The Genetics of Growth and Growth Disorders: From the Hypothalamus to the Epiphysis

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At least 423 common variants with low effect size have been identified by genome-wide association studies (GWAS) to have an effect on height in normal range. Mutations in >130 genes have been found in patients with short stature and in 16 with overgrowth (1,2). The SHOX gene appears to be the "master controller" of human height. Rare deleterious gene mutations affecting height have been described throughout the growth hormone-releasing hormone (GHRH)- GH- insulin-like growth factor-1 (IGF-I) pathway (3), involving the GHRH receptor, pituitary-specific transcription factors, GH, the GH receptor (Laron syndrome), post-GH receptor JAK/STAT signaling (STAT5B), IGF-I, and the type 1 IGF (IGF-1) receptor. More recently, studies have concentrated on investigations of target tissue defects involving the endochondral growth plate and its hormonal regulators. The schema below (4) has been developed in which various growth plate-centered genes have been linked to severe and mild forms of short stature, as well as to tall stature, depending on whether mutations are homozygous or heterozygous, and whether they are inhibitors (red) or activators (green) of protein regulation. With increased identification of genes that regulate growth, the number of cases of "idiopathic short stature" will inevitably decrease.

Gene/ Pathway	Severe short stature	Mild short stature	Tall stature
FGFR3	Achondroplasia, hypochondroplasia, thanatophoric dwarfism	ISS	CATSHL (camptodactyly, tall stature, and hearing loss) (AD)
SHOX	Langer mesomelic dysplasia	Leri-Weill dyschondrosteosis, isolated SHOX deficiency, Turner syndrome	Klinefelter syndrome Triple X syndrome XYY syndrome
FBN1	Acromicric dysplasia, Weill-Marchesani syndrome, Geleophysic dysplasia		Marfan syndrome (AD)
NPR-2	Acromesomelic dysplasia, Maroteaux type (AR)	Non-syndromic ISS (AD)	Tall stature, scoliosis, arachnodactyly, long hallux (AD)
Ras-MAPK	Noonan, LEOPARD, Costello, NF1-Noonan, cardiofaciocutaneous syndromes		Sotos syndrome

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