Congenital hyperinsulinism: activating glucokinase mutations

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Glucokinase is a key regulatory enzyme in the beta-cell and is the rate limiting step for beta-cell glucose metabolism. Mutations in the glucokinase (GCK) gene cause both hyper and hypoglycaemia. In contrast to inactivating GCK mutations activating GCK mutations, causing congenital hyperinsulinism, are rare. Mutations have been reported in 5 families to date. The mutations are inherited as an autosomal dominant trait with affected individuals in each generation.

We described a family where mother and son presented in childhood with nonketotic hypoglycaemic seizures and inappropriate hyperinsulinemia. A 95% pancreatectomy was performed on the mother and both had resolution of hypoglycaemia-related symptoms when treated with diazoxide.

Full sequencing of GCK revealed a novel missense mutation in exon 2 (T65I), in both affected subjects. This mutation was not found in the non-affected family members (proband's father, maternal grandparents and 5 siblings of the mother) or 100 control chromosomes.

In vitro studies of activating GCK mutations have shown an increased affinity for glucose. For the T65I mutation a threshold for glucose stimulated insulin release of 3.1 mmol/l was predicted.

In the structural model of the GCK enzyme, this mutation was located in the same domain of the enzyme as the other mutations, hypothesized as a heterotrophic, allosteric, activator site in the normal GCK enzyme.

Knowledge of the clinical and biochemical characteristics of GCK activating mutations can be of help to develop new drugs to treat diabetes and predict their long term effects.

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