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Genetic approach to ambiguous genitalia and disorders of sex development: What clinicians need to know

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ABSTRACT

Genetic tools such as microarray and next-generation sequencing have initiated a new era for the diagnosis and management of patients with disorders of sex development (DSDs). These tools supplement the traditional approach to the evaluation and care of infants, children, and adolescents with DSDs. These tests can detect genetic variations known to be associated with DSDs, discover novel genetic variants, and elucidate novel mechanisms of gene regulation. Herein, we discuss these tests and their role in the management of patients with DSDs.

Introduction

Disorders of sexual development (DSD) comprise a group of congenital conditions associated with atypical development of chromosomal, gonadal, or anatomical sex. Patients may present with genital ambiguity at birth, postnatal virilization, delayed/absent puberty, or infertility. The reported frequency of genital ambiguity is estimated to be in the range of 1:2000–1:4500.[1] Review of the Danish Cytogenic Central Registry showed that the prevalence of XY females is 6.4 per 100,000 live born females; the prevalence of androgen insensitivity (AIS) was 4.1 per 100,000 live born females while the prevalence of XY gonadal dysgenesis was 1.5 per 100,000 live born females.[2] In this registry, the median age of diagnosis for AIS was 7.5 years whereas the median age for diagnosis of XY gonadal dysgenesis was 17 years.[2] Nevertheless, the incidence of DSD may vary widely among various ethnic groups, with the highest incidence occurring in the southern African population, reflecting differences in gene mutation frequency and secondary environmental and cultural factors, conferring susceptibility risk. Advances in molecular cytogenetics using whole genome DNA microarrays and next-generation sequencing (NGS) techniques have revealed multiple genomic alterations associated with DSD. Investigation into these genomic alterations has elucidated novel genetic mechanisms leading to DSD.

International stakeholders from multiple disciplines have refined the terminology and attempted to categorize specific DSDs to reflect the underlying genetic etiology.[3] In this article, we discuss our current understanding of DSD in both

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Table 1 – Sex chromosomal DSD.

Syndrome	Karyotype	Chromosomal defects	Testing method	Risk factors, comments
Turner syndrome	45,X mos 45,X/46,XX	X monosomy Mosaic monosomy X	G-banding PCR for Y chromosome sequence FISH on uncultured PB/other tissue cells for mosaicism	10% of individuals with 45,X karyotype have hidden Y chromosome in other tissues
Turner syndrome with structural X chromosome rearrangements	46,X,i(Xq) 46,X,del(Xp) 46,X,+mar	isochromosome Xq Deletion Xp Marker chromosome	G-banding Microarray to characterize rearrangement breakpoints, determine the X or Y origin of the marker chromosome	Parental balanced X chromosome rearrangements
Gonadal dysgenesis	45,X/46,XY XX/XY	Mosaic loss of the Y chromosome in X Chimerism	G-banding FISH on uncultured PB/other tissue cells for mosaicism	
XX male SRY gene positive gonadal dysgenesis	46,XX or 46,X,der(X)t(X;Y)	Yp (SRY gene) translocation to the X chromosome or autosome	G-banding FISH using the SRY-containing DNA probe Microarray analysis	Familial sex chromosome rearrangements
Klinefelter syndrome and its variants	XXY mos 46,XXY/46,XY XXYY XX/XXY	Disomy X Mosaic disomy X Disomy X and Y Mosaic loss of the Y chromosome in XXY	G-banding FISH on uncultured PB/other tissue cells for mosaicism SNP containing microarray analysis to exclude X chromosome UPD	

PB, peripheral blood; UPD, uniparental disomy.

XY and XX individuals as well as patients with mixed sex chromosome complement (Table 1). We will outline syndromic and isolated forms of DSD. Conditions with autosomal dominant, autosomal recessive, and sex chromosome-linked inheritance are indicated with consideration of the possible role of specific ethnic backgrounds and environmental factors on DSD predisposition and phenotypic variability. The most recent genetic advances in detection of disease-causing mutations and their importance for individualized therapeutic interventions are highlighted.

Embryology

By 4–6 weeks of gestation, the urogenital ridges have developed as outgrowths of celomic epithelium. Subsequently, urogenital ridges develop into the gonads, adrenal cortex, kidneys, and reproductive tracts. The gonads, internal genital ducts, and external genital structures develop from these bipotential embryologic tissues. The initial step in the process of sex development is gonadal differentiation. This binary switch depends on the presence of the *SRY* gene, a Sex Determining Region on the Y chromosome.[4] Thus, the chromosomal karyotype at fertilization, the presence of Y chromosome, establishes the developmental trajectory of the undifferentiated gonad to become a testis or an ovary. In the presence of *SRY*, the undifferentiated embryonic gonad is normally directed toward the testicular/male developmental program achieved via activation and maintenance of the *SOX9* signaling pathway. In XY embryos, following two regulatory signaling cascades normally accomplish this process: factors activating male gonadal determination and factors repressing female sex differentiation. Subsequently, the hormones made by the testes, testosterone, Müllerian inhibitory hormone, and Insulin-like factor 3 gene (*INSL3*), respectively, induce normal male development of the penis and scrotum, regression of the Müllerian structures, and descent of the testes through the abdomen. In the absence of the *SRY* gene and testicular hormones, the female fetus typically develops ovaries. This process is driven by ovary-specific transcription factors FOXL2, WNT4, and the RSPO1-triggered β-catenin pathway activation. In the absence of testosterone and dihydrotestosterone (DHT), the external genital structures develop into the clitoris, vagina, and labia.

The Wolffian duct originates as the excretory duct of the mesonephros. The fetal Leydig cells in the testes secrete