

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?

William A. Horton, MD

Editorial Board

Chairman

Robert M. Blizzard, MD
Charlottesville, Virginia

Associate Editors

William L. Clarke, MD
Charlottesville, Virginia

William A. Horton, MD
Portland, Oregon

Judith G. Hall, MD
Vancouver, BC, Canada

Fima Lifshitz, MD
Miami, Florida

Allen W. Root, MD
St. Petersburg, Florida

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

been validated in a population in which adult height is far less and there is a secular trend for increased adult stature compared with that of the (stable) Swedish population. If the validity of the Luo equations is further confirmed, they will be more widely utilized and could replace the corrected midparental height of Tanner. Those of you who are particularly interested and/or concerned

about the auxologic tools we use in clinical practice and in research will appreciate this article.

Allen W. Root, MD

Luo ZC, et al. *Pediatr Res* 1998;44:563-571.

Effects of Thyroxine as Compared With Thyroxine (T₄) Plus Triiodothyronine (T₃) in Patients With Hypothyroidism

The authors studied 33 patients receiving either replacement T₄ therapy for chronic lymphocytic thyroiditis (CLT) or suppressive therapy after near-total thyroidectomy because of thyroid cancer. Sixteen had CLT and 17 had thyroid cancer. Mean age was 46±13 years and mean T₄ dose was 175 ± 53 µg/d at baseline. After randomization, patients were assigned to receive T₄ alone for 5 weeks followed by T₄ + T₃ for 5 weeks or vice versa. On the last day of each 5-week period, thyrotropin, thyroid hormones, cholesterol, triglycerides, and sex hormone-binding protein (SHBP) were measured. Physiologic measurements, including pulse, blood pressure, electrocardiogram, sensory threshold, and Achilles tendon reflex, were recorded. Psychological assessment included cognitive function and psychological state.

Significant higher serum T₄ and free T₄ levels were found after T₄ treatment, compared with the combined treatment group. Significantly lower SHBP levels and heart rates also were observed during T₄ treatment. Conversely, after combined treatment, patients showed higher serum total SHBP levels and heart rates. However, those values remained within normal limits in both groups. Serum thyroid-stimulating hormone (TSH), cholesterol, triglycerides, blood pressure, sensory threshold, and Achilles tendon reflex relaxation half-time were similar with both treatment regimens. Significantly higher scores on the digit symbol test indicated better incidental learning, and the higher scores on the digit span test indicated improved mental flexibility and attention. After receiving T₄ + T₃, patients tended to be less depressed and experi-

enced less fatigue-inertia, depression-dejection, and anger-hostility. At the end of the study, 20 patients preferred T₄ + T₃ treatment, 2 preferred T₄ alone, and 11 had no preference.

The authors concluded that patients with hypothyroidism may benefit from partial substitution of T₃, improving their mood and neuropsychological function.

Bunevicius R et al. *N Engl J Med* 1999;340:424-429.

Editor's comment: Triiodothyronine treatment has been proven to be effective in several conditions, including myxedema coma and selective pituitary thyroid hormone resistance. In addition, Escobar-Morreale et al demonstrated that tissue euthyroidism and normal serum concentrations of T₃, T₄, and TSH were achieved in rats only with the administration of a combination of thyroid hormones (*Endocrinology* 1996;137:490-502). In the present study, Bunevicius et al add data to support the potential significance of adding T₃ to the conventional T₄ therapeutic regimen in hypothyroidism. The authors demonstrated not only increases in serum T₃ levels but also improvements in mood and neuropsychological function without total suppression of TSH concentrations. However, long-term studies are necessary to establish the effectiveness of combined treatment with T₄ and T₃, in particular the long-term effects on bone mineralization and cardiovascular function.

Fima Lifshitz, MD

Gene Mutations With Characteristic Deletions in Cord Blood T Lymphocytes Associated With Passive Maternal Exposure to Tobacco Smoke

The risks for cancer, heart disease, and other chronic illness are well known for adults who use tobacco, as are the risks for growth deficiency for fetuses exposed transplacentally to tobacco smoke. Now there is evidence that prenatal exposure to tobacco increases the risk for childhood malignancy. Finette et al used *HPRT* as a reporter gene to study the genetic consequences of tobacco exposure in utero. They analyzed *HPRT* mutations in cord blood T cells from newborn infants of mothers who had been exposed passively to tobacco smoke and of mothers with no known exposure. They searched especially for differences in types of mutations. The results showed the smoke-exposed infants harbored a higher frequency of a genomic deletion commonly associated with early childhood leukemias and lymphomas. The deletions are referred to as "illegitimate" mutational events because they are mediated by V(J)D recombinase activity, which normally mediates genomic rearrangements responsible for T-cell receptor and immunoglobulin diversity. The authors emphasized that the frequency of mutations was not statistically

different between the 2 patient groups; rather, it was the type of mutations that differed. They noted that tobacco-derived nitrosamine derivatives from O6-methylguanine adducts have been detected in fetal cord blood of leukocyte DNA of primates and raise the possibility that these adducts could be related mechanistically to the mutations.

Unfortunately, too few T-cell clones were isolated from infants whose mothers had smoked to be included in the analysis. The authors, as well as the authors of an accompanying editorial (Sozzi G, et al. *Nat Med* 1998;4:1119-1120) cautioned that the results need to be confirmed by other studies.

Finette BA, et al. *Nat Med* 1998;4:1144-1151.

Editor's comment: This is an intriguing article because of its clinical implications. The following is abstracted from the editorial by Sozzi et al appearing in the same issue: