

Supplemental Table 2. Summary of patients with identified hypoglycemia diagnoses

History and initial presentation	Evaluation findings	Treatment and course
Growth hormone deficiency		
Term male, history of uninvestigated neonatal hypoglycemia. Presented at 10 months with vomiting, irritability, and POC PG of 32 mg/dL. Length z score -2.24, weight-for-length 80%ile.	Ketotic hypoglycemia (PG 52 mg/dL, BOHB 2.3 mmol/L) with normal lactate and cortisol (20 mcg/dL) but low GH 0.97 ng/mL. Peak GH after stimulation (arginine/clonidine) was 9.7 ng/mL and MRI revealed a small pituitary gland with possible ectopic pituitary tissue.	Initiated GH with resolution of hypoglycemia. Remains on GH replacement at 9 years of age.
Fatty acid oxidation disorder		
23-month-old female without significant past medical history presented with seizure and POC PG 20 mg/dL in setting of gastroenteritis.	Hypoketotic hypoglycemia with hyperfattyacidemia (PG 39 mg/dL, BOHB 1.4 mmol/L, FFA 3.98 mmol/L). Acylcarnitine profile revealed mild increase of C14:1 and C14:2 and UOA showed markedly increased dicarboxylic acids. Sequencing of <i>ACADVL</i> was negative, however, fatty acid oxidation probe of fibroblasts demonstrated significantly reduced oxidation of palmitate, consistent with impaired long-chain fatty acid oxidation.	Dextrose-containing fluids every 2 hours with illness. Multiple additional episodes of hypoglycemia during illness, one requiring hospitalization.
Dihydrolipoamide dehydrogenase (DLD) deficiency		
14-month-old male without significant medical history presented with gastroenteritis, lethargy, seizures, and PG 9 mg/dL.	Hypoglycemia with lactic acidosis and abnormal urine organic acid profile (PG 40 mg/dL, BOHB 1.3 mmol/L, FFA 2.5 mmol/L, lactate 5.2 mmol/L, ammonia 18 µmol/L, UOA: increased lactate, ketone, 2OH-glutaric acid, TCA cycle intermediates, 2-keto-glutaric acid, 2OH-adipic acid and glutaric acid). WES identified compound heterozygous variants in <i>DLD</i> Gly229Cys / Ser258Pro.	Low-protein diet. Numerous admissions for hypoglycemia and intermittent hepatic dysfunction.
3 methylcrotonyl-CoA carboxylase deficiency		
18-month-old female without significant past medical history presented with vomiting, lethargy, PG 49 mg/dL, and HCO ₃ 16 mmol/L.	Ketotic hypoglycemia with abnormal urine organic acid profile (PG 52 mg/dL, BOHB 3.9 mmol/L, lactate 1.2 mmol/L, ammonia <9 µmol/L, acylcarnitine profile: moderate increase of C5OH-carnitine, UOA: increased 3-methylcrotonylglycine, lactic acid, 3-hydroxy-isovalerate, consistent with deficiency in 3 methylcrotonyl-CoA carboxylase. <i>MCCC1</i> sequencing identified a heterozygous novel pathogenic frameshift variant (Ser622Pro).	Limit fasting. Glucose meter and ketone meter monitoring. Multiple episodes of ketosis during illness, all managed at home.
Hyperinsulinism		
Term female born AGA, limited prenatal care. Presented at 5 days of age with jaundice and diarrhea due to rotavirus. POC PG 49 mg/dL, HCO ₃ 23 mmol/L.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon on fast at 11 days of age (PG 57 mg/dL, BOHB 1.2 mmol/L, FFA 1.04 mmol/L, insulin <2 µIU/mL, C-peptide 0.22 ng/mL, IGFBP-1 167 ng/mL, ammonia 27 µmol/L, cortisol 25 mcg/dL, GH 10.5 ng/mL, Δ PG +45 mg/dl post-glucagon). Fasted 12 hours with PG >70 mg/dL. Genetic testing not performed. Presumed PSI-HI.	Diazoxide not initiated given fasting tolerance. Glucagon PRN, glucose meter monitoring. At 7 months of age, no PG <70 mg/dL on home monitoring.
Term female born AGA to GBS+ mother. Presented at 4 days of age with fever, irritability, POC PG 36 mg/dL, and HCO ₃ 14 mg/dL. Infectious work-up was negative.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon on fast at 14 days of age (PG 43mg/dL, BOHB 0.8 mmol/L, FFA 0.8 mmol/L, insulin <2 µIU/mL, C-peptide 0.16 ng/mL, IGFBP-1 144 ng/mL, ammonia 39 µmol /L, cortisol 17 mcg/dL, GH 18.3 ng/mL, Δ PG +40 mg/dl post-glucagon). Fasted 8 hours with PG >70 mg/dL. Sequencing of <i>ABCC8</i> , <i>KCNJ11</i> , <i>GCK</i> , and <i>GLUD1</i> identified VUS in <i>GLUD1</i> (Ala49Thr).	Diazoxide not initiated given fasting tolerance. Limit fasting to 8 hours, glucagon PRN, glucose meter monitoring. Lost to follow-up.
Term male born SGA, history of uninvestigated neonatal hypoglycemia. Presented at 1 month of age with	Hypoketotic hypoglycemia with hypofattyacidemia (PG 50 mg/dL, BOHB 0.62 mmol/L, FFA 0.57 mmol/L, insulin <2 µIU/mL, C-peptide 0.21 ng/mL, lactate 0.8 mmol/L, ammonia 32 µmol/L, cortisol 10 mcg/dL, GH 4.08 ng/mL, glucagon stimulation not performed). Fasted 12	Glucagon PRN, glucose meter. Repeat fast at age 9 months demonstrated resolution of HI

fever, POC PG 58 mg/dL, and POC BOHB <0.3 mmol/L. + parechovirus.	hours with PG >70 mg/dL. Sequencing and del/dup of <i>ABCC8</i> , <i>KCNJ11</i> and sequencing of <i>GCK</i> , <i>GLUD1</i> , <i>HADH</i> , <i>HNFI1A</i> , <i>HNFI4A</i> , <i>SLC16A1</i> , and <i>UCP2</i> was negative.	(PG 42 mg/dL, BOHB 2.4 mmol/L, IGFBP-1 723 ng/mL).
Term male infant born with AGA. Presented at 2 days with diarrhea, irritability, and POC PG 49 mg/dL. Required max GIR 13 mg/kg/min. Found to have shigella enteritis.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon on fast at 8 days of age (PG 44 mg/dL, BOHB 0.9, FFA 0.72 mmol/L, insulin <2 µIU/mL, C-peptide 0.22 ng/mL, lactate 1.3 mmol/L, ammonia 19 µmol/L, cortisol 6 mcg/dl, GH 4.84 ng/mL, Δ PG +30 mg/dl post-glucagon). Fasted <3 hours with PG >70 mg/dL. Sequencing and del/dup of <i>ABCC8</i> , <i>KCNJ11</i> , <i>GLUD1</i> , <i>HADH</i> , <i>HNFI1A</i> , <i>HNFI4A</i> , <i>INSR</i> , <i>SLC16A1</i> , and <i>UCP2</i> and sequencing of <i>GCK</i> was negative.	Diazoxide 5 mg/kg/d, glucagon PRN, glucose meter monitoring. Transferred care to local endocrinologist at discharge.
Term female born AGA with failure to thrive and GERD. Presented at 5 months of age with fever, congestion, seizure, POC PG 42 mg/dL, HCO3 24 mmol/L, and negative urine ketones.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon (PG 42 mg/dL, BOHB <0.3 mmol/L, FFA 0.19 mmol/L, insulin <2 µIU/mL, C-peptide 0.35 ng/mL, lactate 1.3 mmol/L, ammonia 33 µmol/L, cortisol 11.6 mcg/dl, GH 8.07 ng/mL, Δ PG +45 mg/dl post-glucagon). Fasted <3 hours with PG >70 mg/dL. Sequencing and del/dup of <i>ABCC8</i> , <i>KCNJ11</i> , <i>GLUD1</i> , <i>HADH</i> , <i>HNFI1A</i> , <i>HNFI4A</i> , <i>INSR</i> , <i>SLC16A1</i> , and <i>UCP2</i> and sequencing <i>GCK</i> was negative for genes analyzed, revealed partial deletion of X chromosome, cytogenic analysis subsequently confirmed mosaicism for monosomy X and ring X confirming a diagnosis of Turner syndrome.	Enteral dextrose via G-tube. Later started lanreotide. At age 5 years, repeat fast off therapy demonstrated a safe fasting tolerance (PG >70 for 12 hours) but continued evidence of HI.
Female born at 34 weeks, SGA with heterotaxy syndrome. Presented at 18 months with fever, URI, diarrhea, POC PG 54 mg/dL, HCO3 28 mmol/L, and negative urine ketones.	Hypoketotic hypoglycemia with glycemic response to glucagon (PG 50 mg/dL, BOHB 1.7 mmol/L, FFA 2.1 mmol/L, insulin <2 µIU/mL, C-peptide 0.3 ng/mL, lactate 1.8 mmol/L, ammonia <9 µmol/L, cortisol 8.5 mcg/dL, GH 1.6 ng/mL, Δ PG >30 mg/dl post-glucagon). Fasted 3 hours with PG >70 mg/dL. Sequencing and del/dup of <i>ABCC8</i> , <i>KCNJ11</i> , <i>GLUD1</i> , <i>HADH</i> , <i>HNFI1A</i> , <i>HNFI4A</i> , <i>INSR</i> , <i>SLC16A1</i> , and <i>UCP2</i> and sequencing of <i>GCK</i> was negative.	Enteral dextrose via G-tube. Required treatment through age 3 years when demonstrated ability to fast 18 hours with PG >70 mg/dL off treatment.
Term female with history of uninvestigated neonatal hypoglycemia. Presented at 18 months with gastroenteritis and POC PG 16 mg/dL.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon (PG 45mg/dL, BOHB 0.62 mmol/L, FFA 0.5 mmol/L, insulin <1 µIU/mL, C-peptide 0.5 ng/mL, lactate 1.2 mmol/L, ammonia 33 µmol/L, cortisol 5.1 mcg/dL, Δ PG + 68 mg/dl post-glucagon). Sequencing and del/dup of <i>ABCC8</i> , <i>KCNJ11</i> and sequencing of <i>GCK</i> and <i>GLUD1</i> identified an autosomal dominant paternally inherited mutation in <i>ABCC8</i> (pSer1387del)	Enteral dextrose via G-tube and lanreotide. Overnight enteral dextrose discontinued by 3 years of age. Remains on lanreotide.
Impaired hepatic insulin clearance		
22-month-old female with fever, URI, gastroenteritis, PG 48 mg/dl, HCO3 25 mmol/L, AST 6774 U/L, ALT 4847 U/L, and prolonged PT and PTT. Diagnosed with acute hepatic insufficiency due to rhinovirus and enterovirus. Hypoglycemia persisted despite improved liver function.	Hypoketotic hypoglycemia with elevated insulin and appropriately low C-peptide (PG 50 mg/dL, BOHB <0.3 mmol/L, FFA 2.0 mmol/L, insulin 8.6 µIU/mL, C-peptide 0.3 ng/mL, lactate 2.0 mmol/L, ammonia 32 µmol/L, cortisol 18.6 mcg/dL, GH 1.53 ng/mL, no glycemic response to glucagon, normal acylcarnitine profile and UOA). Fasting study repeated x 3 with consistent results.	Enteral dextrose via NG-tube overnight. Discontinued at 26 months of age following repeat fast demonstrating resolution of inappropriate insulin action (PG 47 mg/dL, BOHB 3.0 mmol/L, FFA 3.46 mmol/L, insulin <2 µIU/mL, and C-peptide < 0.1 ng/mL).

AGA appropriate for gestational age, ALT alanine aminotransferase, AST aspartate aminotransferase, BOHB β-hydroxybutyrate, FFA free fatty acids, GBS Group B *Streptococcus*, GERD gastroesophageal reflux disease, GH growth hormone, GIR glucose infusion rate, G-tube gastrostomy tube, HCO3 bicarbonate, HI hyperinsulinism, IGFBP-1 insulin-like growth factor binding protein 1, MRI magnetic resonance imaging, NG nasogastric tube, PG plasma glucose, POC point-of-care, PRN *pro re nata*, PSI-HI perinatal stress induced hyperinsulinism, PT prothrombin time, PTT partial thromboplastin time, SGA small for gestational age, TCA tricarboxylic acid cycle, UOA urine organic acids, URI upper respiratory infection, WES whole exome sequencing