

(NGSP) as traceable to the DCCT reference.  $\text{GH}_b$  levels should be maintained at <7% and the treatment regimen should be reevaluated if  $\text{GH}_b$  is >8% as measured by NGSP - certified methods.

Routine measurement of genetic markers is not recommended for the diagnosis or management of patients with DM. Likewise, autoimmune markers lack specificity and are not recommended for routine diagnosis or screening of DM.

An annual search for micro albuminuria should be performed on patients without clinical proteinuria. To be useful, semiquantitative or quantitative screening

tests must be shown to be positive in >95% of patients with micro albuminuria. Positive results must be confirmed by quantitative testing in an accredited laboratory.

All adults with DM should receive annual lipid profiles.

Sacks DB, et al. *Clinical Chemistry* 2002;48:3,436-472.

**Editor's Comment:** *This is only the very essential infrastructure of the Executive Summary. The article is endowed with significant substance.*

Robert M. Blizzard, MD

## Mutations of the *Great* Gene Cause Cryptorchidism

The investigators previously identified a mutant strain of mice (*crsp*) with high intraabdominal bilateral cryptorchidism due to a 550 kb deletion of the proximal arm of mouse chromosome 5. Within the deleted region, the investigators identified a G-protein coupled receptor gene (GPCR) termed "G-protein coupled receptor affecting testis descent" or *Great*. *Great* was expressed in testis, brain, and skeletal muscle. In the current paper, the authors developed a mouse "knock-out" model of this gene. The phenotypes of the wild type mice and those who were heterozygous (*Great*<sup>+/−</sup>) were normal. However, animals who were homozygous for the mutation (*Great*<sup>−/−</sup>) were similar in phenotype to *crsp* mice. In (*Great*<sup>−/−</sup>) mice, there was failure of development of the gubernaculum (the ligament whose shortening is partially responsible for the inguinal-scrotal phase of testicular descent). The investigators then cloned human *GREAT* (chromosome 13q12-13), an 18 exon gene encoding a GPCR, and analyzed its structure in 61 men with bilateral (N=31) or unilateral cryptorchidism. In one subject with bilateral cryptorchidism, a heterozygous loss-of-function mutation was identified (exon 8, A C, Tyr222Pro was identified). The authors concluded that mutations in *GREAT* are responsible for cryptorchidism in some human males but the frequency of a *GREAT* as a cause of cryptorchidism mutation remains to be determined.

Gorlov IP, et al. *Hum Molec Genet* 2002;11:2309-2318.

**First Editor's Comment:** *GREAT had been cloned by other workers and termed LGR8 - Leucine-rich repeat-containing GPCR. Relaxin had been identified as a ligand for GREAT. However, testicular descent is normal in the Relaxin "knock-out" male mouse. *Insl3* - insulin-like factor 3 - is a member of the relaxin family and is synthesized in the testes; its loss results in bilateral cryptorchidism due to maldevelopment of the gubernaculum. Thus, *Insl3* may be the natural ligand*

*for GREAT. While homozygous loss of Great is needed for cryptorchidism in mice, apparently its heterozygous loss appears to be sufficient in humans to cause this malformation; the mechanism(s) of this species difference is/are not defined at present.*

*There are two phases of testicular descent - transabdominal and inguinal-scrotal. The first phase is conditioned by failure of development of a cranial suspensory ligament mediated by testosterone. The second phase is stimulated by development of the gubernaculum, demonstrated to be related to the interaction of *Insl3* and *GREAT*. Mullerian duct inhibitory factor and its receptor also play a role in this phase of testicular descent. The manuscript also suggests that it would be inappropriate to tell another gentleman that he is "not so GREAT!"*

Allen W. Root, MD

### References

1. Overbeek PA, et al. *Genesis* 2001;30:26-35.
2. Nef S, Parada LF. *Nat Genet* 1999;22:295-299.
3. Teixeira J, et al. *Endocrine Rev* 2001;22:657-674.

**Second Editor's Comment:** *This article is the best I have read concerning the development and descent of the testes. Work in mice and in humans is blended in describing the embryological development of both testes and ovaries. The 11 authors come from diverse and multiple fields - urology, genetics, pharmacology, embryology, molecular biology, etc., which largely accounts for the excellence of the article. Those interested in gonadal development, normal and/or abnormal, will be gratified in reading the article in its entirety.*

Robert M. Blizzard, MD