Genetic Techniques in the Evaluation of Short Stature

Christopher J. Romero, MD[a,b,*], Lakshmi Mehta, MD[c], Robert Rapaport, MD[a,d]

KEYWORDS

• Short stature • Height • Genome-wide analysis • Microarray analysis
• Whole-exome sequencing

KEY POINTS

- Many children with short stature do not have a cause to explain the disorder.
- Several genetic techniques, some of which are clinically available and others at the research stage, are helping to identify potential variants to explain short stature.
- Understanding these techniques will assist clinicians in their appropriate use and also help to foster support in expanding genetic screening to delineate mechanisms of poor growth.

INTRODUCTION

Normal growth is a complex dynamic process dependent on the coordination of multiple factors, including genetics and nutrition, as well as biological factors such as hormones, all working in balance. Any acute or chronic pathologic process may interfere with normal growth.[1] The typical endocrine evaluation comprises a history, physical examination, and laboratory testing, including hormone levels and radiological studies. A genetic evaluation usually depends on initial clinical and laboratory findings. In many cases an endocrine, nutritional, or chromosomal abnormality is not apparent. However, the expansion of genetic technology has increased the diagnostic yield of genetic testing. Ongoing research efforts to identify genes influencing growth will provide a better understanding of mechanisms underlying abnormal growth and will eventually lead to novel management approaches.

Disclosure: The authors have nothing to disclose.
[a] Division of Pediatric Endocrinology and Diabetes, Kravis Children's Hospital at Mount Sinai, One Gustave L. Levy Place, Box 1616, New York, NY 10029, USA; [b] Department of Pediatrics, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1616, New York, NY 10029, USA; [c] Division of Medical Genetics, Department of Genetics and Genomic Sciences & Department of Pediatrics, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1616, New York, NY 10029, USA; [d] Division of Pediatric Endocrinology and Diabetes, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1616, New York, NY 10029, USA
* Corresponding author.
E-mail address: christopher.romero@mountsinai.edu

Endocrinol Metab Clin N Am 45 (2016) 345–358
http://dx.doi.org/10.1016/j.ecl.2016.02.006 **endo.theclinics.com**
0889-8529/16/$ – see front matter

This article focuses on describing some of the current advances in genetic testing that can be used as part of the diagnostic evaluation of children with short stature. This article is not intended to be comprehensive, but rather to educate the reader on the increasing efficiency of genetic screening tools that will eventually provide clinicians with important diagnostic capabilities for the evaluation of children with abnormal stature.

GENETIC TESTING STRATEGIES

The approach to understanding disorders at the level of the DNA currently has several options. Depending on the clinical phenotype or the specific trait of interest, clinicians or investigators have several choices for how to screen a patient or cohort of patients. Some testing is commercially available, whereas other genetic tests have not been fully validated or standardized and are only available through research protocols. This testing ranges from conventional chromosome analysis and microarray analysis, to sequencing of single genes, sequencing of a panel of genes, or to whole-exome sequencing (WES). Each technique has advantages as well as limitations. The article explores how these techniques have affected clinical practice and helped further the understanding of the mechanisms of growth. Abnormal expression of imprinted genes has been associated with overgrowth and poor growth in syndromes such as Beckwith-Wiedemann and Russell-Silver syndrome. Methylation testing to detect active and inactive genes in imprinted areas of the genetic material is also available to screen children presenting with features suspicious for these syndromes. However, this group of disorders is not discussed in detail.

CHROMOSOME ANALYSIS

Chromosomal analysis or karyotyping has become an effective and efficient tool in the diagnosis of patients with short stature. It involves the visual examination of G-banded chromosomes in order to detect large structural deletions and duplications, monosomies, trisomies, and balanced rearrangements. Typically, these patients present with characteristic phenotypic features that include short stature. An example is mosaic Turner syndrome; however, short stature in a female patient may be sufficient justification to study chromosomes and thus has been argued as means to identify Turner syndrome at an earlier age.[2] In the case of tall stature, phenotypic features of Klinefelter syndrome (XXY), is another example in which the evaluation of chromosomes is useful. Fluorescence in situ hybridization (FISH) can complement karyotyping in order to detect various small chromosomal abnormalities, such as deletions and duplications. This technique has been used, for example, to detect whole-gene deletions of the short stature homeobox-containing gene (*SHOX*), which have been associated with Leri-Weill dyschondrosteosis (LWD), but have also been implicated as a cause of short stature in children in whom full endocrine evaluations have not identified causes for their poor growth.[3]

A karyotype with FISH may also detect specific suspected microdeletion syndromes. Deletions of chromosome 22q11.2 are among the commonest of all microdeletions and are associated with short stature, often in conjunction with other birth defects, typically congenital heart defects or cleft palate (DiGeorge or velocardiofacial syndromes). However, the presence of a supernumerary chromosome derived from chromosome 22 has been reported to cause cat-eye syndrome.[4,5] It is associated with anal atresia, coloboma of the iris, ear malformations, and short stature, and in rare cases growth hormone (GH) deficiency.[5] In another example, there is a