Editorial

Disorders of Sex Development: Challenges for the Future

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The perpetual challenge in the diagnosis and management of patients with disorders of sex development (DSD), to paraphrase the adage, is that as our circle of knowledge in the genetic mechanisms of DSD expands, so does the circumference of darkness surrounding it. New technologies (comparative genomic hybridization, sequencing by hybridization, and next generation sequencing) are rapidly generating massive amounts of information on the pathogenesis of DSD (1). The caveat is that identifying a pathogenic mutation may not predict the clinical picture because phenotype can be highly variable, even within the same family (2). Oligogenic modulators, developmental switches, epigenetic influences, environmental stimuli, and even imbalanced *cis*-regulation of mutant *vs.* wild-type alleles when mutations are present in a heterozygous state may also be contributing factors to the variable expression of phenotype (3).

A major step forward in organizing the molecular and clinical information was the recent change in nomenclature and classification of DSD. In 2006, the Pediatric Endocrine Society (formerly known as the Lawson and Wilkins Pediatric Endocrine Society) and the European Society for Pediatric Endocrinology consensus group defined DSD as congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical, and broadly classified DSD into three groups based upon cytogenetic, hormonal, gonadal histology, and clinical findings: 46,XY DSD, 46,XX DSD, and sex chromosome DSD (4). The classification reflected the natural history of the diagnostic process in which the sex chromosomes are the usual starting point for investigations of a child with atypical genitalia. As our genetic and endocrine understanding of unclassified or syndromic conditions improves, the DSD classification, which continues to gain wide acceptance across the globe (5), has the flexibility to incorporate them into its current structure. But there is still a long way to go to where the genetic information can be used to predict long-term outcomes to provide personalized care for the DSD patient.

In some DSD, clinical diagnosis can be confirmed by hormonal and molecular testing. For example, in complete androgen insensitivity syndrome there is an 80–90% chance that a 46,XY infant with normal female genitalia and normal testosterone synthesis will have a mutation in androgen receptor gene (6). Similarly, the majority of 46,XX presenting with virilized genitalia will have congenital adrenal hyperplasia with a mutation in *CYP21A2* where genotype-phenotype correlations are excellent (7).

In cases of XY DSD with partially virilized genitalia, a molecular diagnosis has been relatively elusive so that diagnosis is guided by a thorough clinical, biochemical, and anatomical evaluation of the affected infant. For instance, only about 20% of these cases associated with normal androgen synthesis will have a mutation in the androgen receptor gene (6).

Discordance between molecular changes and functional *in vitro* transactivation studies complicate even further the efforts for attributing the particular DSD phenotype to the identified gene change. Furthermore, such functional studies continue to remain in the realms of research laboratories, and their large-scale clinical utility remains unclear. The recent identification of mutations associated with DSD in a poorly characterized MAPK sig-

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Abbreviation: DSD, Disorders of sex development.

naling pathway (8) suggests that there may be a number of other genes that may remain unidentified.

In this issue of the *JCEM*, the study by Camats *et al.* (9) highlights the perpetual challenges that are faced by the DSD classification as well as our understanding of the genetic etiology of DSD. The investigators detected and characterized 10 novel heterozygote *NR5A1* mutations from a group of 100 46,XY DSD and two primary ovarian insufficiency patients from centers in Spain, Switzerland, and Turkey. Through an international collaboration, the authors found high variability in the clinical, biochemical, histological, genetic, and functional characteristics of the 10 novel *NR5A1* mutations. Although the genotype-phenotype correlation remains elusive, the study adds to the accumulating body of evidence that approximately 10% of XY DSD patients will have a mutation in *NR5A1* and highlights the importance of collaborative efforts in building our knowledge base of DSD.

The Camats *et al.* study (9) also raises the issue that some of the phenotypic variability may be a manifestation of time-dependent deterioration of gonadal tissue and/or steroid secretion. This is an important phenomenon in DSD, where the manifestation of the gene mutation may vary depending on the age of the patient, as has been seen in other defects of testosterone synthesis and/or metabolism caused by *StAR*, *SRD5A2*, or *CYP17A1* gene mutations.

To be able to take a critical step forward and begin better utilization of the information provided in this and other studies, careful collection of clinical data that describe the phenotype at diagnosis as well as at a later stage remains a critical cornerstone for understanding etiology and long-term outcome. For these rare conditions, these data need to be serially collected in a standardized method and should ideally include a structured description of the genitalia and gonads, the endocrine biochemistry, psychological and psychosocial development, and medical and surgical therapeutic intervention.

However, to date the tools that have been available to collect these data have been very variable, have lacked uniformity, and have not been developed specifically for DSD. The 2006 Consensus Workshop on DSD stressed the need for creating and maintaining databases that can facilitate standardized collection of data that can cross-talk across geographical boundaries and facilitate international collaboration (5). An international web-based registry, the I-DSD Registry (www.i-dsd.org), has now been in operation for over 4 yr and has encouraged the development of multicenter projects as well as the development of other registries (10). It is now important that these registries continue to collect standardized uniform data so that they can cross-talk in the future. In addition to research, these registries have the potential to act as a patient management tool and can also facilitate the development of a professional and patient network.

The need for collecting standardized information and involving the clinician in this exercise is now much greater as the output from genetic analysis increases. Because increasing numbers of people with syndromal DSD are undergoing analysis using array comparative genomic hybridization and next generation sequencing, more pathogenic rearrangements are being reported, and whereas they may reveal unique insights into the mechanism of gonadal development, they may also highlight the involvement of other coexisting disease (1). In patients with disorders of gonadal development, small deletions or duplications that are likely to be causative of the condition can be found in 25% of cases where other organ systems are affected, whereas they are only found in 6% of cases where only testis development was affected (11). With the reducing costs of next generation sequencing, exome and complete genome sequencing offer much richer possibilities for understanding disease. Nevertheless, the introduction of expanded genetic testing is not without its own risk, and there is a need to develop a clinical infrastructure that can cope with the increased level of genetic information that will be available in the future. The clinical validity and relevance of the results can only be judged after thorough evaluation of the clinical features of the case. Recent guidance issued in the United Kingdom has also called for greater involvement of the clinical geneticist in the management of this information in a multidisciplinary clinical setting (12). In addition to complex genetic analysis, recent technological advances in the field of steroid analysis will lead to the identification of new enzymatic causes of DSD (13). However, this analysis will also yield a large amount of information that will require bioinformatic analysis. These specialist techniques shall only be available in a handful of centers and thus require the clinical and scientific community to increase their ability to work as a network.

Finally, future research initiatives should incorporate a move toward a greater understanding of how genetic knowledge in DSD affects the quality of life of the patient and the family. It is generally believed that the knowledge of a genetic cause of DSD helps with explaining the condition to the family and may help with genetic counseling and discussing future risks. Although this may be clear from the point of view of a condition such as congenital adrenal hyperplasia, there is little published evidence that the possession of genetic data in cases of XY DSD characterized by partial virilization alters the long-term quality-of-life outcomes.

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