

Letter to the editor: Genetic testing for the child with short stature – Has the time come to change our diagnostic paradigm?

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I deeply appreciate the article published by Dauber in the *JCEM* titled “Genetic testing for the child with short stature – Has the time come to change our diagnostic paradigm?” (1), which outline a “Copernical revolution” in short stature management, with the major points being the crucial role of familial short stature (FSS) in order to discover dominantly inherited disorder (and not anymore a normal variant, undeserving of any evaluation and treatment) (2) and the suggestion to focus more attention on the growth plate as the primary site of growth disturbances in contrast to the classic endocrine hormonal pathways, even in absence of clear skeletal dysplasia.

Until a few years ago, in a case of FSS only genes involved in the GH-IGF-1 axis were evaluated (eg GH1). The use of the NGS has allowed to understand that normal variation in height is due in largely to genes outside the GH-IGF-1 axis, therefore growth failure may be caused by multiple molecular defects involving paracrine signaling (eg FGFR3, IHH, NPR2), extracellular matrix molecules (eg. ACAN), intracellular processes (e.g. SHOX, PTPN11 ...), apart from hormones (and not just GH and IGF-1, its binding protein ALS, but also GH and IGF-1 receptors, and its downstream signaling molecule, STAT5B) (3).

What is not stressed enough in this article are the practical implications that this revolution could have, being a change not only in the diagnostic but also in the therapeutic paradigm.

The gain on definitive stature was reported to be lower in children with FSS treated with rhGH (4), while we now know that sub-classes of patients with mutations in specific genes may have a good response to treatment (eg IHH, SHOX, PTPN11 ...). As for other conditions (eg Turner syndrome ...) the use of rhGH will not be a replacement therapy (filling a specific defect), but may provide a recovery growth in any case, although it is always conceivable that children with the same genetic defect may respond differently to rhGH, as in PTPN11 mutations.

On the contrary, genetics can also tell us in which cases a treatment with rhGH is useless (eg NPR2) or even dangerous, as in chromosomal instability syndromes which contraindicate the use of rhGH therapy for an increased oncological risk. Some of these children (eg Bloom syndrome and Fanconi anemia) may be eligible for rhGH treatment because of small-for-gestational-age (SGA)

indication, therefore it is mandatory to rule out these conditions before starting treatment with rhGH.

Understanding what we can (or cannot) and should (or should not) do therapeutically is therefore the next step in this “revolution”, leading to a tailored medicine. Comprehensive large scale studies aimed to test the causative gene-specific GH responsiveness are now needed to better personalize the management of short stature.

I really believe that patients with pediatric short stature (not just idiopathic, but also FSS and SGA) should undergo genetic screening and that in 21st century this cannot be just an option, since it could be more worthwhile than GH stimulation tests in many instances.

References

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