GENETIC DIAGNOSTIC LABORATORY
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DEPARTMENT OF GENETICS
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CONGENITAL HYPERINSULINISM

Background: Congenital hyperinsulinism (HI), also referred to as familial hyperinsulinism is the most common cause of frequent episodes of hypoglycemia in infancy. The incidence is estimated to be 1 in 50,000 live births and may be more common in certain populations. Multiple episodes of hypoglycemia increase the risk for complications such as seizures, intellectual disability, vision loss and brain damage. Early medical intervention can help prevent these secondary complications. This testing targets 19 genes associated with congenital hyperinsulinism: ***ABCC8*** (OMIM 600509), ***KCNJ11*** (OMIM 600937), ***GLUD1*** **(**OMIM 138130), ***GCK*** (OMIM 138079), ***HNF1A*** (OMIM 142410), ***HNF4A*** (OMIM 600281), ***HADH*** (OMIM 601609), ***SLC16A1*** (OMIM 600682), ***UCP2*** (OMIM 601693), ***NSD1*** (OMIM 606681), ***NFIX*** (OMIM 164005), ***KMT2D*** (OMIM 602113), ***KDM6A*** (OMIM 300128), ***PMM2*** (OMIM 601785), ***PGM1*** (OMIM 171900), ***FOXA2*** (OMIM 600288), ***AKT2*** (OMIM 164731), ***INSR*** (OMIM 147670), and ***HK1*** (OMIM 142600).

Assay: **Level 1 (v.1) Congenital Hyperinsulinism (HI) Panel:**
Sequencing: Sanger sequencing of the three genes: *ABCC8*, *KCNJ11*, and *GCK.*
Deletion/Duplication: qPCR is performed to analyze copy number state of *ABCC8* and *KCNJ11.*

Level 2 (v.2) Expanded Congenital Hyperinsulinism (HI) Panel:
Sequencing: Multiplex PCR and Next Generation Sequencing on the Illumina platform is done to analyze 19 genes: *ABCC8, KCNJ11, GLUD1, GCK, HNF1A, HNF4A, HADH, SLC16A1, UCP2, NSD1, NFIX, KMT2D, KDM6A, PMM2, PGM1, FOXA2, AKT2, INSR,* and *HK1.* Targeted coverage is >100X per amplicon. Sanger sequencing is performed for regions in specific genes that provide an insufficient number of sequence reads on the NGS platform.
Deletion/Duplication: A custom comparative genomic hybridization and single nucleotide polymorphism (CGH + SNP) array designed using Agilent technologies. This high-density array is designed to detect exonic and intronic copy number changes as small as 400 bp and 1.5kb, respectively, in the targeted gene(s). The analysis of the array hybridization data for targeted gene(s) is performed using Cytogenomics software (Agilent Technologies). These results may be confirmed by qPCR.

HK1 Analysis of Specific Regions within Intron 2:
Sequencing: Sanger sequencing of the chr10:71108664-71108957 (hg19) region of intron 2 of the *HK1* gene.

Utility: Confirmation of a clinical diagnosis, prognostic evaluation and/or clinical management.

Sensitivity: Approximately 90% of individuals affected by diazoxide-unresponsive HI will have an identifiable mutation in *ABCC8*, *KCNJ11* and *GCK*. About 50% of individuals with diazoxide-responsive HI will have an identifiable mutation in the 19 genes included on the Level 2: Expanded Congenital Hyperinsulinism panel.

Reference: Snider, KE, et al. Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. J Clin Endocrinol Metab. 2013 Feb;98(2):E355-63.
De Leon DD, Arnoux JB, Banerjee I, et al. International Guidelines for the Diagnosis and Management of Hyperinsulinism. Horm Res Paediatr. Published online July 14, 2023. doi:10.1159/000531766

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Name of Test	Turnaround Time	Cost	CPT codes
Level 1 CHI panel: ABCC8, KCNJ11, GCK	7-10 days	$2,800	81407, 81403, 81406x2
Level 2 CHI Panel (ABCC8, KCNJ11, GLUD1, GCK, HNF1A, HNF4A, HADH, SLC16A1, UCP2, NSD1, NFIX, KMT2D, KDM6A, PMM2, PGM1, FOXA2, AKT2, INSR, HK1)	4-6 weeks	$3,000	81479
HI: ABCC8 sequence analysis	2-3 weeks	$1,000	81407
HI: KCNJ11 sequence analysis	2-3 weeks	$600	81403
HI: GLUD1 sequence analysis	2-3 weeks	$700	81406
HI: GCK sequence analysis	2-3 weeks	$700	81406
HI: Deletion/Duplication analysis	3 weeks	$750	81479
HI: Site specific sequence analysis (familial) *Please call the lab for copy number mutation pricing.	1-3 weeks	$360	81403
PRENATAL HI: Site specific sequence analysis (familial) *Please call the lab for copy number mutation pricing.	7-10 days	$460	81403, 81265
Sequence analysis of specific regions of intron 2 the *HK1* gene	2-3 weeks	$360	81403