis, vas deferens, and seminal vesicles. Peripheral prostate gland differentiation proceeds from the influence of dihydrotestosterone (DHT), which is produced locally by conversion of testosterone via 5α-reductase activity. The central and transition prostate zones are under different signal control, probably of Wolffian origin, and, therefore, testosterone regulation. The female homologue of the prostate gland is the upper vagina.

In the female, the Müllerian ducts give rise to the fallopian tubes, uterus and upper third of the vaginal canal.[1,2]

EXTERNAL GENITALIA

External genital differentiation commences in the fifth week postconception. In the eighth postconceptual week, the external genitalia appear as a midline urogenital sinus (forerunner to the female vagina), a midline genital tubercle (forerunner to the clitoris and distal penis), two lateral genital folds (forerunner to the labia minora and proximal penis), and two lateral labioscrotal folds (forerunner to the labia majora and scrotal sac). Although to an experienced observer external genitalia are grossly discernible as male or female after the first trimester, confident assessment may lag by a few weeks.

External male genital development requires DHT, which is converted locally from testosterone