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Genetics of congenital hyperinsulinemic hypoglycemia

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A genetic diagnosis is now possible for approximately 45%-55% of patients with hyperinsulinemic hypoglycemia. Understanding the genetic etiology of the disease in these patients is clinically important because a genetic diagnosis will provide information on prognosis, recurrence risk, and importantly may also guide clinical management. The aim of this review is to provide an outline of the 7 different molecular mechanisms underlying this heterogeneous disease and to demonstrate that the clinical phenotype can act as a useful guide when prioritizing the order of genetic testing.

Hyperinsulinemic hypoglycemia (HH) is a genetically heterogeneous disease with mutations in 7 different genes described to date (*ABCC8*, *KCNJ11*, *GLUD1*, *GC*K, *HADH*, *HNF4A*, and *SLC16A1*; Figures 1 and 2). Although dominant mutations have been reported in a number of these genes, recessively inherited HH is more common. This finding is reflected in the increase in incidence of HH from 1 in 50,000 live births in outbred populations to 1 in 2500 in communities with high rates of consanguinity.[1] Mutations in the *ABCC8* and *KCNJ11* genes are by far the most common cause of HH and are estimated to account for 40%-45% of all cases, whereas mutations in the remaining 5 genes are identified in approximately 5%-10% of cases (Fig 2). The genetic etiology for the remaining 45-55% of patients remains unknown.

Clinically, it is important to confirm the genetic subtype of HH because this can provide important information that can help guide clinical management. For example, the response to treatment is often dependent on the genetic etiology with most patients with *GLUD1*, *HADH*, and *HNF4A* mutations demonstrating a good response to diazoxide whereas patients with *KCNJ11* and *ABCC8* mutations will often require surgery (Fig. 2). Identification of a *GLUD1* or *HADH* mutation also informs clinicians of the protein-sensitive nature of hypoglycemia, allowing for the manipulation of diet (protein restriction) as a useful, sometimes mandatory, adjunct to diazoxide therapy in controlling recurrent hypoglycemic episodes.

Perhaps the most important example of how molecular genetic analysis can aid in the management of HH comes with the advent of rapid molecular genetic testing for newly diagnosed patients who are unresponsive to medical management and require surgery. Because the histologic subtype is dependent on the genetic etiology, identification of recessively or dominantly inherited K_{ATP} channel mutations will confirm diffuse pancreatic disease, thus preventing the need for a fluorine-18 dihydroxyphenylalanine-positron emission tomography (PET) scan in these patients.[2]

Finally, the identification of a disease causing mutation in a proband will also have implications for other family members. For patients with a dominantly inherited mutation, the proband's siblings and future offspring will have a 50% chance of inheriting the mutation. In contrast, siblings of probands with recessively inherited mutations will have a 25% risk of inheriting both mutations and developing the

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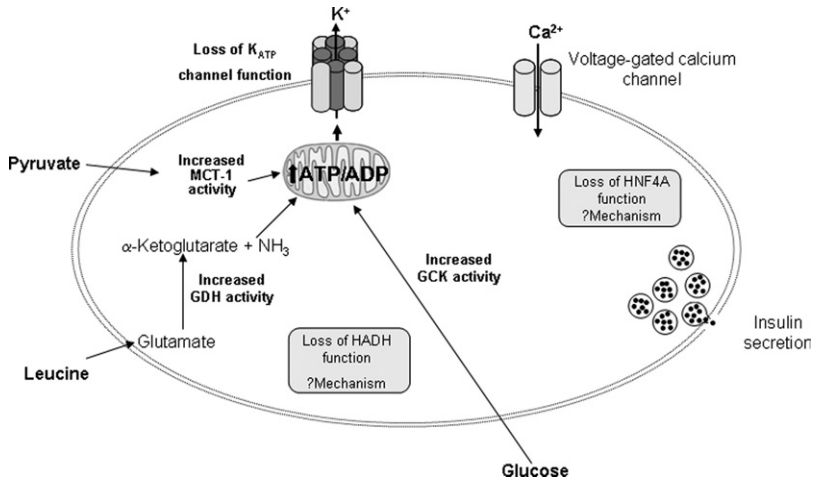

Figure 1 Schematic representation of the known causes of HH in the pancreatic β-cell. Loss of function mutations in the genes encoding the Kir6.2 (dark gray) and the SUR1 (light gray) subunits of the K_{ATP} channel are the commonest cause of HH. Gain-of-function mutations in the *GCK* and *GLUD1* (encoding GDH) genes have been described in patients with HH and *SLC16A1* gene mutations, which cause an increase in MCT-1 activity result in exercise-induced hyperinsulinism. The molecular mechanisms that lead to HH in patients with *HADH* and *HNF4A* mutations are not known.

disease, whereas the risk to future offspring will be less than 1%. Furthermore, the identification of an *HNF4A* mutation in a proband would identify infants who are at a risk of developing maturity-onset diabetes of the young. Unless the mutation has arisen de novo, one of the parents, and potentially other family members, will also be heterozygous for the *HNF4A* mutation and at an increased risk of developing diabetes, if it has not already developed. For these patients, a genetic diagnosis is important because this monogenic form of diabetes can be successfully managed with low-dose sulfonylureas. A molecular genetic diagnosis in the proband may therefore also be of benefit for other relatives.

K_{ATP} channel mutations (*KCNJ11* and *ABCC8*)

Loss-of-function mutations in the *ABCC8* and *KCNJ11* genes, which encode the SUR1 and Kir6.2 subunits of the pancreatic β-cell adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channel, are the most common known cause of congenital HH.[3,4] The K_{ATP} channel plays a pivotal role in regulating insulin secretion in the β cell by coupling glucose metabolism to membrane electrical activity. The metabolism of glucose results in an increase in the intracellular ATP/adenosine diphosphate ratio; ATP then binds to the Kir6.2 subunits to affect channel clo-

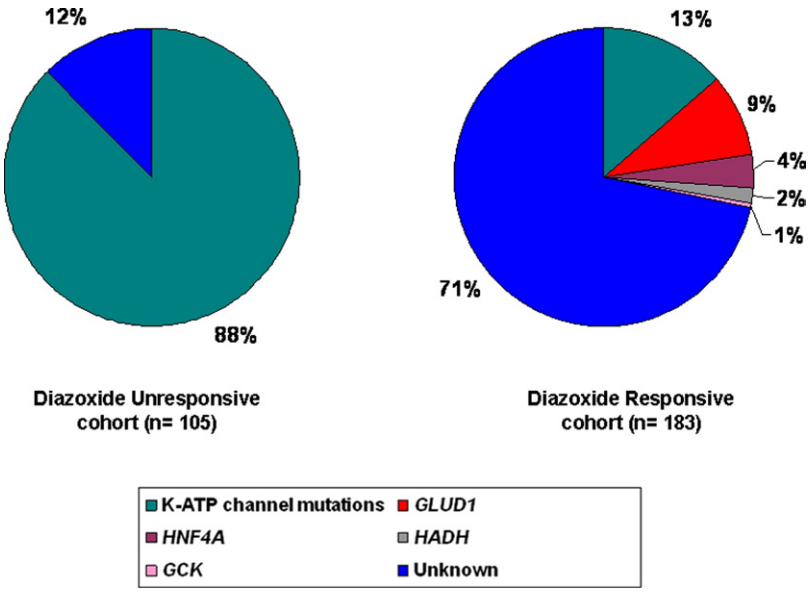

Figure 2 Charts showing the genetic etiologies for 288 patients with congenital HH. A genetic diagnosis was possible for 51 of 183 (28%) patients with diazoxide-responsive HH and for 92 of 105 (88%) patients who did not respond to diazoxide therapy (unpublished data). (Color version of figure is available online.)