

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 α -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)

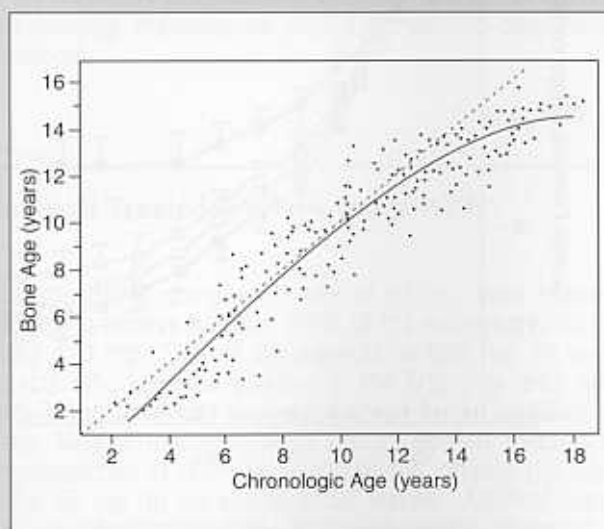
The investigators employed the computer-assisted skeletal age system (CASAS) to examine skeletal maturation in 265 radiographs of 116 untreated patients with Turner syndrome (TS). CASAS is based on the TW2-RUS (Tanner-Whitehouse 2-Radius, Ulna, Short Bones) method of bone age (BA) determination. In this 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.



Reprinted with permission from Schwarze DP, et al. *Acta Paediatr* 1998;87:1146-1150.