

Intriguingly, previously unanswered questions in all probability will now be answered. Application of this methodology to measurement of other substances present in small amounts in other body fluids is anticipated. The importance of this article is 2-fold: (1) it sets the precedent for a new type of assay for measuring exceedingly small quantities of substances in fluids; and

(2) estrogen is measured in serum at levels never before attainable. Readers may wish to refer to the original article for details concerning the methodology. Congratulations Dr. Klein and collaborators.

Allen W. Root, MD

Identical Mutations in the *FGFR2* Gene Cause Both Pfeiffer and Crouzon Syndrome Phenotypes

Pfeiffer and Crouzon syndromes are 2 well-characterized autosomal dominant malformation syndromes. Both exhibit craniosynostosis, or premature fusion of the skull bones. Patients with Pfeiffer syndrome also manifest digital abnormalities, including broad, medially deviated great toes and thumbs and variable degrees of syndactyly or brachydactyly of other digits. Although subtle differences exist in the craniofacial features, it is the presence or absence of digital abnormalities, which typically breeds true in families, that distinguishes the 2 syndromes.

Very recently, mutations in the fibroblast growth factor receptor 1 (*FGFR1*) gene have been found in Pfeiffer syndrome and mutations in the *FGFR2* gene have been identified in Crouzon syndrome. The mutations map to similar locations in the respective genes. Surprisingly, Rutland et al now have demonstrated that both Pfeiffer and Crouzon syndromes can result from *FGFR2* mutations. Five patients with Pfeiffer syndrome had a mutation identical to one found previously in a patient with Crouzon syndrome, and 1 patient with Pfeiffer syndrome had the same mutation detected in 3 cases of Crouzon syndrome. Furthermore, the amino acid substitutions that resulted involved residues immediately adjacent to one another: Cys 342 and Pro 341.

These observations raise interesting questions about how the same mutations can give rise to 2 syndromes that have been considered distinct. This article and an accompanying editorial discuss several possibilities. One is genetic variation in other loci whose gene products interact functionally with the

mutant *FGFR2* gene product. The interaction between fibroblast growth factors and FGFRs is known to be very complex. Another possibility is a genetic variation in the second "normal" *FGFR2* allele or a variation occurring at another location in the same "mutant" *FGFR2* allele.

Rutland P, et al. *Nat Genet* 1995;9:173-176

Editor's comment: *Ignorance is a wonderful thing. In the absence of facts it is easy, even fun, to speculate about how diseases come about. Indeed, as pointed out in Mulvihill's editorial, the classic genetic concepts of variable expressivity and pleiotropy have served us well to explain phenomena such as reported here. Differences in genetic background also were commonly invoked to explain such observations. However, as knowledge chips away at ignorance, our explanations must be revised accordingly. The findings reported here provide an excellent opportunity to explore specific mechanisms by which identical mutations can produce seemingly different clinical syndromes. In any event, it is now clear that signaling through the *FGFR2* receptor is very important to both craniofacial and limb development and that alterations in the extracellular domains of this receptor protein can lead to well-defined malformation syndromes.*

William A. Horton, MD

Mulvihill JJ. Craniofacial syndromes: no such thing as a single gene disease. *Nat Genet* 1995;9:101-102. Editorial.

Deconvolution Analysis of Spontaneous Nocturnal Growth Hormone Secretion in Prepubertal Children With Preterminal Chronic Renal Failure and With End-Stage Renal Disease

Tönshoff et al studied spontaneous nocturnal growth hormone (GH) secretion in 12 children with end-stage renal disease (ESRD) and in 11 children with preterminal chronic renal failure (CRF), and in a control group of 12 matched children with idiopathic short stature (ISS). All subjects were prepubertal. The children with ISS were defined by normal plasma GH responses to pharmacologic stimulation and height ≤ 2 standard deviations (SD) below age- and sex-matched normative values and the exclusion of any endocrine or other metabolic disorders. The children with preterminal CRF were defined as those with a glomerular filtration rate (GFR) of < 70 mL/min/ 1.73m^2 . Children with ESRD were on regular continuous ambulatory peritoneal dialysis. All had growth retardation defined

as a height SD score for chronologic age ≤ -2 and a height velocity SD score for chronologic age ≤ 0 . The primary renal disease in these children was renal dysplasia/hypoplasia ($n=8$) and chronic glomerulopathy ($n=6$). Patients with renal disease were receiving vitamin D, water-soluble vitamins, oral phosphate binders, and oral sodium bicarbonate; they did not receive glucocorticoids, immunosuppressants, or clonidine.

All subjects underwent blood sampling (0.5 mL) every 20 minutes for 10 hours, beginning at 2000. Multiparameter deconvolution analysis was used to determine the number, duration, amplitude, and mass of GH secretory bursts, and to estimate the subject-specific GH half-life in children with preterminal CRF and ESRD. Data were reported as means