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## Risk association of congenital anomalies in patients with ambiguous genitalia: A 22-year single-center experience

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### Summary

#### Background

Ambiguous genitalia refers to a form of differences of sex development (DSD) wherein the appearance of the external genitalia is atypical. This rare condition presents challenges in decision-making and clinical management. Review of historical data may reveal areas for clinical research to improve care for patients with ambiguous genitalia.

#### Objective

This chart review was performed to identify patients with ambiguous genitalia, and to classify them as having 46,XX DSD, 46,XY DSD, or sex chromosome DSD. Within these categories, we looked at establishment of specific diagnoses, type and frequency of other congenital anomalies and neoplasms, and gender assignment, as well as incidence of gender reassignment and transition.

#### Methods

We performed a retrospective chart review of patients diagnosed with DSD conditions from 1995 to 2016 using ICD9 codes. For the purpose of this study, review was limited to individuals assessed to have neonatal "ambiguous genitalia" or "indeterminate sex."

#### Results

Review identified 128 patients evaluated for ambiguous genitalia from 22 years of experience (Figure). Approximately half of these (53%) had 46,XY karyotype, 35% had 46,XX, and the remaining 12% had sex chromosome

aberrations. Diagnostic rate for 46,XX DSD was higher at 64%, all of which were congenital adrenal hyperplasia, while diagnostic rate for 46,XY DSD was 11.7% for a molecularly confirmed diagnosis and 24% if clinical diagnoses were included. The most common anomalies included cardiac anomalies in 28/128 (22%), skeletal anomalies in 19/128 (15%), and failure to thrive or growth problems in 19/128 (15%). Additional congenital anomalies were found in 53 out of 128 patients (41%). There were three reported neoplasms in this group: gonadoblastoma, hepatoblastoma, and myelodysplastic syndrome with monosomy 7. Gender assignment was consistent with chromosomes in approximately 90% of XX and XY patients. There were three recorded gender reassignments or transitions.

#### Discussion

Diagnostic rate for ambiguous genitalia is low, especially in 46,XY DSD. Most neonates were assigned gender consistent with their chromosomes. Given the high rate of associated anomalies, screening for cardiac or other anomalies in patients with ambiguous genitalia may be beneficial.

#### Conclusion

Patients with ambiguous genitalia often have additional congenital anomalies. Establishment of a specific diagnosis is uncommon in 46,XY patients. A few patients have gender reassignment outside of the newborn period. Ongoing collection of clinical data on this population may reveal new information regarding long-term health, quality of life, and establishment of more diagnoses with improved molecular techniques.

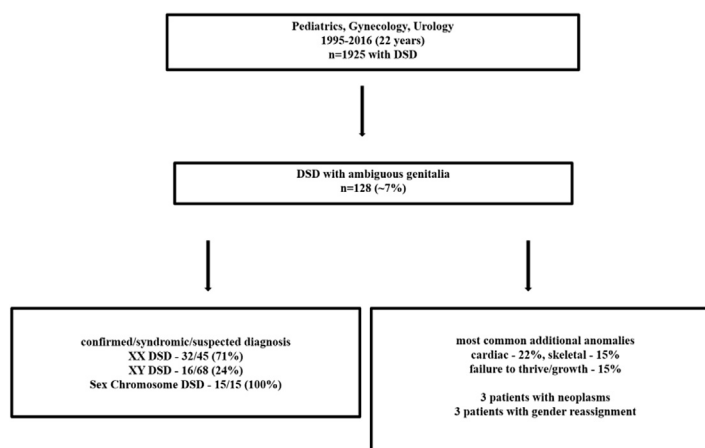


Figure Flow chart of patients with ambiguous genitalia.

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## Introduction

The formation of male or female-specific gonads and other reproductive structures involves a complex interplay of sex chromosomes, genes, hormones, and biochemical processes. Spatiotemporal disruptions in any of these genetic and environmental components could result in ambiguous genitalia or other forms of differences of sex development (DSD). Although DSD has previously been defined as disorders of sex development, patients have clearly expressed a negative view of the term “disorder” [1], so our group uses “differences” as our preferred term.

Infants born with ambiguous genitalia need care by a multidisciplinary DSD team. The sex chromosomes for these patients may be XX, XY, or reveal a sex chromosome abnormality. Identification of the sex chromosome complement may facilitate differential diagnosis and clinical management by the DSD team. For example, individuals with ambiguous genitalia and 45,X/46,XY mosaicism are monitored for the same medical problems as those individuals with Turner syndrome, and screening is recommended for coarctation of the aorta and bicuspid aortic valve, as well as for renal anomalies [2]. Additionally, for individuals with 45,X/46,XY mosaicism and intraabdominal gonads, the risk for gonadal malignancy is elevated, and gonadectomy can be recommended [3]. Specific molecular diagnoses can also guide treatment for patients with ambiguous genitalia. Individuals who are found to have Denys-Drash syndrome caused by a mutation in *WT1* have increased health risks for focal segmental glomerulosclerosis (FSGS), end stage renal disease requiring transplant at an early age, Wilms tumor, and gonadoblastoma [4–6]. Individuals with 46,XY DSD presenting with ambiguous genitalia, who are found to have *CYP11A1* deficiency, have risk of adrenal insufficiency which can be of late onset [7]. In other types of DSD, such as congenital adrenal hyperplasia (CAH), early diagnosis is also important for the risk of adrenal insufficiency and salt-wasting crisis [8–11].

Through the years, the ability to determine a diagnosis in patients with DSD has improved with the advent of advanced genomic technologies, and clinical management has evolved into more patient-centered multidisciplinary care. In this report, we performed a retrospective chart review of DSD patients with ambiguous genitalia, providing some historical data of our institution’s clinical experience in diagnosis and management of DSD. This study focuses on sex chromosomes, underlying diagnoses and comorbidities present in patients with ambiguous genitalia, sex assignment, and gender-related outcomes.

## Materials and methods

This study was approved by the institutional review board of Washington University in St Louis Human Research and Protection Office. Patients with any DSD conditions seen by the Departments of Pediatrics (1995–2013), Obstetrics and Gynecology (1995 and 2016), and Division of Urology (2004 and 2013) of the Washington University in St. Louis School of Medicine (Fig. 1) were identified using ICD-9 codes (Table S1). Original patient data were reviewed for demographics, clinical and follow-up history, physical

examination, imaging, genetic testing, endocrinology, surgery, neoplasm, psychosociology, and gender-related information. All data were entered into the REDCap database.

For this study, we focused on patients referred for or assessed to have “ambiguous genitalia” or “indeterminate sex,” including those with diagnostic testing by an outside provider or DSD team and those with no available birth records. Incompleteness of ICD9 codes meant that patients who met criteria above were included even if the ICD9 code for “ambiguous genitalia” was not listed. Data were collected regarding each subject’s demographics, physical exam findings, genetic testing results and diagnosis, radiology and pathology data relevant to DSD, gender assignment and gender transitions, and comorbidities.

We then categorized each patient based on updated DSD Classification [12–15] (Table 1, Figs. 1 and 2, Table S2). Diagnosis was given based on pathology, biochemical, or genetic testing but not solely on clinical assessment. For example, many patients with ambiguous genitalia had been given the presumed diagnosis of partial androgen insensitivity syndrome despite no confirmatory testing performed, for example androgen receptor binding assays or gene sequencing. With no evidence of reduced androgen receptor function this diagnosis may be inaccurate, so these patients were categorized based on pathology (if performed) or appearance of the genitalia. For the purposes of this study, individuals were considered to be “syndromic” if there was at least one additional congenital anomaly outside of the reproductive systems. Individuals with acquired genital abnormalities such as circumcision complications, labial adhesions, trauma, or infection were excluded. Individuals with endocrine problems without genital ambiguity, such as 46,XY individuals with congenital adrenal hyperplasia, were excluded.

## Results and discussion

Based on ICD9 codes, 2017 DSD patients were identified from Pediatrics, Obstetrics and Gynecology, and Urology. In the preliminary record review, 2017 DSD patients were identified, with 1925 unique individuals (5% redundancy) (Fig. 1). Year of birth ranged from 1967 to 2013, and age ranged from 10 days to 46 years (mean age of 11.1 years). Mean length of follow-up was 6.8 years. Further investigation identified 128 individuals referred for evaluation of, or assessed to have ambiguous genitalia or indeterminate sex (Table 1, Fig. 1). Of these patients, 53.1% ( $n = 68$ ) had an XY sex chromosome complement, 35.2% ( $n = 45$ ) XX, and the remaining 11.7% ( $n = 15$ ) had a sex chromosome numerical or structural aberration, a trend similar to the distribution obtained by large international studies [16,17]. The high frequency of XY sex chromosomes in those with genital ambiguity has been attributed to a more intricate process in male sexual development [17,18]. The rate of confirmed molecular or biochemical diagnosis was higher in patients with an XX chromosome complement (64%, 29/45) than in patients with an XY chromosome complement (12%, 8/68) (Fig. 2). All of the XX patients with confirmed diagnosis had congenital adrenal hyperplasia, and most were found to have androgen excess caused by steroid 21-

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