Genetics of Short Stature

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KEYWORDS

• Short stature • Genetic causes • Growth plate • Genome-wide association study • Exome sequencing

KEY POINTS

- Over the past decades, advances in clinical genetics, including exome sequencing, have accelerated the identification of new genetic growth disorders and thereby greatly contributed to the understanding of the underlying molecular mechanisms of longitudinal bone growth and growth failure.
- This new knowledge will help the individual patient seeking medical attention due to severe short stature, as it will improve the chances of an exact mechanistic diagnosis, which in turn enables individualized diagnosis/management, prognostic accuracy, and better genetic counseling and may also help avoid unnecessary testing for endocrine and other disorders.
- As more genetic causes become identified, better classifications of growth disorders will become possible.

INTRODUCTION

Short stature is a common medical concern that pediatricians and pediatric endocrinologists often evaluate in their daily practice because poor growth may be a symptom of an underlying, treatable medical condition.[1] Linear growth is the result of

Disclosure: This work was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (ZIA HD000640), NIH (ZIA HD000640). Dr O. Nilsson was supported by grants from the Swedish Research Council (Grant no. 521-2014-3063 and 2015-02227), the Swedish Governmental Agency for Innovation Systems (Vinnova) (2014-01438), Marianne and Marcus Wallenberg Foundation (2014.0096), the Stockholm County Council (2015-0442), Byggmästare Olle Engkvist's Foundation (2015/27), Stiftelsen Frimurare Barnhuset i Stockholm, and Karolinska Institutet. Dr A.C. Andrade was supported by grants from Sällskapet Barnavård.

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Endocrinol Metab Clin N Am 46 (2017) 259–281
http://dx.doi.org/10.1016/j.ecl.2017.01.001 **endo.theclinics.com**
0889-8529/17/Published by Elsevier Inc.

chondrogenesis at the growth plate and all forms of short stature are therefore due to decreased chondrogenesis at the growth plates.[2] Growth plate chondrogenesis and therefore linear growth are regulated by multiple systemic factors, including nutritional intake, hormones, and inflammatory cytokines.[3] Consequently, systemic diseases, such as hypothyroidism, celiac disease, and other chronic disorders impair childhood growth. In addition, growth plate chondrogenesis is regulated by multiple local factors, including intracellular regulatory mechanisms in the growth plate chondrocytes, cartilage extracellular matrix components, and paracrine factors in the growth plate. As a result, genetic defects in these local growth plate systems can also result in short stature (**Fig. 1**).

Height variation within the normal range involves similar mechanisms. In 2010, a genome-wide association (GWA) study revealed 180 loci that explain approximately 10% of height variation[4] and a more recent GWA study identified approximately 400 loci that are associated with adult height in the general population.[5] It is likely that many children have mild short stature because they have inherited multiple polymorphisms, each of which tends to slightly inhibit growth plate chondrogenesis and in fact, the loci implicated by GWA studies are shown enriched in genes that are expressed and important for growth plate function.[4–6] Taken together, these findings suggest that normal growth is modulated by several hundred or maybe even thousands of genes that affect growth plate function. Therefore, polymorphism and mild mutations in these identified genes may modulate height within the normal range and perhaps cause mild polygenic short stature, whereas mutations with a stronger effect on protein function and/or biallelic mutations may cause significant monogenic short stature or skeletal dysplasias.

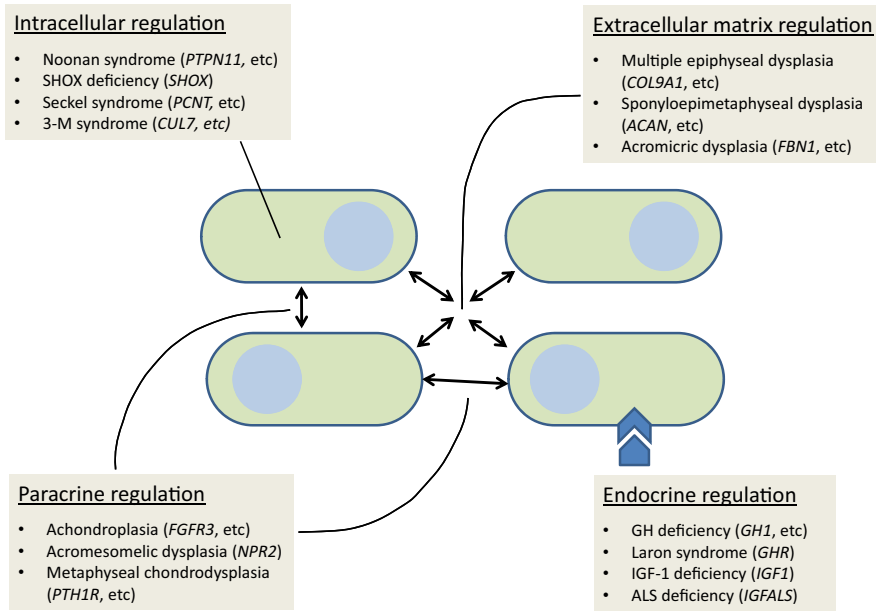

Fig. 1. Molecular mechanisms of short stature. Short stature is caused by multiple molecular defects, including intracellular signaling, extracellular matrix, and paracrine and endocrine regulation. Ovoid shapes represent growth plate chondrocytes. Arrows indicate mechanisms regulating chondrocytes. Examples of clinical syndrome and the genetic cause under different molecular mechanisms are shown in each box.

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