

## A Gene Encoding a Transmembrane Protein Is Mutated in Patients With Diabetes Mellitus and Optic Atrophy (Wolfram Syndrome)

Wolfram syndrome is an autosomal recessive neurodegenerative disorder defined by young-onset, nonimmune insulin-dependent diabetes mellitus (IDDM), progressive optic atrophy, and diabetes insipidus. It is also called the DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) syndrome. Most patients with this progressive disorder eventually develop all four cardinal manifestations and die prematurely with widespread atrophic changes throughout the brain. Onset of IDDM occurs at a mean age of 6 to 8 years. The pancreatic islets are atrophic and insulin-producing beta-cells are selectively absent. The disease is believed to account for 1 of every 150 patients with young-onset IDDM.

The investigators confirmed the localization of the gene to chromosome 4p and isolated a gene (*WFS1*) from this region with 8 exons encoding a probable cell membrane protein with 890 amino acids that is related to the prenyltransferase  $\alpha$ -subunit. Hydrophilic amino and carboxyl terminal regions encompass a central hydrophobic core. Further analysis suggested that the protein had approximately 10 transmembrane domains. The function of *WFS1* protein was not identified but

its mRNA was expressed in pancreatic islets, brain, heart, skeletal muscle, kidney, and placenta. Inactivating homozygous and compound heterozygous mutations in exon 8 of *WFS1* were found in all affected members of 6 families, but not in control subjects, including deletions, insertions, and nonsense and missense mutations. The authors conclude that mutations in *WFS1* are related to Wolfram syndrome and suggest that the *WFS1* protein is important in the maintenance of islet cell and brain function.

Inoue H, et al. *Nature Genet* 1998;20:143-148.

**Editor's comment:** Further proof of the relationship of *WFS1* to Wolfram syndrome awaits the characterization of the phenotype in a mouse model in which the homologous gene has been "knocked out." Identification of the biologic function of *WFS1* protein will be of great interest as in its absence pancreatic islets and beta cells, as well as the brain, atrophy. Thus, the *WFS1* protein may be involved in the regulation of organ-specific apoptosis. Perhaps it is even an "antiaging" agent!

Allen W. Root, MD

## Bone Age in 116 Untreated Patients With Turner's Syndrome Rated by a Computer-Assisted Method (CASAS)

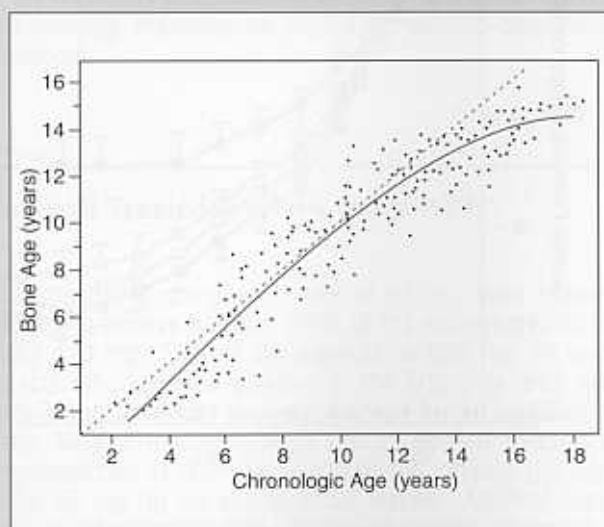
The investigators employed the computer-assisted skeletal age system (CASAS) to examine skeletal maturation in 265 radiographs of 116 untreated patients with Turner syndrome (TS). CASAS is based on the TW2-RUS (Tanner-Whitehouse 2-Radius, Ulna, Short Bones) method of bone age (BA) determination. In this procedure, the operator identifies on the radiograph the bones of the wrist and hand to be scored; the computer program then digitizes and analyzes the images and computes a score that is translated into a BA. There is apparently good reliability between the CASAS BA and that interpreted by human operators (Tanner JM, et al. *Hormone Research* 1994; 42:487).

In this study, the investigators reported that in untreated TS subjects the BA was delayed relative to chronologic age (CA) from the 3rd to the 6th years of life, advanced rapidly between 6 and 7 years of age, was similar to CA between 7 and 12 years of age, and was delayed after 12 years of age; epiphyseal fusion was not achieved until after 17 years of age (see Figure). The authors provided normative data for BA in TS and compared their data with those reported using the Greulich and Pyle and TW2-RUS atlases.

The authors concluded:

*In this study a reference curve was presented for bone age progression in TS for use in clinical practice. Knowledge of bone age and consequently accurate bone age rating at diagnosis and during longitudinal follow-up is essential in order to be able to counsel the patient, advise on therapy,*

Figure  
Plot of Bone Age Ratings Versus  
Chronologic Age of 116 Untreated Patients  
With Turners Syndrome:  
A Regression Curve to the  
Data Was Fitted by Polynomial  
Regression Analysis.



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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 D<sub>3</sub>) 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/AQG at the first start site.

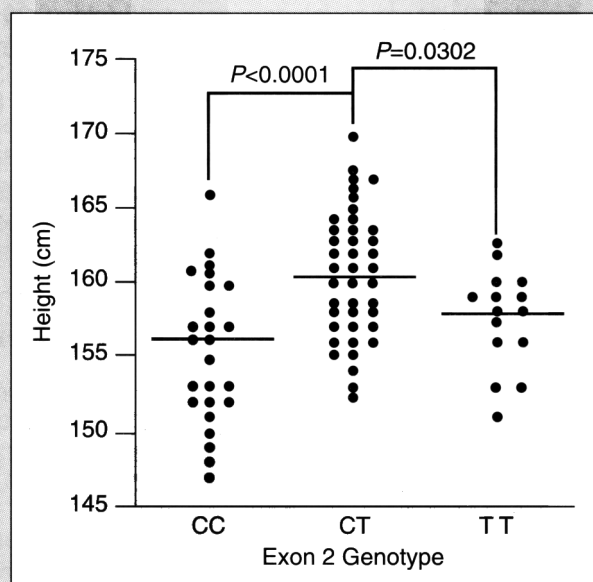
The authors examined the relationship between the presence/absence of the 2 variants of the VDR and the adult height in 90 healthy Japanese females (Figure), the height at age 13 years of 159 healthy Japanese children, and the height of 24 children aged 6 to 10 years with constitutional short stature (<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



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