

A Novel Skeletal Dysplasia With Developmental Delay and Acanthosis Nigricans Is Caused By a LYS650MET Mutation in the Fibroblast Growth Factor Receptor 3 Gene

Mutations that cause the achondroplasia group of human chondrodysplasias map to a small number of codons in the fibroblast growth factor receptor 3 (*FGFR3*) gene. For example, almost everyone with typical achondroplasia has a mutation of codon 380, and all infants with the type II variant of thanatophoric dysplasia (TDII) have mutations at codon 650. This genetic homogeneity contrasts with the dispersion of mutations through host genes in many disorders that involve extracellular matrix proteins. There is now a new twist regarding *FGFR3* mutations.

Groups from California and Maryland have identified a novel clinical phenotype associated with a mutation of *FGFR3* codon 650 that is distinct from TDII. In TDII, the mutation changes the normal lysine at position 650 to a glutamic acid. A methionine residue is substituted for lysine 650 in the new disorder. This single amino acid difference produces substantial differences in manifestations.

Four unrelated patients were reported by Tavormina and colleagues. They all exhibited growth deficiency comparable to the type I variant of TD. However, they survived past infancy without prolonged life-support measures. The patients developed extensive areas of acanthosis nigricans beginning in early childhood, and they all suffered from severe neurologic impairment. The authors refer to the clinical phenotype as SADDAN (Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans). Lysine 650 resides in the activation loop of the tyrosine kinase domain of *FGFR3*, where it helps to regulate kinase activity in response to fibroblast growth factor ligand binding to the receptor. The kinase phosphorylates intracellular substrates, thereby initiating signals that influence bone growth. The TDII mutation has been shown to activate kinase activity in absence of ligand binding. A similar constitutive activation of kinase activity was demonstrated for the SADDAN mutation. In fact, the level of activation was higher for the SADDAN mutation than for TDII and achondroplasia mutations. The authors suggest that the SADDAN mutation may do more than activate the receptor in the absence of ligand. For example, it may affect downregulation of the activated receptor. They also suggest that the different amino acid substitution in SADDAN versus TDII may

alter the specificity for substrate-signaling molecules that transmit *FGFR3* signals inside cells.

Tavormina PL, et al. *Am J Hum Genet* 1999;64:722-731.

Editor's comment: The *FGFR3* story continues to unfold. This report highlights the importance of the kinase region of the receptor, lysine 650 in particular, in understanding the pathogenesis of the achondroplasia group of disorders. It also underscores the importance of delineating differences in clinical phenotypes so that the functional consequences of mutations can be defined.

The report raises some interesting questions. For example, is acanthosis nigricans a consequence of the SADDAN and not the TDII mutation? Or would TDII infants develop the skin lesions if they survived longer? Why is codon 650 so mutable? Will other mutations be found in *FGFR3*, or have most or nearly all the mutations already been found, as is commonly believed?

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A Comparison of Target Height Estimated and Final Height Attained Between Swedish and Hong Kong Children

The investigators compared the target height (TH) equations of Luo et al, the final parental height method, derived for a Swedish population (see *GGH* 1999;15:13-14), and those of Tanner (derived from an English population) in Chinese subjects living in Hong Kong in whom adult stature was 10 to 12 cm less than that of the Swedish subjects. They found that on average the Tanner equations (corrected midparental height) underestimated adult stature by 4.5 cm, whereas the Luo equations gave values close to achieved mean adult heights in both males and females. However, there were wide ranges (± 10 cm) of calculated TH for both sets of equations. The discrepancy between the 2 sets of TH

prediction equations was exaggerated in subjects with low midparental heights. The authors conclude that the Luo equations are superior to the Tanner equations for estimation of TH.

Luo ZC, et al. *Acta Paediatr* 1999;88:248-252.

Editor's comment: This article is brought to your attention as only a limited number of pediatricians know about the Luo equations (final parental height) method for estimation of TH, which may more accurately evaluate the effect of growth-promoting agents on the growth of pediatric patients. These equations have now