

Letter to the Editor

Disorders of Sex Development: Nomenclature

The European Society for Paediatric Endocrinology (ESPE) published a classification of pediatric endocrine diagnoses in 2007. Diagnoses made by pediatric endocrinologists were divided into 14 groups, including *Disorders of Sex Development* (DSD). DSD were subdivided into the categories of Sex Chromosome DSD; 46,XY DSD; 46,XX DSD; and Unclassified Forms of Abnormal Sexual Development/Anatomical Disruptions. The impetus for this letter is the exclusion by ESPE of “disorders of gonadal differentiation that do not result in sex reversal/virilised female infant/undervirilised male” from the category of Sex Chromosome DSD. Specific examples of conditions excluded are Klinefelter syndrome and Turner syndrome, both of which are instead classified under the general category of Syndromes with Endocrine Features (subcategory of Chromosomal Abnormalities).

Although a comment on a nomenclature first published in November 2007 may seem overdue, the dilemma that the ESPE DSD classification system has created remains unresolved. To the best of our knowledge, the points we raise have not previously been enunciated, and the issue remains every bit as problematic as when the new nomenclature was first published.

In 2005, working groups, comprised of 50 international experts (including Sandberg and Vilain), members of the Lawson Wilkins Pediatric Endocrine Society (LWPES) and ESPE, assembled in Chicago to formulate a consensus document on the clinical management of individuals born with intersex conditions.¹ One of the working groups focused on nomenclature and several significant changes were adopted by the whole consensus group. The most visible modification to the previous nomenclature recommended was the removal of terms perceived as offensive such as “hermaphrodite” and “pseudohermaphrodite,” and the change of “intersex” –a politically charged and somewhat vague term–to DSD. Yet two additional profound changes were implemented. One was to incorporate all aspects of sexual variations under one umbrella term (DSD) defined as “congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical.” This allowed doing away with the simplifying notion that gonads are the only parameter defining sex. The other major modification was to remove references to gender in the diagnostic nomenclature in order to avoid gender labeling—often psychologically disturbing to the patient.

ESPE's revised classification of Sex Chromosome DSD contradicts the nosology endorsed just two years earlier at a meeting co-sponsored by ESPE itself. A group of distinguished international clinical and scientific experts from a large variety of fields (genetics, endocrinology, psychology, psychiatry, surgery) and representatives of patient support groups participated in a long and complex process involving preparation of draft documents prior to the consensus meeting, working group, and general discussions during the meeting, group writing of the consensus statement, and multiple post-meeting edits. It is unclear why one party to a consensus agreement, representing only one subspecialty (pediatric endocrinology), from one region of the world (Europe), would unilaterally modify the product of an International Consensus Group which had painstakingly considered the complex issues of nosology for DSD.

The principle guiding exclusion from Sex Chromosome DSD (ie, “disorders of gonadal differentiation that do not result in sex reversal/virilised female infant/undervirilised male”) implies that atypical genital appearance is the sine qua non of DSD. If we follow the argument that Turner and Klinefelter syndromes should not be classified as DSD because the external genitalia are normal, we should also exclude from DSD women with XY pure gonadal dysgenesis—who have normal external genitalia, males who are XX caused by a translocation of SRY, who often have normal male genitals, and even Complete Androgen Insensitivity Syndrome (CAIS), who appear at birth with normal female genitalia. One of the reasons why the term “intersex” was set aside was its vague meaning. Intersex implied sexual ambiguity, yet every physician agreed that CAIS was encompassed by the term intersex.

In addition, the nomenclature adopted at the International Consensus Conference was designed to overturn the practice of classifying DSD exclusively based on the characteristics of the gonads, which did not reflect the various parameters influencing sexual development. The definition of DSD now includes not only the gonads and the genitals, but also the sex chromosomes as a parameter.

Furthermore, excluding Klinefelter syndrome from the subcategory of sex chromosome DSD because it does not result in “undervirilised males” is questionable and depends on one's definition of “undervirilised.” Suggesting that small, dysgenetic testes, which do not support spermatogenesis—a major male function—are not undervirilised seems to be a subjective interpretation.

Finally, the ESPE document uses the word “sex reversal” that was clearly abandoned in the consensus statement because of its uncertain meaning, but reemerges in the ESPE document.

By using an argument based exclusively on the appearance of the external genitalia to eliminate Klinefelter and Turner from sex chromosome DSD, the ESPE classification implicitly undermines the value of the DSD nomenclature introduced in the consensus statement by weakening the inherent logic behind the classification system, which is about multiple aspects of sexual development, and not exclusively focused on the appearance of the genitals and the issue of gender assignment.

An argument favoring the removal of Klinefelter and Turner syndromes from the category of DSD is articulated by the editors in the foreword of the ESPE classification, where they note that “we have tried to follow the logic of the paediatric endocrine clinician as much as possible, so that it would be as easy as possible to find the diagnosis in the structure of each chapter.” However, they also state that the coding system should “follow one general principle (e.g. nosology, aetiology, pathogenesis or symptomatology).” The editors have followed both standards: the latter, principle-driven, by embracing the term DSD and its definition, and the former, practitioner-friendly, by inserting Klinefelter and Turner syndrome in a different section where it has traditionally been found. The classification of DSD could indeed be entirely based on clinical phenotype and clinician observations. Turner syndrome could then be classified with XY gonadal dysgenesis and

CAIS, based on the appearance of the external genitalia. This would discount recent advances in the understanding of DSD, which are crucial in outcome and prognosis studies. Classifications and nomenclatures evolve with science, and the comfort of practicing endocrinologists should be balanced with the realities of biology and the specific needs of our patients. This is why Turner and Klinefelter syndromes, which are clear disorders of sexual development, undoubtedly belong within the DSD classification.

Reference

1. Lee PA, Houk CP, Ahmed SF, Hughes IA, in collaboration with the participants in the 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. *Pediatrics*. 2006;118:e488-500.

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REVIEWS & COMMENTS FROM THE LITERATURE

Another Cause of Primary IGF Deficiency

Primary insulin-like growth-factor deficiency (PIGFD), abnormally low levels of IGF-I despite normal or elevated levels of growth hormone (GH), has been attributed to mutations in 4 genes to date: *GHR*, *IGF1*, *STAT5b*, and *IGFALS*. *IGFALS* encodes the acid-labile subunit (ALS) of the ternary complex, also under GH control. Fofanova-Gambetti et al reported 2 patients with 3 novel mutations in *IGFALS*, plus another 2 patients in the amendment while the paper was in press, to add to the currently published tally of 5 patients from 3 families harboring 4 different mutations. Of note, in contrast to patients with mutations of the other PIGFD genes, all patients with *IGFALS* mutations presented with modest short stature (height z-scores above -3 SD).

Previously published patients:

Case 1: A boy aged 14.6 years from Argentina with a height z-score of -2.05 SD and homozygous *IGFALS* mutation 1338delG (E35fsX120), in the amino terminal flanking region.¹

Case 2: A Turkish boy aged 12.1 years with a height z-score of -2.9 SD and homozygous *IGFALS* D440N missense mutation in the 17th leucine-rich repeat (LRR) domain.²

Cases 3-5: Three Norwegian/German siblings (2 male, 1 female) aged 15.3 to 19.6 years, with height z-scores of -0.5 to -2.0 SD and compound heterozygous C540R/583_591dup9 *IGFALS* mutations in the cysteine-rich region of the carboxy terminus and the 7th LRR domain, respectively.³