

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

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ERIC VILAIN, MD, PHD

*Professor of Human Genetics, Pediatrics and Urology
Director, Center for Gender-Based Biology
Chief, Medical Genetics, Department of Pediatrics
David Geffen School of Medicine at UCLA
Los Angeles, California*

DAVID E. SANDBERG, PHD

*Associate Professor, Pediatrics and Communicable Diseases
Director, Division of Child Behavioral Health
University of Michigan Medical School
Ann Arbor, Michigan*

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

Currently reported patients:

Case 1: A boy of 6.7 years of Mayan origin with a height z-score of -2.91 SD, delayed bone age (5.5 years) and homozygous *IGFALS* 1308_1316 dup9 mutation in the 17th LRR domain. GH treatment began at the age of 8.5 years and was discontinued 1 year later due to development of nonalcoholic steatotic hepatitis. The patient's transaminase levels continued to climb when he was off treatment, however they subsequently returned to normal. GH therapy was tried again from age 10 years for another 2 years. Despite increasing doses of GH, he failed to improve his growth velocity or normalize his IGF-I and IGF binding protein (IGFBP)-3 levels. During this time, at the chronological age of 10.5 years, he initiated spontaneous puberty and was started on LH-RH analogue therapy to preserve growth potential while on GH. At age 12 years, he was switched from GH to IGF-I therapy.

Case 2: A girl aged 4.1 years of Eastern European Jewish/Icelandic-Western European ethnic origin with a height z-score of -2.14 SD, bone age consistent to her chronologic age, and compound heterozygous *IGFALS* C60S/L244F missense mutations in the 1st and 9th LRR domains, respectively. She started GH treatment at age 4.4 years, increasing her height z-score in 13 months to -1.67 SD; IGF-I and IGFBP-3 levels nonetheless remained abnormally low, and ALS was undetectable.

Patients reported in the amendment:

Case 1: An Indian/Pakistani boy aged 15.2 years with a height z-score of -3.17 SD, delayed bone age (11 years), sexual infantilism and homozygous *IGFALS* L134Q missense mutations in the 4th LRR domain. His parents, both heterozygous carriers, had normal heights (-0.09 and -1.35 SDS).

Case 2: An Ashkenazi Jewish boy aged 12.7 years with a height z-score of -2.87 SD, bone age of 11.5 years, sexual infantilism and compound heterozygous *IGFALS* P73L/L241P missense mutations in the 1st and 8th-9th LRR domains, respectively. His parents, both heterozygous carriers of one of the mutations, had normal heights (-1.68 and $+0.85$ SDS).

ALS protein, a member of the LRR superfamily of proteins involved in protein-protein interactions, contains 20 LRR domains that form a donut shape with a closed structure. The LRRs contain β -strands that form sheets inside the donut, and α -helices that flank the structure's outer circumference. This paper highlights the ethnic

and genetic heterogeneity of *IGFALS* mutations that are pathogenic in causing PIGFD and modest short stature that responds poorly to GH therapy. Although GH can induce IGF-I and IGFBP-3 production, without ALS, circulating levels of the growth factor are not sustained. This is a nice in vivo illustration of the importance of the ternary complex in prolonging the circulating half-life, and hence activity, of IGF-I.

Fofanova-Gambetti OV, Hwa V, Kirsch S, et al. Three novel *IGFALS* gene mutations resulting in total ALS and severe circulating IGF-I/IGFBP-3 deficiency in children of different ethnic origins. *Horm Res.* 2009;71:100-110.

Editor's Comment: *Genotyping of the parents of Girl #2 in this paper was not available. The authors hypothesized that her mutations must be in the compound heterozygous state because her ALS protein was undetectable; had her mutations occurred in cis, then her wild-type allele would be expected to produce wild-type ALS that should have been detected, as was the case for the carrier parent of the Turkish boy with a homozygous missense mutation.² Another possibility is that the double mutations in cis so altered the ALS protein product that it functioned as a dominant negative, tying up the wild-type ALS in the ER or Golgi and preventing its secretion. This second hypothesis would require that one of the parents similarly carry the dominant negative in cis mutations, have undetectable ALS, and be affected. The father's height z-score was $+0.30$ SD while the mother's was -2.13 SD. Since one of the main teaching points of this paper is that ALS mutations cause PIGFD with only modest short stature, perhaps the mother is affected like her daughter?*

Adda Grimberg, MD

References

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3. Domene HM, Scaglia PA, Lteif A, et al. Phenotypic effects of null and haploinsufficiency of acid-labile subunit in a family with two novel *IGFALS* gene mutations. *J Clin Endocrinol Metab.* 2007;92:4444-4450.

Acute Vascular Effects of GH Appear to be Independent of Both Local and Systemic IGF-I Production

Growth hormone (GH) has been shown to regulate vascular tone and reactivity in humans, but it is unclear whether this action is a result of a direct stimulatory effect of GH or if it is dependent on systemic and local insulin-like growth factor (IGF)-I production. In this study, Li et al

evaluated the mechanisms underlying the acute vascular effects of GH. Ten healthy lean young volunteers (20 to 27 years of age; 7 male and 3 females) were studied after an overnight fast. GH was infused for 6 hours at 0.06 mcg/kg/minute and a biopsy of the vastus lateralis muscle was