

demonstrated that Fanconi's anemia is frequently associated with GHD and pituitary stalk interruption syndrome. The demonstration by MRI of the latter abnormality is a new finding, which had not been documented in the past in such patients. The pathogenesis of pituitary stalk interruption syndrome is unknown. It could be related to injury at birth or perhaps to the same deletions in the genes that lead to Fanconi's anemia. It is interesting to note that patients with Fanconi's syndrome might not always have the severe type of GHD. Pituitary stalk interruption probably needs to be considered only in patients with Fanconi's anemia who are severely growth retarded and in whom treatment with GH will induce catch-up growth. However, it should be kept in mind that patients with

chromosomal abnormalities, including patients with Fanconi's anemia, in particular are at a higher risk for malignancies when treated with GH. Therefore, the question has been raised about the dilemma of initiating a treatment that may improve growth but also might increase the risk for cancer. Although the incidence of leukemia in GH-treated patients without predisposing risk factors is believed not to be different from that of the general population (J Clin Endocrinol Metab 1996;81[693]:1692-1696 and 1704-1710), in patients with Fanconi's anemia this complication might ensue (Lancet 1994;343:1576).

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## Neonatal Diabetes Mellitus Due to Complete Glucokinase Deficiency

Diabetes mellitus is a heterogeneous disorder. Neonatal diabetes, defined as insulin-requiring hyperglycemia occurring within the first month of life, is a rare form of diabetes but also is heterogeneous. Transient or permanent neonatal diabetes can occur. Recently, it has been recognized that transient neonatal diabetes is often associated with abnormalities of chromosome 6, including imprinting abnormalities. Mutations of insulin promoter factor 1, resulting in pancreatic agenesis, are seen in permanent neonatal diabetes.

This report describes 2 patients with permanent neonatal diabetes due to complete glucokinase deficiency, the result of identified mutations in the glucokinase gene. The affected individuals had poor fetal growth and intrauterine growth retardation, and required insulin in the first days of life. Interestingly, diabetes of many forms was seen within the family among the carriers (heterozygotes) of the gene defects. Among the carriers (heterozygote), maturity-onset diabetes, diabetes of the young, type 1 diabetes, and type 2 diabetes were all observed. One affected infant also had total situs inversus, which was not seen in any other family members.

Glucokinase mutations are relatively common in diabetes, and the homozygous state may actually be a common cause for neonatal diabetes. Glucokinase plays a key role in the regulation of insulin secretion in humans. Thus, the authors tested for mutations in other genes along the pathway, including hepatocyte nuclear factors 1 and 4, insulin promoter factor 1, NK-2 homeobox homologue 2, neurogenic differentiating factor 1-beta-cell, and E box transactivator 2. They found no abnormalities in any of those genes.

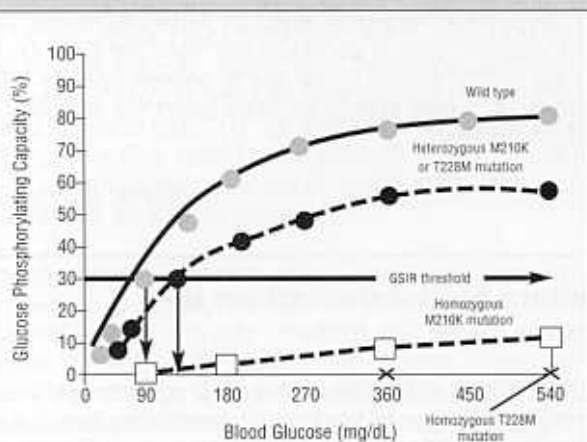
Interestingly, mouse models of glucokinase deficiency also have growth retardation and hypoglycemia at birth, but they also have hypertriglyceridemia, hepatic steatosis, and reduced stores of glycogen, which apparently are not seen with the human mutations.

Njølstad PR, et al. *N Engl J Med* 2001;344:1588-1592.

**Editor's comment:** The variabilities seen in the families of these infants with neonatal prone diabetes are quite remarkable, suggesting that heterozygotes have problems of many varieties. The authors worked out the kinetics of complex control of glucose metabolism and showed very nicely that the homozygous state simply does not produce enough enzyme to have a normal role, whereas the heterozygous state has variable levels and thus must interact with other factors to produce the various types of diabetes seen (Figure).

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Figure



Comparison of the modeled functional properties of wild-type glucokinase, glucokinase with the M210K mutation, and glucokinase with the T228M mutation in the homozygous and heterozygous state. GSIR, glucose-stimulated insulin release.

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