

initiate treatment and monitor development during treatment. The determination of bone age using a computer-assisted system proved a valid and reliable method. This will compensate for the additional time that needs to be invested. Future studies evaluating the effect of growth-promoting treatment in TS, by growth hormone or other means, should use such a computerized method for the determination of bone age.

Schwarze CP, et al. *Acta Paediatr* 1998;87:1146-1150.

Editor's comment: There are currently 2 computer programs for the analysis of BA, both based on the TW2-RUS system: (1) CASAS, and (2) the Royal Orthopedic Hospital Skeletal Aging System – in which the digitized image can be obtained from a radiograph or directly from files and the bones are recognized

by their position on the image (Aicardi G, et al. *Acta Med Auxol* 1998;30:121-127). In addition, investigators at the Universities of Genoa and Florence are in the preliminary stages of developing computer programs for BA determination. Apparently, computer programs utilizing the Greulich and Pyle atlas or other methods for BA determination have yet to be developed. One wonders if current technology permits the computerized construction of 3-dimensional images of the wrist, hands, and other epiphyses that might afford further insight into the developmental changes that accompany growth and development of the skeleton and perhaps even better assessment of skeletal maturation—perhaps by determination of bone volume or other measurement. Regardless, more widespread utilization of CASAS is important for consistency within and among institutions.

Allen W. Root,

Difference in Height Associated With a Translation Start Site Polymorphism in the Vitamin D Receptor Gene

Because calcitriol (1,25-dihydroxyvitamin D₃) is an important regulatory factor in the differentiation and proliferation of chondrocytes, the investigators speculated that various isoforms of the vitamin D receptor (VDR) might influence the effect of calcitriol on these processes and ultimately on linear growth. The VDR is polymorphic, in part because of 2 possible "start sites" in exon 2, one encoding a 427 amino acid peptide, the other a 424 amino acid molecule. The 2 isoforms are designated T and C, respectively, for the polymorphic alleles ATG/ACG at the first start site.

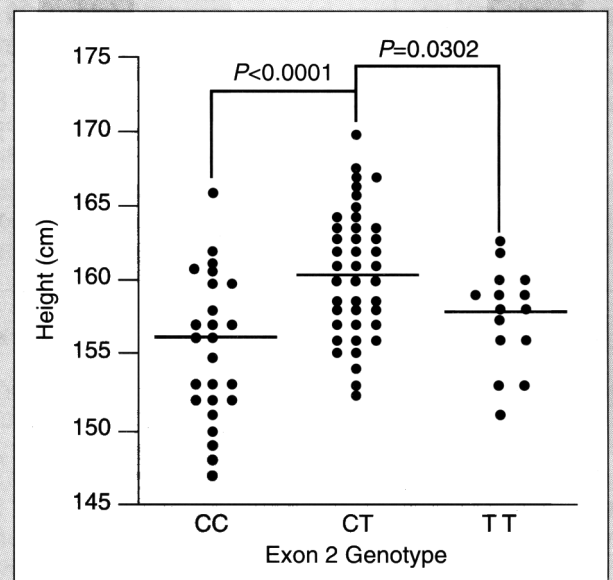
The authors examined the relationship between the presence/absence of the 2 variants of the VDR and the adult height in 90 healthy Japanese females (Figure), the height at age 13 years of 159 healthy Japanese children, and the height of 24 children aged 6 to 10 years with constitutional short stature (<1.5 SD), mostly with parents of normal height. They found that adult females with the CT genotype (ie, heterozygotic subjects with both the long and short forms of the VDR) were 4.4 cm taller than those with the CC genotype (ie, homozygous for the short form of the VDR) and 2.7 cm taller than those with the TT genotype (ie, homozygous for the long form of the VDR). There was no relationship between VDR genotype and age at menarche or between height and age at menarche in this population. Among the children (87 female, 72 male), height SDS also was greatest in those with the CT genotype. The frequency of the 3 VDR genotypes was CT 0.51, CC 0.37, and TT 0.12 in 249 normal subjects. Among constitutionally short children, the distribution of genotypes was CT 0.21, CC 0.62, and TT 0.17.

Thus, the frequency of the CT genotype was lower in children with constitutional short stature than in the general population.

The investigators suggest that the VDR genotype very possibly influences the growth of children and the height of adult females in the population studied, although the mechanism by which this effect might act is unknown, as are the complementary roles played by the polymorphic variants of the VDR.

Minamitani K, et al. *Pediatr Res* 1998;44:628-632.

Figure
Exon 2 Polymorphism and Adult Height
in 90 Female Subjects



Reprinted with permission from Minamitani K, et al. *Pediatr Res* 1998;44:628-632.

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Editor's comment: It would have been interesting to learn if the sex of the subject influenced the height-promoting effect of the polymorphic forms of the VDR, but no data were provided on the relationship of the VDR genotype to the adult height of Japanese men or to the group of children studied. In addition to the exon 2 polymorphism of the VDR, there are several other polymorphic variants of the VDR. Suarez et al reported that absence of the BsmI endonuclease site in intron 8 (homozygous for the presence of the endonuclease site designated BB) was associated with greater length and weight in females at 2 years of age than those with the genotype bb (homozygous for the presence of the endonuclease site), while the size of those with genotype Bb (heterozygous for the presence of the endonuclease site) was intermediate. On the other

hand, 2-year-old BB males were smaller than those with either the Bb or bb genotype. Subsequently, these investigators observed that there was an interactive effect upon growth in male infants between the polymorphic genotypes of the estrogen receptor and the VDR, although the mechanism remains enigmatic. The polygenic mechanisms that affect growth and stature are slowly being deciphered. In addition to the effects of SHOX and LHB on growth, we may now add the VDR and the ER genes.

Allen W. Root, MD

Suarez F, et al. *J Clin Endocrinol Metab* 1997;82:2966-2970.

Suarez F, et al. *J Clin Endocrinol Metab* 1998;83:3563-3568.

Role of Nonexercise Activity Thermogenesis in Resistance to Fat Gain in Humans

The authors studied the mechanisms by which some individuals are able to prevent substantial weight gain when ingesting excessive calories while others cannot so do. For 8 weeks, 16 healthy, nonobese young adults (12 males, 4 females) were fed a diet that had 1,000 calories in excess of that necessary for weight maintenance. Body composition was measured by dual energy X-ray absorptiometry. Total energy expenditure (TEE) was determined by quantitating carbon dioxide production. TEE is composed of basal metabolic rate (BMR), postprandial thermogenesis (PPT), and physical activity thermogenesis. BMR was assessed by indirect calorimetry to measure oxygen consumption and carbon dioxide production. PPT also was measured by indirect calorimetry. Thermogenesis due to total physical activity was calculated as TEE minus the sum of BMR and PPT. The latter was subdivided into volitional exercise, which was maintained at low and constant levels and assessed by pedometer, and nonexercise activity thermogenesis (termed NEAT), which was calculated as the difference between total physical activity and volitional physical activity. They found: (1) individual fat gain varied 10-fold (0.36 to 4.23 kg); (2) fat gain was inversely related to TEE; (3) on average, 43% of the excess calories were stored, and 53% were expended; (4) a 5% increase in BMR accounted for 8% of the excess energy ingested; (5) a 14% increase in PPT; (6) NEAT increased on average by 66% during overfeeding, but there were wide interindividual differences in NEAT (-98.3 to +692 kcal/d); and (7) NEAT was inversely related to the gain in fat mass. The investigators concluded that "activation of

NEAT" explained individual variability in weight/fat increase during overfeeding.

Levine JA, et al. *Science* 1999;283:212-214.

Editor's comment: These investigators have NEATly documented what we have been taught for many decades—that obese subjects expend far fewer calories than nonobese subjects in everyday activities of living such as sitting, standing, and "existing." Obese individuals sit and stand in an impassive, almost motionless manner that conserves every possible calorie. They choose to sit rather than stand whenever possible. Now, the question is, How does one "activate" NEAT, that is, can we induce fidgeting? Since NEAT appears to be a familial trait, it is likely to be of multifactorial/genetic origin. Among the factors that may influence NEAT might be stimulation of the sympathetic nervous system, leading to uncoupling of oxidative phosphorylation in brown fat and synthesis of or response to leptin or other appetite and energy expenditure regulating agents. Interestingly, Levine and colleagues found that the 4 female volunteers had the lowest increases in NEAT. The significance of this gender-related difference awaits further evaluation. The accompanying commentary (Ravussin E, Danforth E Jr. *Science* 1999;283:184-185) also is recommended reading.

Allen W. Root, MD

Cellular Therapy May Be Successful for Severe Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a relatively common autosomal dominant disorder of connective tissues. It results from mutations of genes encoding the $\alpha 1$ or $\alpha 2$ chain of type I collagen that lead to varying degrees of generalized osteopenia with fractures, progressive deformities, and growth deficiency. Until the recent introduction of the bisphosphonate compound, pamidronate, which shows promise as an agent for increasing bone density, there has been no therapy for OI other than symptomatic treatment. However, Horwitz et al now report encouraging results from the transplantation of bone marrow-derived mesenchymal stem cells in 3 children with severe OI.

The children ranged in age from 13 to 32 months. They had clinical phenotypes consistent with OI type III and documented mutations of *COL1A1* or *COL1A2*. After bone marrow ablative chemotherapy, each received a bone marrow infusion from an HLA-matched sibling (partial or complete). The children were evaluated extensively for at least 6 months.

Two of the children showed complete hematopoietic engraftment, while the third exhibited partial engraftment. Osteoblasts cultured from iliac bone of the first 2 children after transplantation showed 1.5% to 2% donor cells. Comparison of pretrans-