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# Disorders of sex development

Selma Feldman Witchel, MD

*Division of Pediatric Endocrinology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224, USA*

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Normal sex development depends on the precise spatio-temporal sequence and coordination of mutually antagonistic activating and repressing factors. These factors regulate the commitment of the unipotential gonad into the binary pathways governing normal sex development. Typically, the presence of the SRY gene on the Y chromosome triggers the cascade of molecular events that lead to male sex development. Disorders of sex development comprise a heterogeneous group of congenital conditions associated with atypical development of internal and external genitalia. These disorders are generally attributed to deviations from the typical progression of sex development. Disorders of sex development can be classified into several categories including chromosomal, gonadal, and anatomic abnormalities. Genetic tools such as microarray analyses and next-generation sequencing techniques have identified novel genetic variants among patients with disorders of sexual development. Most importantly, patient management needs to be individualized, especially for decisions related to sex of rearing, surgical interventions, hormone treatment, and potential for fertility preservation.



## Introduction

Disorders of sex development (DSDs) encompass a group of congenital conditions associated with atypical development of internal and external genital structures. These conditions can be associated with variations in genes, developmental programming, and hormones. Affected individuals may be recognized at birth because of ambiguity of the external genitalia. Others may present later with

*E-mail address:* witchelsf@upmc.edu.

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postnatal virilization, delayed/absent puberty, or infertility. The estimated frequency of genital ambiguity is reported to be in the range of 1:2000–1:4500 [1]. According to the Danish Cytogenetic Central Registry, the prevalence of XY females is 6.4 per 100,000 live born females. In this registry, the prevalence of androgen insensitivity was 4.1 per 100,000 live born females with median age at diagnosis of 7.5 years. The prevalence of XY gonadal dysgenesis was 1.5 per 100,000 live born females, with median age at diagnosis of 17 years [2]. The incidence of DSDs varies among ethnic groups, with the highest incidence in the southern African population.

International stakeholders representing multiple disciplines continue to modify the terminology used to categorize specific DSDs to emphasize the underlying genetic etiologies [3]. Ongoing development and use of novel molecular cytogenetic techniques have enriched the understanding regarding the genomic alterations associated with DSDs. In addition, analyses regarding these genomic alterations have illuminated novel genetic regulatory mechanisms associated with DSDs [4].

When presented with a child with ambiguous genitalia, unique decision-making challenges can occur regarding sex of rearing, parent and patient education, and medical management [5]. It is important to note that sex does not indicate gender; sex refers to the biology of the internal and external genital structures, which is traditionally considered to be a binary categorization. Gender identity is the self-defined experience of one's gender. Tales from Greco-Roman cultures, e.g., Hermaphrodite and Daphne, have documented and celebrated transformations and fluidity in sex and gender identity [5].

## Embryology

Sexually dimorphic development of the reproductive tracts is influenced by multiple factors. Normal sex development is dependent on the synergistic orchestration of activating and repressing factors interacting in a precise spatio-temporal pattern [6]. Sex determination is governed by the sex chromosomes. The sex determining region on the Y chromosome (SRY) gene located on the short arm of the Y chromosome is the binary switch that initiates the male developmental program [7]. The pivotal experiments performed by Dr. Alfred Jost established the relevance of testosterone for male sexual differentiation [8].

Urogenital ridges develop by 4–6 weeks of gestation as outgrowths of the coelomic epithelium. Subsequently, the urogenital ridges develop into the kidneys, adrenal cortices, gonads, and reproductive tracts. SRY functions as a transcription factor to trigger the developmental trajectory that directs differentiation of the bipotential gonad into a testis during the 6th week of human gestation. SRY induces SOX9 expression; SOX9 activates and maintains the male gonadal differentiation pathway. With differentiation of the Sertoli cells, the developing testis becomes organized into two compartments. One compartment consists of the testis cords that are aggregates of the germ cells surrounded by Sertoli cells and encased by the peritubular myoid cells. The other compartment is the testis interstitium, which contains the Leydig cells and testis vasculature.

Initially, both Wolffian and Müllerian ducts develop. The Wolffian ducts originate as the excretory ducts of the mesonephros. Testosterone, secreted by the fetal Leydig cells, stabilizes the Wolffian ducts, resulting in the development of the epididymis, vas deferens, ejaculatory duct, and seminal vesicle. Another hormone secreted by the testis, insulin-like factor 3 (INSL3), mediates testicular descent from the original perinephric location through the abdomen. Testosterone promotes testicular descent into the scrotum. Testicular descent is generally completed by 32 weeks' gestation. Sertoli cells secrete anti-Müllerian hormone (AMH), which induces regression of the Müllerian ducts.

Ovarian differentiation occurs slightly later than testicular differentiation. In the absence of SRY in the female fetus, ovary-specific transcription factors, namely forkhead transcription factor 2 (FOXL2), wingless type MMTV integration site family, member 4 (WNT4), R-spondin 1 (RSPO1), and the activated β-catenin pathway, initiate and maintain ovarian differentiation [9]. In the absence of testosterone and dihydrotestosterone (DHT), the external genital structures develop into the clitoris, vagina, and labia. Both the urethra and the vagina open onto the perineum.