

## **Abstract**

### **Williams Syndrome Animal Model**

*F. H. Ruddle and D. Bayarsaihan*  
*Yale University, New Haven, CT 06511*

Williams Syndrome (WS) is an autosomal dominant genetic condition characterized by an ensemble of physical, cognitive, and behavioral traits. The syndrome has been mapped to 7q11.23 where genetic causation is attributed to a microdeletion of approximately 1.5 Mb in length. To date, 17 genes have been identified in the haplo-insufficiency region which serve as specific candidates for the multiple features of the condition. While the 1.5 Mb deletion occurs most commonly, smaller more informative deletions occur at a lower frequency and facilitate the presumptive identification of genes that are causal to specific craniofacial and neurological attributes of WS. Currently, deletion mapping implicates genes near the telomeric terminus of the deletion as most critical in phenotype causation. Two genes are viable candidates. These are BEN (GTF2IRD1) and TFII-I (GTF2I). TFII-I and BEN are closely related helix-loop-helix transcription factors. We have recently isolated the BEN gene in mice in a search for factors that bind to the early enhancer of the developmentally important Hoxc8 gene. This implicates BEN and TFII-I as candidate developmental factors, deficiencies of which may be expected to generate the symptomology of WS. In an effort to establish the molecular basis of WS, we have used chromosome engineering and other transgenic methodologies to simulate a haploinsufficiency for these three candidate genes in mice. We have taken three approaches: (1) a classical knockout of BEN using embryonal stem cell technology, (2) a gene trap approach directed at both BEN and TFII-I, and (3) a dominant/negative approach directed against TFII-I. We will describe our progress using these methodologies. Mutant mice will be examined for physical, biochemical, and behavioral phenotypes that are typical of persons with WS.