

## Disorders/Differences of Sex Development: A World of Uncertainty

Eric Vilain

*Department of Human Genetics,  
David Geffen School of Medicine, UCLA,  
Los Angeles, California, United States of America*

Disorders/Differences of sex development (DSD) are congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical (1). DSD encompass a very large spectrum of phenotypes, from minor malformations (hypospadias, undescended testes, hypertrophy of the clitoris) to sexual ambiguity of the genitalia. In the aggregate, DSD have an estimated incidence of about 1% and can result in serious consequences for fertility, cancer risk, behavioral health, and quality of life. In addition, recently, the debate about the management of intersex patients has intensified over issues of gender assignment and the indication for early genital surgery. Yet, the scientific data on patient outcome have remained scarce. The main obstacles to the optimal management of these patients with DSD have been a combination of lack of controlled outcome data and the lack of understanding of their pathophysiology, which prevents precise diagnostic categorization of patients. Despite much progress in the past 15 years, the molecular mechanisms underlying mammalian sex determination are still far from understood, and the molecular basis of sex reversal in the majority of XY patients (>50%) and a significant minority of XX patients (about 10%) cannot yet be explained.

Such conditions can be stressful for patients and their families and have historically been difficult to diagnose, especially at the genetic level. In particular, for cases of 46,XY gonadal dysgenesis, once variants in SRY and NR5A1 have been ruled out, there are few other single gene tests available. We used exome sequencing followed by analysis with a list of all known human DSD-associated genes to investigate the underlying genetic etiology of

46,XY DSD patients who had not previously received a genetic diagnosis. We were able to identify a likely genetic diagnosis in more than a third of cases, including 22.5% with a pathogenic finding and an additional 12.5% with likely pathogenic findings. In addition, 15% had variants of uncertain clinical significance (VUS) that may be reclassified as literature evolves (2). Exome sequencing allowed a remarkable and unprecedented level of genetic diagnostic success in this cohort, especially considering that, for most patients, all other endocrine and genetic testing had been exhausted. Early identification of the genetic cause of a DSD will in many cases streamline and direct the clinical management of the patient, with more focused endocrine and imaging studies and better informed surgical decisions. When unaffected parents are also genotyped, there is the additional possibility of identifying novel genes that will further enhance our understanding of these complex conditions and allow for better care and prognostic information for the patients and their families (3).

### References

1. Lee PA, Houk CP, Ahmed SF, Hughes IA; International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics* 2006;118:488-500.
2. Arboleda VA, Sandberg DE, Vilain E. DSDs: genetics, underlying pathologies and psychosexual differentiation. *Nat Rev Endocrinol* 2014;10:603-615. Epub 2014 Aug 5
3. Baxter RM, Arboleda VA, Lee H, Barseghyan H, Adam MP, Fechner PY, Bargman R, Keegan C, Travers S, Schelley S, Hudgins L, Mathew RP, Stalker HJ, Zori R, Gordon OK, Ramos-Platt L, Pawlikowska-Haddad A, Eskin A, Nelson SF, Délot E, Vilain E. Exome sequencing for the diagnosis of 46,XY disorders of sex development. *J Clin Endocrinol Metab* 2015;100:333-344. Epub 2014 Nov 10