

2 years the growth of such slow-growing normal short adolescents, and slightly improve their predicted height in relation to the result of the first year of treatment. However, the expected results should not be overestimated, nor should this be considered as an indication for any routine use of GH in endocrinologically normal and constitutionally short pubertal individuals.

Job JC, et al. *Horm Res* 1994;41:177-184.

Editor's comment: *This report will discourage only the most desperately short children from trying to achieve normal height by using GnRHa plus GH.*

Robert M. Blizzard, MD

Susceptibility Gene Loci for Insulin-Dependent Diabetes Mellitus (IDDM): A Review

Insulin-dependent diabetes mellitus (IDDM) is a polygenic multifactorial disease, ie, it is caused by different susceptibility genes and environmental factors in different people. Other disorders thought to be polygenic multifactorial include ischemic heart disease, asthma, and schizophrenia.

In mice, IDDM has been shown to be a polygenic trait, with the major locus encoded in the major histocompatibility complex (MHC) with at least 10 other loci contributing to the development of the disease. In humans, the MHC HLA region on chromosome 6p21 and the insulin gene region on chromosome 11q23 have been associated with IDDM. However, in families with multiple affected individuals, these 2 loci have been suggested to account for less than 50% of the genetic risk of the disease.

Two recent papers by Hashimoto et al and Davies et al reported genome-wide linkage studies for the localization of IDDM susceptibility loci. Hashimoto et al applied highly informative markers to a panel of 314 white IDDM-affected sibling pairs and found evidence for the localization of a previously undetected susceptibility locus for IDDM in the region of the fibroblast growth factor 3 (*FGF3*) gene on chromosome 11q.

These results were confirmed by Davies et al, who also used the same method of genome-wide searches to study 96 sibpair

families and a linkage map of 290. This group also found linkages between IDDM and chromosomes 11q and 6q, and suggested that there may be a fifth susceptibility locus on chromosome 18. Davies et al point out, however, that the genome linkage map had an average spacing of 11 centimorgans (cM) and that gaps still exist in this map. They suggest that in order to detect all the susceptibility loci for IDDM, it may be necessary to test with markers that are only 3 cM apart.

Hashimoto L, et al. *Nature* 1994;371:161-163.

Davies JL, et al. *Nature* 1994;371:130-136.

Editor's comment: *The genome-wide search method has been used for other multifactorial disorders, especially psychiatric disorders (Lander and Botstein. *Genetics* 1989;121:185), but has not provided any linkage data so far, much less specific genes. These new methods are very powerful and should hasten the progress of the Human Genome Project effort to identify all 100,000 human genes.*

Judith G. Hall, MD

Prenatal Treatment of Congenital Adrenal Hyperplasia: A Review

Congenital adrenal hyperplasia (CAH), an autosomal recessive disorder, is the most common cause of ambiguous genitalia in females. Ninety percent of CAH cases are caused by 21-hydroxylase deficiency. In order to prevent virilization in utero, maternal glucocorticoid therapy (specifically, dexamethasone) is started immediately after detection and continued throughout pregnancy; this suppresses fetal androgen production.¹⁻³ Most of the reported cases that were treated early and adequately were born with normal female genitalia.

A recent paper by Wudy et al⁴ documents another successful prenatal treatment of CAH. They report a newborn girl born with normal female genitalia after prenatal dexamethasone treatment (the index case in the family was a boy suffering from 21-hydroxylase deficiency). Molecular genetic diagnosis was not available, and prenatal diagnosis relied on amniocentesis with karyotyping and 17 α -hydroxyprogesterone determination. In order to get an accurate amniotic fluid steroid analysis, dexamethasone treatment was suspended for 5 days prior to amniocentesis.

Previous reports have shown that prenatal dexamethasone treatment must begin as early as the 5th to 9th week of gestation, which may be before the diagnosis of a female fetus is made by amniocentesis or chorionic villus sampling (CVS). Both the dosage and temporary suspension of dexamethasone have been controversial issues in prenatal CAH treatment.

Some authors suggested that excessive virilization may occur due to a rebound effect.³ However, Wudy et al's paper has shown that this is not necessarily true. Furthermore, with the advent of molecular diagnosis, interruption of maternal glucocorticoid therapy may not even be necessary. The potential maternal side effects of dexamethasone therapy include development of a cushingoid face, massive weight gain, and marked striae. Hypertension and increased urinary glucose have also been reported.³ Nevertheless, many families will opt for prenatal therapy for affected female fetuses.

1. Pang S, et al. *Trends Endocrinol Metab* 1990;1:300-307.

2. Forest MG, et al. *Horm Res* 1990;33:43.

3. Loeuille GA. *Eur J Pediatr* 1990;149:237-240.

4. Wudy S, et al. *Eur J Pediatr* 1994;153:556-559.

Editor's comment: *Major progress has been made in diagnostic and therapeutic modalities for this common disorder. With the identification of the gene structure and common mutations, more accurate diagnosis is possible both prenatally and at birth. However, therapy must begin before accurate diagnosis of the fetus is possible, since CVS and amniocentesis are contraindicated before the 10th to 11th week of pregnancy.*

Judith G. Hall, MD