THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Permanent neonatal diabetes and hyperinsulinemia of infancy: Mutation analysis of *KCNJ11*

Clinical Features:

- Permanent neonatal diabetes: Neonatal diabetes is hyperglycemia that presents at 0-6 months of age (rarely later) and requires insulin. Approximately 50-60% of cases are considered transient neonatal diabetes [OMIM #601410] and resolve within 18 months. The remaining cases are considered permanent neonatal diabetes (PNDM) [OMIM #606176]. These patients have low birth weight and require insulin treatment throughout life. PNDM does not include autoimmune diabetes that almost never occurs before 6 months of age. Most patients have isolated diabetes, but approximately 20% will also have neurological findings. Patients have been described with developmental delay, epilepsy, and neonatal diabetes (DEND syndrome), relapsing and remitting diabetes, or intermediate phenotypes (1).
- Hyperinsulinemia of infancy (HI): HI, also known as familial hyperinsulinism and persistent hyperinsulinemic hypoglycemia of infancy, is inappropriate oversecretion of insulin despite hypoglycemia. It usually presents with seizures, hypotonia, poor feeding, apnea, and coma in the neonatal period or infancy, along with high birth weight. In the absence of treatment, HI can result in permanent brain damage (1, 2).

Molecular and Biochemical Genetics:

- Permanent neonatal diabetes: Mutations of the *KCNJ11* [OMIM #600937] gene have been identified in patients with PNDM (3). Studies have shown that approximately one-third to one-half of all cases of PNDM are due to activating mutations in *KCNJ11*. Genotype-phenotype correlations have been reported (1).
- Hyperinsulinemia of infancy (HI): Mutations of the *KCNJ11* gene have also been identified in patients with HI (4). Approximately 5% of individuals with HI have inactivating mutations in *KCNJ11* (1).

KCNJ11 encodes Kir6.2, an essential subunit of the beta-cell K_{ATP} channel. It has one coding exon, and more than 32 mutations have been identified in patients with PNDM, HI, DEND and some instances of transient neonatal diabetes. A majority of mutations are missense mutations (1).

Management:

Patients with diabetes caused by mutations in the *KCNJ11* gene have K_{ATP} channels with decreased sensitivity to ATP. Thus, they remain open in the presence of glucose, decreasing the secretion of insulin. The most common mutation (R201H) associated with PNDM leads to a 40-fold reduction in sensitivity to ATP and failure of the channel to close. These patients have low levels of circulating insulin, and are therefore treated with insulin. Oral sulfonylureas are a class of drugs that close K_{ATP} channels independent of ATP, inducing secretion of insulin. Most patients with *KCNJ11* mutations can get better glycemic control without increasing hypoglycemic events by switching from insulin treatment to oral sulfonylureas (5, 6).

Inheritance:

- Permanent neonatal diabetes: *KCNJ11* mutations that cause PNDM are gain-of-function mutations inherited in an autosomal dominant pattern. Most cases are sporadic and have no family history of this condition. Approximately 90% of autosomal dominant cases are spontaneous mutations (6). Paternal germline mosaicism for the R201C mutations has been reported in a family with PNDM (1).
- Hyperinsulinemia of infancy (HI): *KCNJ11* mutations that cause HI are loss-of-function mutations inherited in an autosomal recessive pattern.

Additional Resources:

Dr. Louis Philipson is available for consultation prior to genetic testing. He is Director of the Comprehensive Diabetes Center at The University of Chicago. Patient's that do not have an identified *KCNJ11* mutation may be eligible for enrollment in Dr. Philipson's research project. Please contact him at lphilip@bsd.uchicago.edu.

Test methods:

We offer mutation analysis of the coding exon and intron/exon boundaries of *KCNJ11* by direct sequencing of amplification products in both the forward and reverse directions. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

KCNJ11 sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$400
CPT codes:	81402, 81403
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

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2. Glaser B. Familial Hyperinsulinism. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2003.
3. Gloyn AL, Pearson ER, Antcliff JF et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004: 350: 1838-1849.
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5. Pearson ER, Flechtner I, Njølstad PR et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med 2006: 355: 467-477.
6. Hattersley A, Bruining J, Shield J et al. ISPAD Clinical Practice Consensus Guidelines 2006-2007. The diagnosis and management of monogenic diabetes in children. Pediatr Diabetes 2006: 7: 352-360.

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