Congenital Hyperinsulinism Family Conference
September 29-30, 2015
Hospital Sant Joan de Déu
Barcelona, Spain

Tuesday, September 29, 2015

8:00 a.m. **Registration**

8:30 a.m. **Welcome and Introductions**
Julie Raskin, Congenital Hyperinsulinism International (Conference Moderator)
Dr. Paula Casano, Hospital Sant Joan De Déu

8:40 a.m. **The Historical Perspective: How Basic Scientific Understanding has Led to Improvements in Hyperinsulinism Treatment**
Joseph Bryan, PhD, Pacific Northwest Diabetes Research Institute
Charles Stanley, MD, Children's Hospital of Philadelphia

9:25 a.m. The **Genetics of Hyperinsulinism**
Sian Ellard, PhD FRCPath, Head of Molecular Genetics, Royal Devon & Exeter NHS Foundation Trust and Professor of Human Molecular Genetics, University of Exeter Medical School

10:05 a.m. **Tools for Diagnosing Hyperinsulinism**
Jean Baptiste-Arnoux, MD, Necker Hospital and Klaus Mohnike, MD, University of Magdeburg

10:35 a.m. **Break**

10:55 a.m. **Current Hyperinsulinism Treatment**
Diva DeLeon, MD, Children's Hospital of Philadelphia, Khalid Hussain, MD, GOSH,

11:30 a.m. **Patients and their Families Share Triumphs and Challenges**
Moderated by Sheila Bose, Patient Advocate
Confirmed Speakers: Adrienne Burton, Jessica Burton, Connie Ward, Matthew Hammond

Topics: Feeding

Historical Perspective:
How Basic Science has Improved Treatment of HI

Part 2: The Clinician's Perspective

Charles A. Stanley, MD
Hyperinsulinism Center
Children's Hospital of Philadelphia

1954….First Cases of HI

A. M. A.
American Journal of Diseases of Children
VOLUME 87 APRIL 1954 NUMBER 4

IDIOPATHIC SPONTANEOUSLY OCCURRING HYPOGLYCEMIA IN INFANTS

Clinical Significance of Problem and Treatment

IRVINE McQUARRIE, M.D.
MINNEAPOLIS

IN KEEPING with tradition concerning the choice of subject for a presidential address, I originally prepared a semiphilosophical dissertation for this occasion. Now, I must apologize to you for the sin of "deviation," because I suddenly decided only a few days ago to scrap that laboriously composed oration and substitute a résumé of some observations that my associates and I have made during the past few years in dealing with the clinical problem of spontaneous hypoglycemia in infants.

My seemingly impulsive decision to change to the latter title was the direct result of my seeing the seventh young child, among a series of cases recently examined in our clinic, who had suffered irreparable brain damage from severe hypoglycemia. Three of these were children who were victims of the misuse of insulin in the treatment of diabetes mellitus. The remaining four were examples of severe spontaneous hypoglycemia in infants who were victims of delayed diagnosis and inadequate early therapy.

The tragedy of permanent brain damage resulting from therapeutically induced hypoglycemia * is too well known and the precautions necessary for its avoidance are too obvious to justify special consideration at this time. The situation is quite different, however, in regard to the special group of infants with spontaneous hypoglycemia which I have felt compelled to discuss here today. There have been well-documented cases of brain damage associated with spontaneous hypoglycemia.†

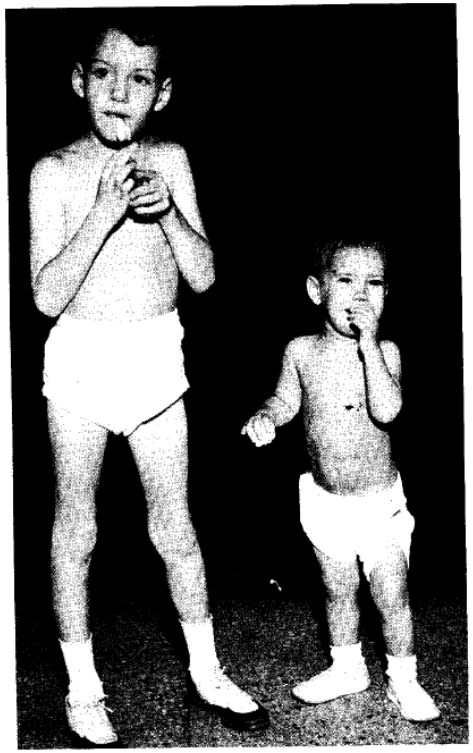
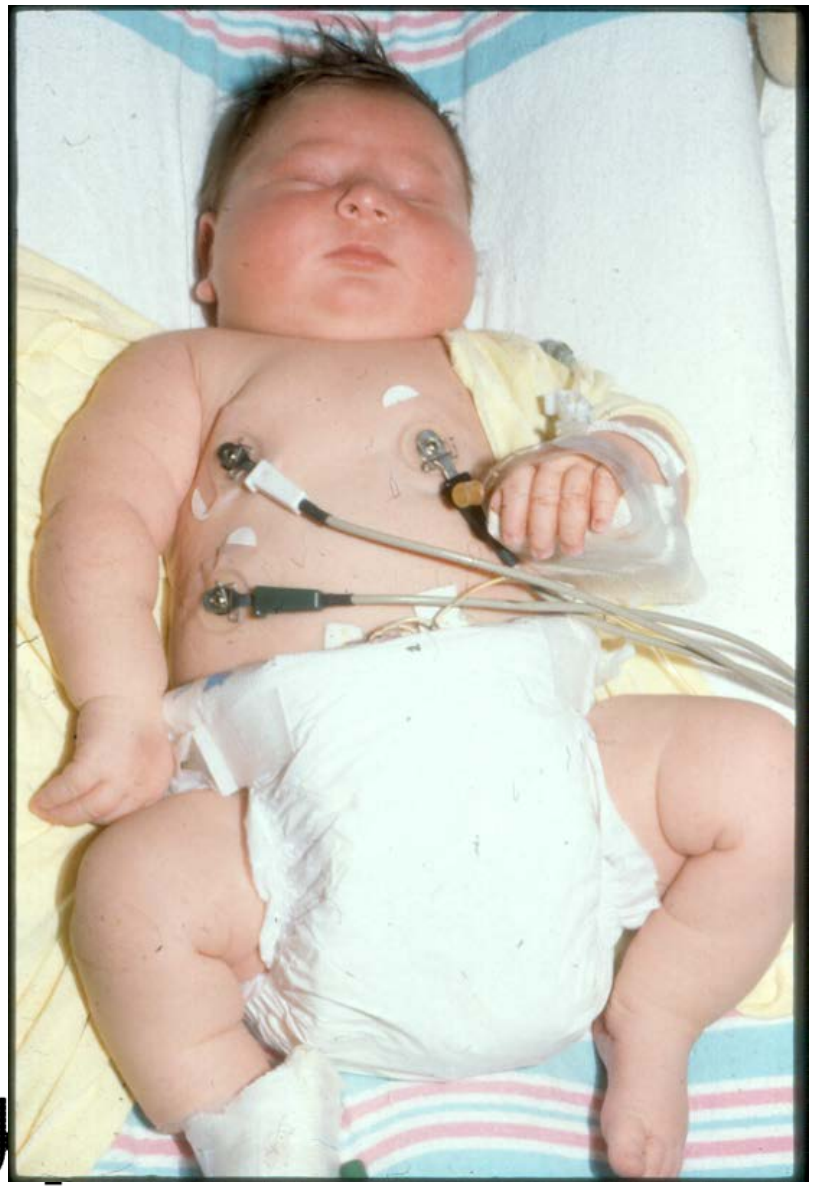


Fig. 3.—Photograph of J. G., aged 6 years, and B. G., aged 15 months. Taken two months after beginning of corticotropin therapy. Pancreatic resection scars visible.

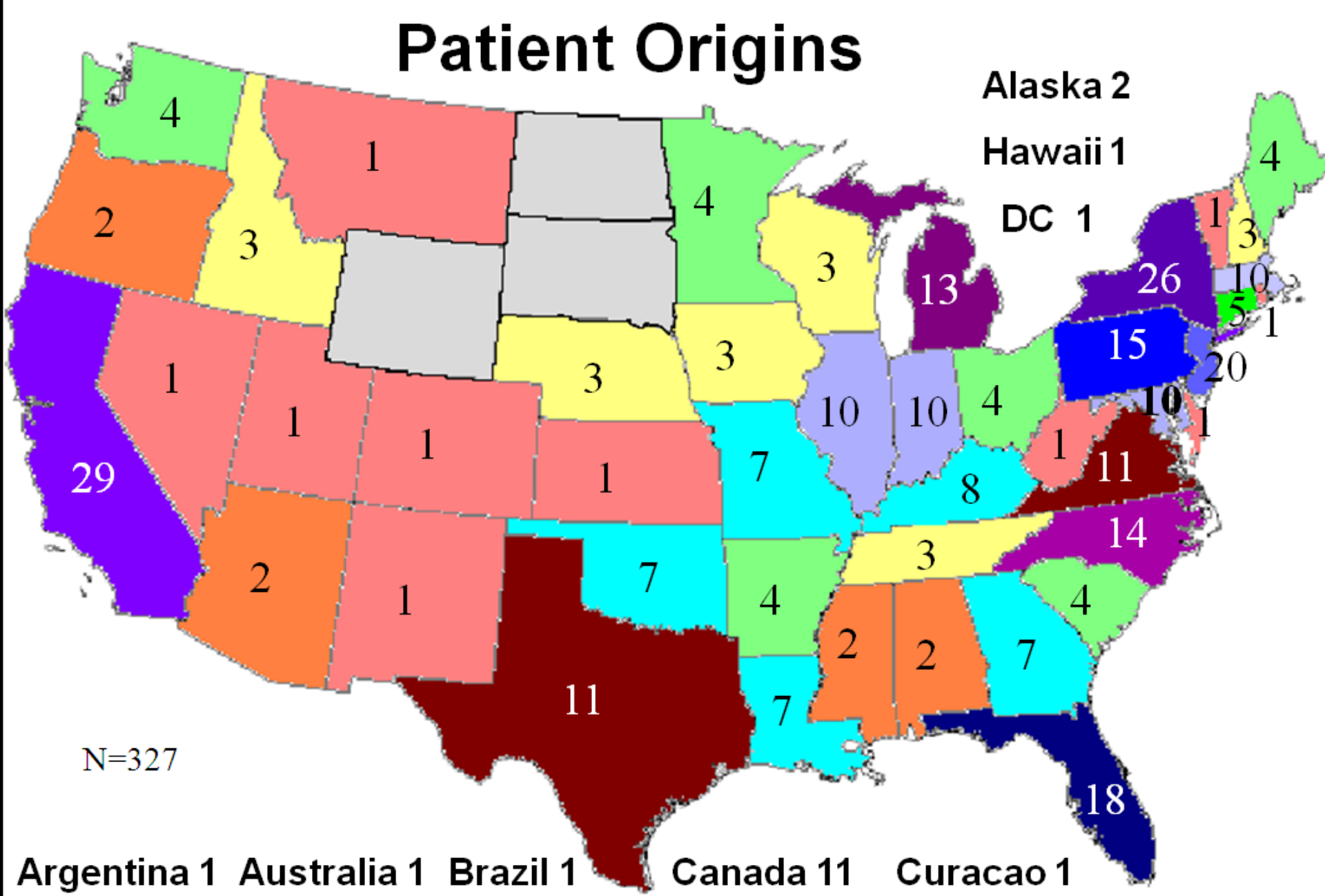
Congenital Hyperinsulinism



- Most common form of hypoglycemia in children
  - >1 in 20,000 births
  - 1 in 10 SGA babies (Transient)
- Glucose requirement up to 50 mg/kg/min (10x normal)
- High risk of seizures & brain damage
- Pancreatectomy often needed
- Half of surgical cases have a curable focal lesion
- 9+ genetic loci


CHOP Hyperinsulinism Center
http://hyperinsulinism.chop.edu
hyperinsulinism@email.chop.edu
215-590-7682

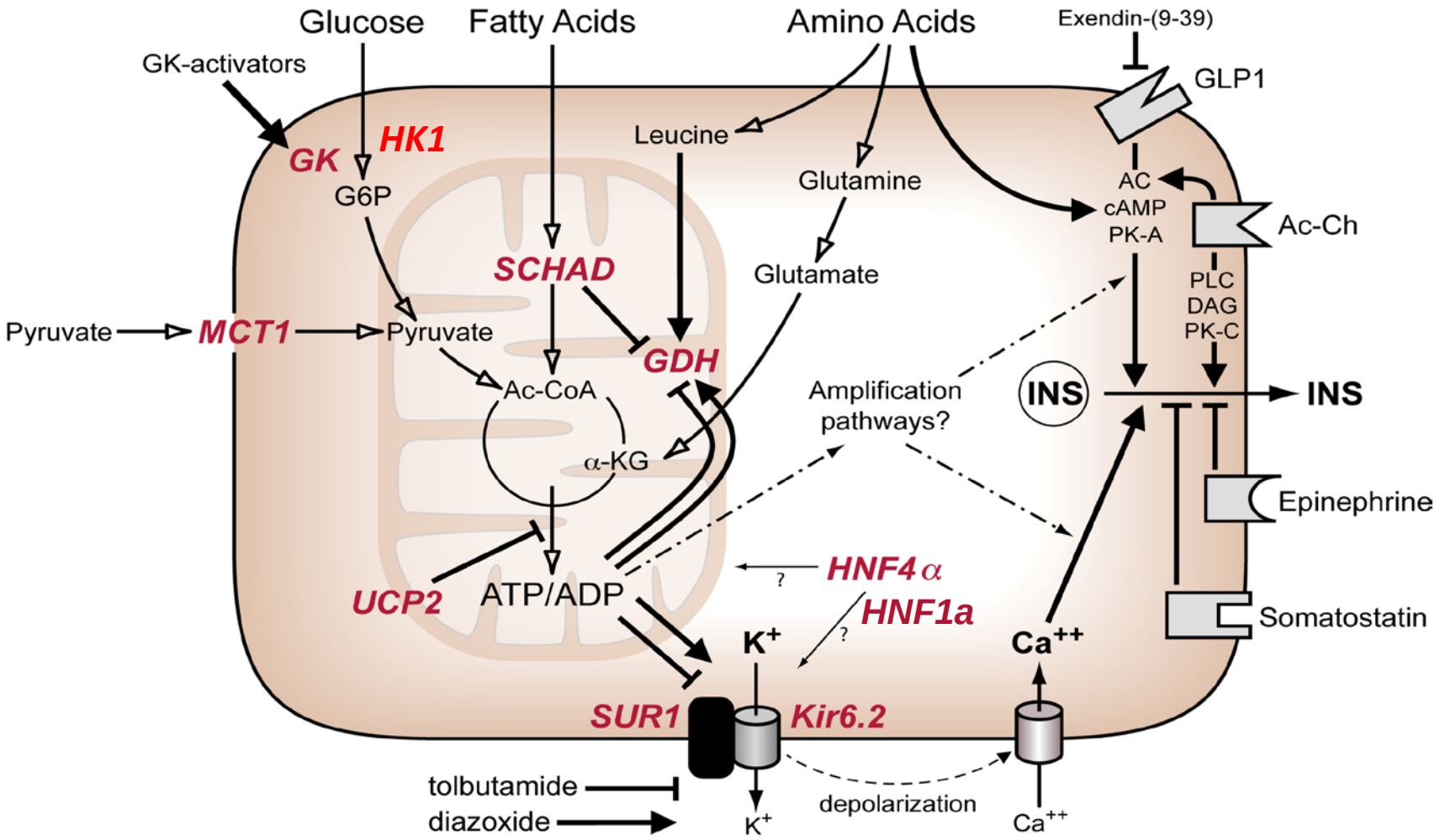
Patient Origins



Argentina 1 Australia 1 Brazil 1 Canada 11 Curacao 1

Ecuador 1 Iran 1 Israel 2 Japan 1 Saudi Arabia 1 Venezuela 1

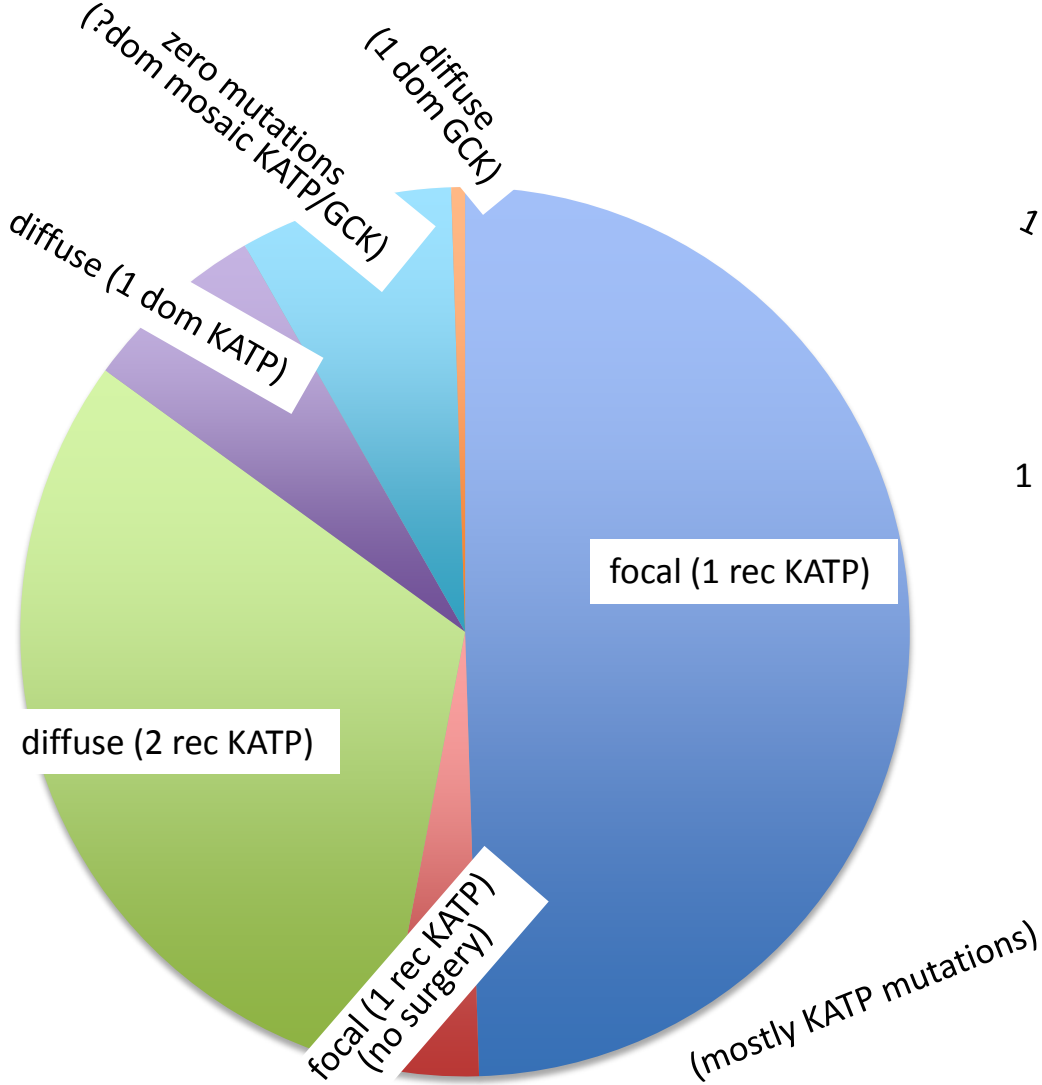
Congenital Hyperinsulinism: 10 Genes



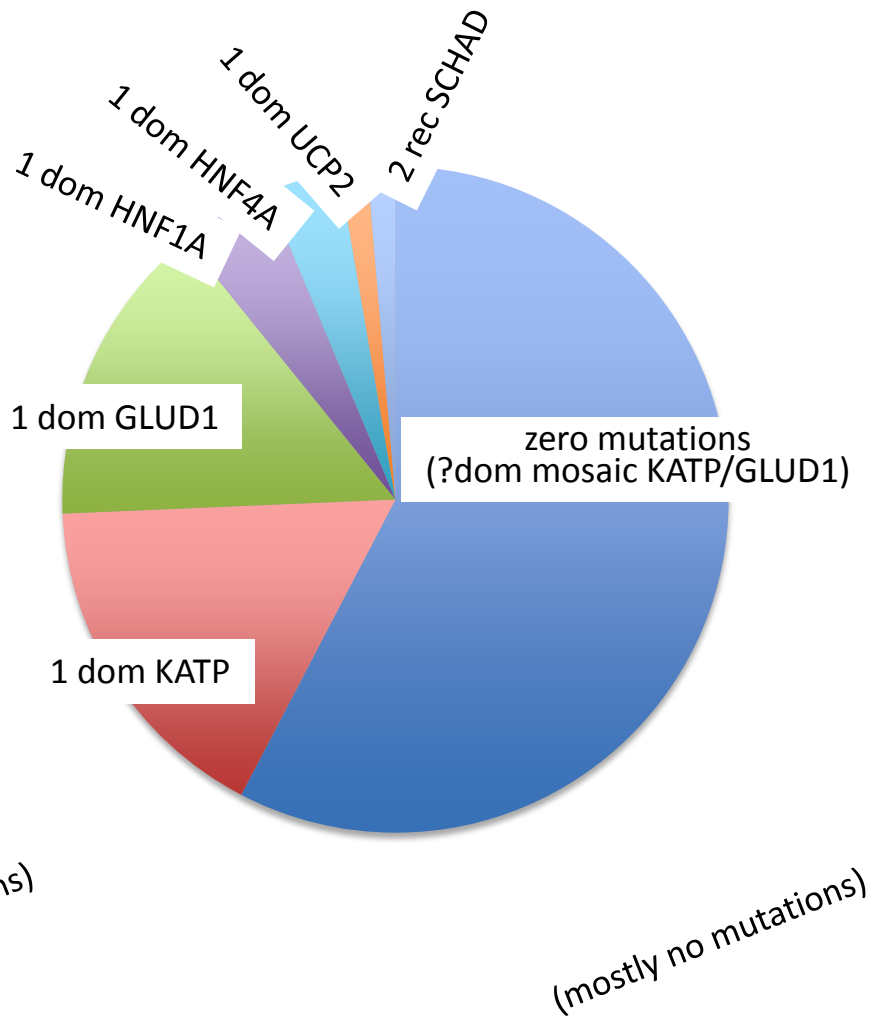
Phenotypes of Congenital Hyperinsulinism

gene	genetics	Sensitivity to stimuli / inhibitors				
		diazoxide	protein	leucine	calcium	exercise
KATP	rec	-	+	-	+	-
KATP	dom	+	+	-	+	-
GDH (HI-HA)	dom	+	+	+	-	-
GCK	dom	-	-	-	-	-
SCHAD	rec	+	+	+	-	+
MCT1	dom	?	-	-	-	+
HNF4a	dom	+	?	?	?	-
UCP2	dom	+	?	?	?	?
Peri-natal stress	NA	+	?	-	-	?

Mutations in 705 Children with Congenital HI (1997-2014)

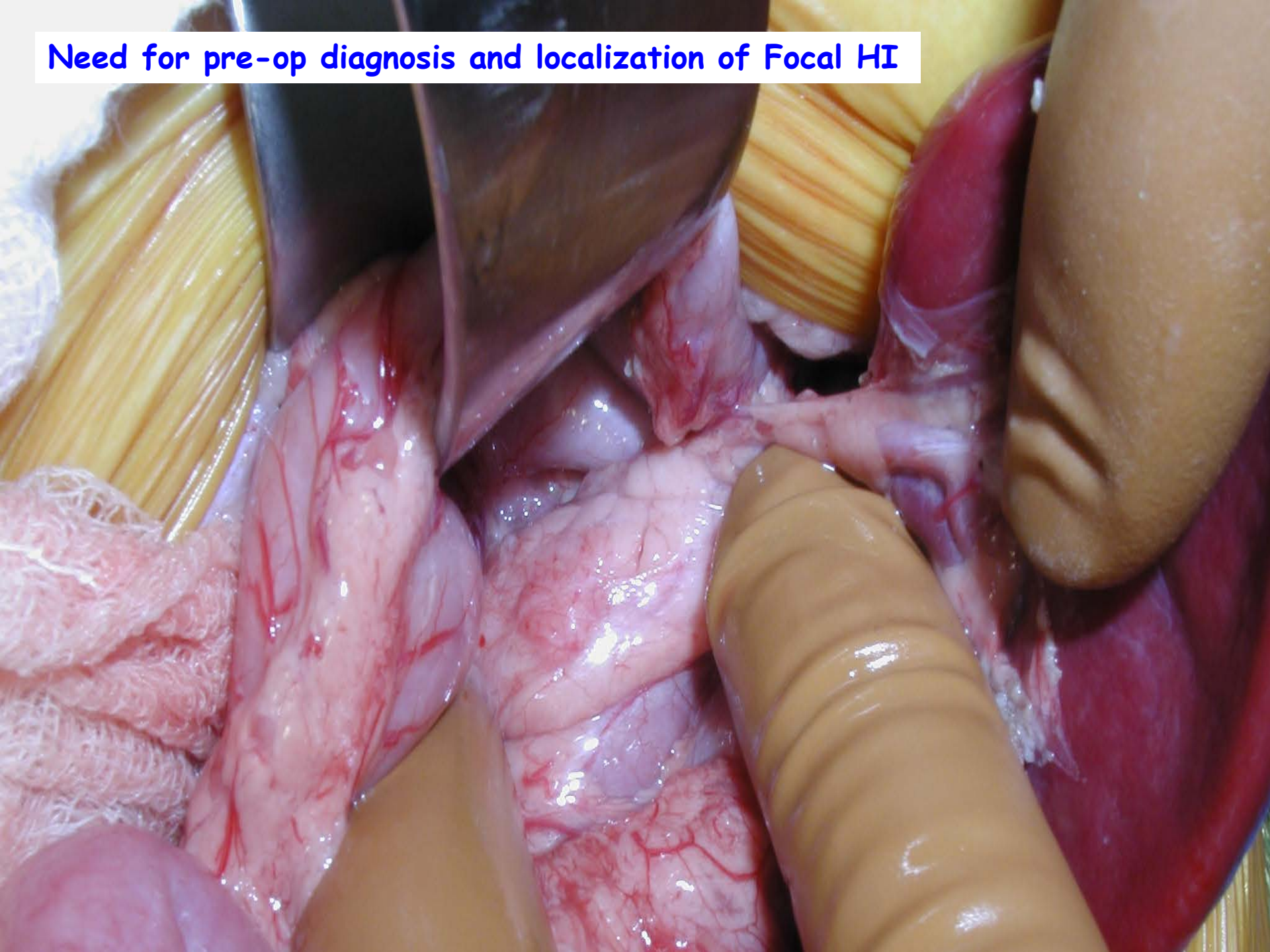


Diazoxide-Unresponsive (434)



Diazoxide-Responsive (219)

Need for pre-op diagnosis and localization of Focal HI

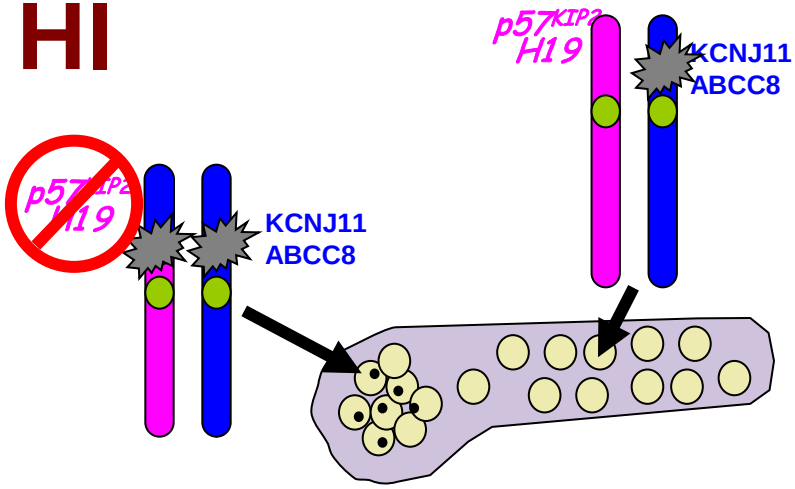


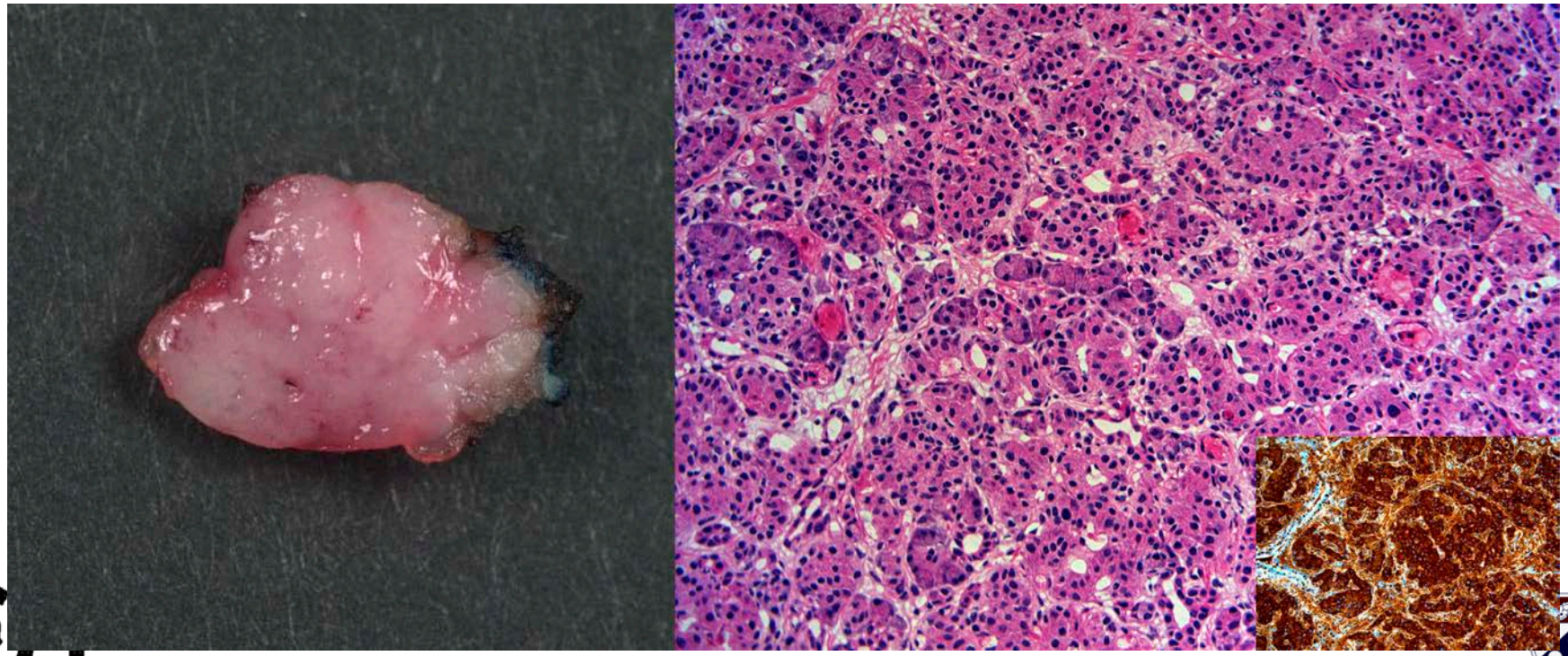
Focal HI

Genetic cause – “two hit” mechanism:

1) Paternal mutation (present in all cells)
2) LOH of maternal allele on 11p (no KATP genes and no growth regulatory genes)

Result: Uncontrolled islet cell proliferation forming a focal lesion that continuously releases insulin due to a knock out paternal mutation in ABCC8 or KCNJ11





Parental Genotyping

Predicting Focal-HI

	Focal-HI	Diffuse-HI
Single recessive KATP mutation	144	9
No single recessive KATP mutation	4	95

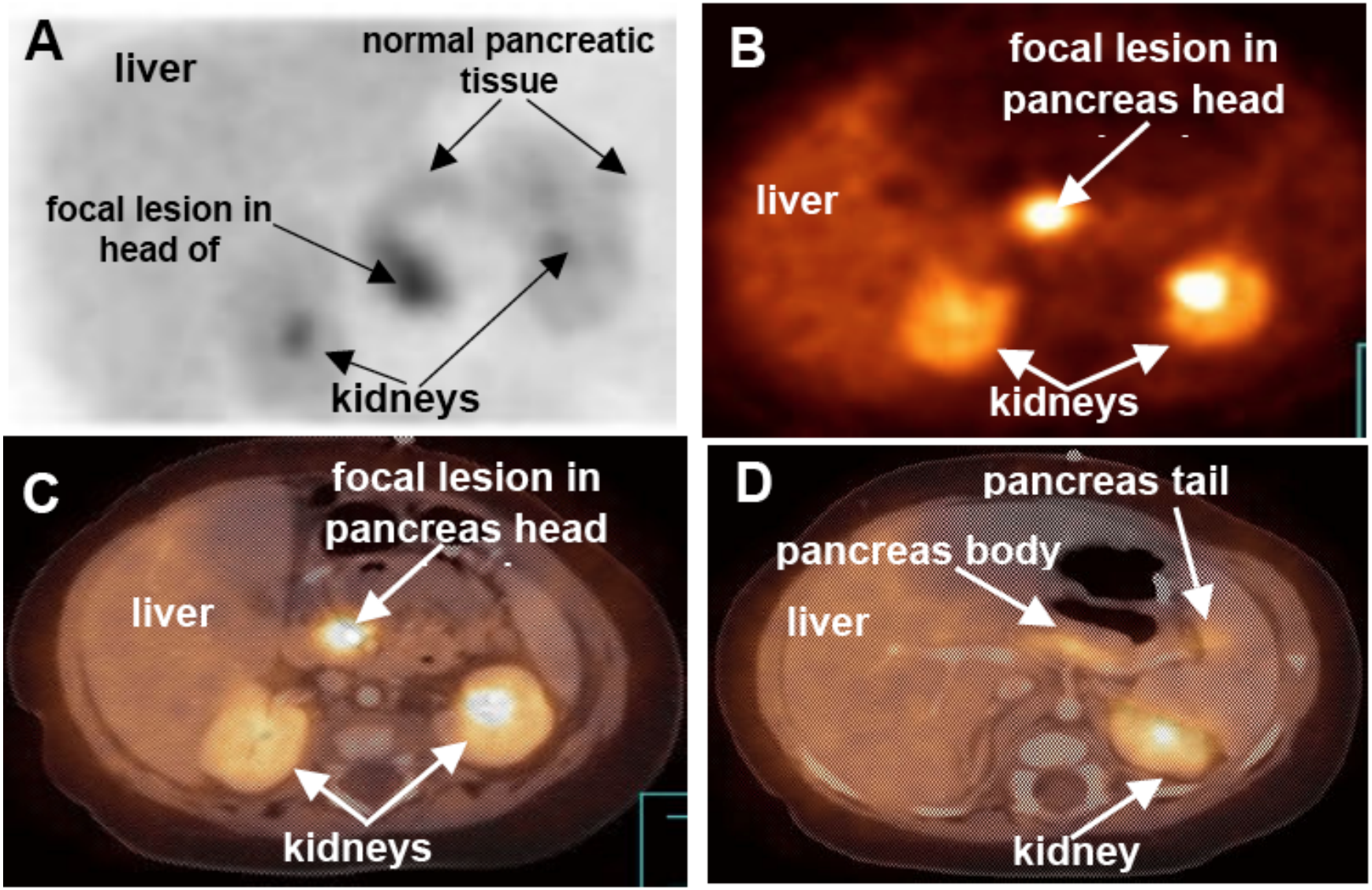
A single heterozygous recessive mutation accurately predicts focal-HI:

Sensitivity: 97%
Specificity: 91%

When paternal inheritance is confirmed:

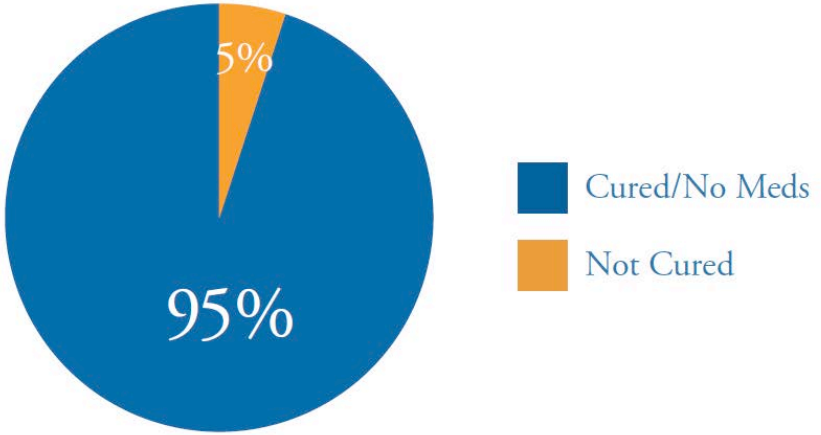
Sensitivity: 97%
Specificity: 93%

F-DOPA PET images--Focal HI

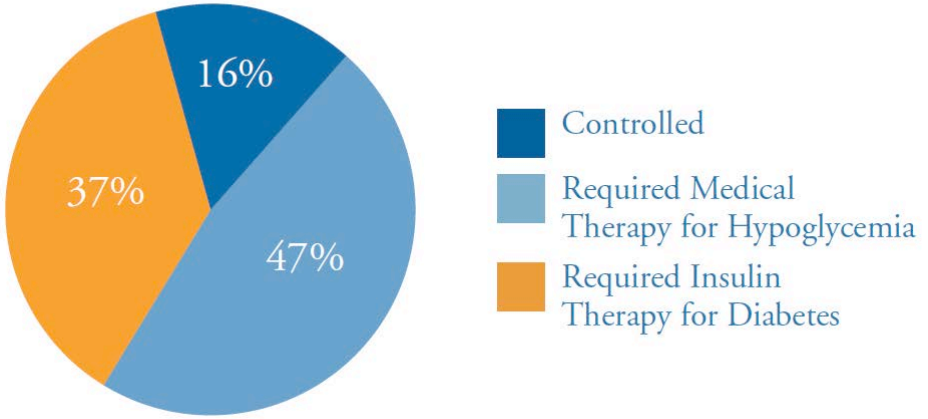


Post-Surgery Outcomes of CHOP Focal vs Diffuse HI (since 2008)

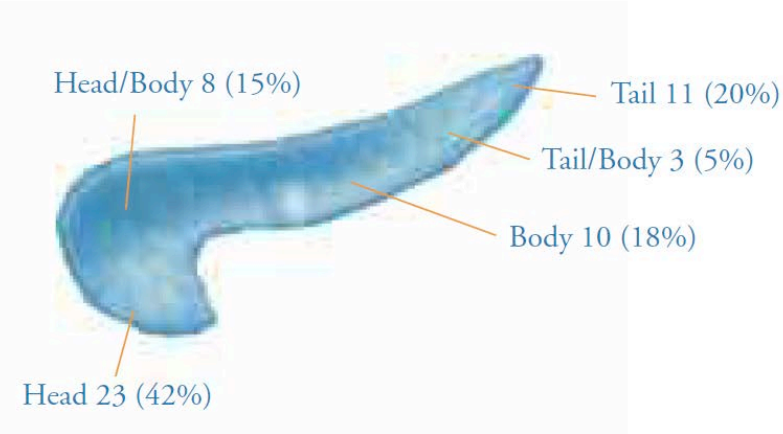
Outcomes of Focal Patients (55 cases)



Outcomes of Diffuse Patients (43 cases)



Location of Focal Lesions



HI Treatment Options 1985-now

Medical:

- Diazoxide
- Octreotide
- Continuous tube feedings

Surgery

- Diffuse: near-total pancreatectomy
- Focal: cure by excision

Futuristic HI Treatments

Long-acting Octreotide (Paris, etc.)

GLP-1 antagonist (Philly)

Sirolimus (London)

….at least 3 other potential agents in the pre-clinical pipeline (…that I know about!)

New Guidelines to Aid in Diagnosing Congenital HI from the PES (free on-line!!)

COMMENTARY www.jpeds.com • THE JOURNAL OF PEDIATRICS

Re-Evaluating "Transitional Neonatal Hypoglycemia": Mechanism and Implications for Management

Charles A. Stanley, MD[1], Paul J. Rozance, MD[2], Paul S. Thornton, MB, BCh[3], Diva D. De Leon, MD[1], Deborah Harris, PhD[4], Morey W. Haymond, MD[5], Khalid Hussain, MD, MSc[6], Lynne L. Levitsky, MD[7], Mohammad H. Murad, MD, MPH[8], Rebecca A. Simmons, MD[9], Mark A. Sperling, MBBS[10], David A. Weinstein, MD[11], Neil H. White, MD[12], and Joseph I. Wolfsdorf, MB, BCh[13]

A Committee of the Pediatric Endocrine Society was recently formed to develop guidelines for evaluation and management of hypoglycemia in neonates, infants, and children. To aid in formulating recommendations for neonates, in this review, we analyzed available data on the brief period of hypoglycemia, which commonly is observed in normal newborns during the transition from fetal to extrauterine life, hereafter referred to as transitional neonatal hypoglycemia in normal newborns. The goal was to better understand the mechanism underlying this phenomenon in order to formulate recommendations for recognizing neonates requiring diagnosis and treatment during the first days of life for disorders causing severe and persistent hypoglycemia.

It has long been known that plasma glucose concentrations are lower in the first 1-3 days of life in normal newborn infants than at later ages. Not until the 1960s was it appreciated that hypoglycemia in neonates could sometimes be symptomatic and, as in older infants and children, cause seizures or permanent brain damage.[1,2] Although studies in laboratory animals have demonstrated postnatal developmental changes in specific enzymes involved in hepatic gluconeogenesis and ketogenesis,[3,4] it is unclear that such changes adequately explain transitional neonatal hypoglycemia in human newborns or if other mechanisms may be involved.[5,6] A National Institutes of Health conference outlined many of the "gaps in knowledge" about neonatal hypoglycemia and lamented the lack of a rational basis for defining hypoglycemia in neonates.[7]

For this re-evaluation of transitional neonatal hypoglycemia in normal newborns, we used the strategy routinely employed by pediatric endocrinologists for evaluation of hypoglycemia in older infants and children. This strategy, based on an examination of the major metabolic fuel and hormone responses to hypoglycemia, makes it possible to focused on mean responses as being most likely representative of normal newborns, recognizing the possibility of heterogeneity, particularly with regard to peripartum stresses and feeding practices. We found that transitional neonatal hypoglycemia most closely resembles known genetic forms of congenital hyperinsulinism, which cause a lowering of the plasma glucose threshold for suppression of insulin secretion. This conclusion is based on strong evidence supported by 2 or more independent reports and provides a novel perspective on both the diagnosis and management of hypoglycemia in the first several days after birth.

Patterns of Plasma Glucose Concentrations in Normal Newborns during the First Days of Life

Prior to birth, fetal fuel metabolism is based primarily on oxidation of glucose, which is supplied from maternal plasma glucose whose levels are regulated by maternal insulin secretion.[9] The fetal brain is exposed to circulating glucose concentrations only slightly below those of maternal plasma; with normal maternal glucose concentrations of 70-90 mg/dL (3.9-5.0 mmol/L), the mean fetal-maternal plasma glucose difference at term is only 9 mg/dL (0.5 mmol/L).[10] Fetal insulin secretion is responsive to fetal plasma glucose concentrations, but fetal glucose concentrations are determined primarily by maternal glucose concentration whereas fetal insulin primarily functions to regulate growth.[11]

Immediately following birth, in normal newborns, the mean plasma glucose concentrations drop by 25-30 mg/dL

From the [1]Division of Endocrinology, Children's Hospital of Philadelphia,

the period of transitional neonatal hypoglycemia. We

AGA	Appropriate for gestational age
FFA	Free fatty acid
P1	Postnatal day 1
SGA	Small for gestational age

Pittsburgh Children's Hospital, Pittsburgh, PA; [11]Division of Pediatric Endocrinology, University of Florida College of Medicine, Gainesville, FL; [12]Division of Endocrinology and Diabetes, Department of Pediatrics, Washington University in St. Louis and St. Louis Children's Hospital, St. Louis, MO; and [13]Division of Endocrinology, Boston Children's Hospital, Boston, MA

The authors declare no conflicts of interest.

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http://www.ncbi.nlm.nih.gov/pubmed/25957977

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Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children

Paul S. Thornton, MB, BCh[1], Charles A. Stanley, MD[2], Diva D. De Leon, MD, MSCE[2], Deborah Harris, PhD[3], Morey W. Haymond, MD[4], Khalid Hussain, MD, MPH[5], Lynne L. Levitsky, MD[6], Mohammad H. Murad, MD, MPH[7], Paul J. Rozance, MD[8], Rebecca A. Simmons, MD[9], Mark A. Sperling, MBBS[10], David A. Weinstein, MD, MMSc[11], Neil H. White, MD[12], and Joseph I. Wolfsdorf, MB, BCh[13]

During the first 24-48 hours of life, as normal neonates transition from intrauterine to extrauterine life, their plasma glucose (PG) concentrations are typically lower than later in life.[1-3] Published guidelines for screening at-risk newborns and managing low PG concentrations in neonates focus on the immediate neonatal period, but do not address the diagnosis and management of disorders causing recurrent and prolonged hypoglycemia.[4-6] Distinguishing between transitional neonatal glucose regulation in normal newborns and hypoglycemia that persists or occurs for the first time beyond the first 3 days of life is important for prompt diagnosis and effective treatment to avoid serious consequences, including seizures and permanent brain injury.

Moreover, the evaluation and management of pediatric hypoglycemia differ in several respects from that in adults, for whom guidelines were recently published.[7] First, persistent hypoglycemia most often results from a congenital or genetic defect in regulating secretion of insulin, deficiency of cortisol and/or growth hormone, or defects in the metabolism of glucose, glycogen, and fatty acids. Second, it may be difficult to identify and distinguish newborn infants with a persistent hypoglycemia disorder from those with transitional low glucose levels in the initial 48 hours of life, as detailed in the separate document on transitional neonatal hypoglycemia prepared by our committee.[8] Third, the first few months of life are the most vulnerable period for develhelp physicians recognize persistent hypoglycemia disorders, guide their expeditious diagnosis and effective treatment, and prevent brain damage in at-risk babies.

Methods

Evidence Retrieval and Rating

The committee searched for existing evidence synthesis reports, systematic reviews, and meta-analyses. The committee also evaluated guidelines published by the Endocrine Society, American Academy of Pediatrics, Canadian Pediatric Society, and others, and reviewed their bibliographies.[4-7] Committee members identified additional individual studies.

The committee adopted the framework of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group,[11] in which guideline developers rate their confidence in the evidence as very low (+000), low (++00), moderate (+++0), or high (++++). Randomized trials start as high, and observational studies start as low.[11]

Grading the Strength of Recommendations

The guideline developers considered the quality of the evidence. They also considered the balance between benefits and harms, patients' values and preferences, cost and resource utilization, and other societal and contextual factors, such as availability of technology and health services

http://www.ncbi.nlm.nih.gov/pubmed/25819173

ciety convened an expert panel of pediatric endocrinologists and neonatologists to develop guidelines for managing hypoglycemia in neonates, infants, and children, but excluding children with diabetes. The goals of these guidelines are to

BOHB	Beta-hydroxybutyrate
FFA	Free fatty acid
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GSD	Glycogen storage disease
HAAF	Hypoglycemia-associated autonomic failure
IV	Intravenous
PG	Plasma glucose

From the [1]Division of Endocrinology, Cook Children's Medical Center, Fort Worth, TX; [2]Division of Endocrinology, The Children's Hospital of Philadelphia, Philadelphia, PA; [3]Newborn Intensive Care Unit, Waikato District Health Board, Hamilton, New Zealand; [4]Children's Nutrition Research Center, Texas Children's Hospital, Houston, TX; [5]Department of Endocrinology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; [6]Pediatric Endocrine Unit, Massachusetts General Hospital, Boston, MA; [7]Division of Preventive Medicine, Mayo Clinic, Rochester, MN; [8]Division of Neonatology, University of Colorado School of Medicine, Aurora, CO; [9]Division of Neonatology, The Children's Hospital of Philadelphia, Philadelphia, PA; [10]Division of Endocrinology, Diabetes and Metabolism, Children's Hospital of Pittsburgh, Pittsburgh, PA; [11]Glycogen Storage Disease Program, University of Florida College of Medicine, Gainesville, FL; [12]Department of Pediatrics and Medicine, Washington University in St Louis, St Louis, MO; and [13]Division of Endocrinology, Boston Children's Hospital, Boston, MA

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CONGENITAL
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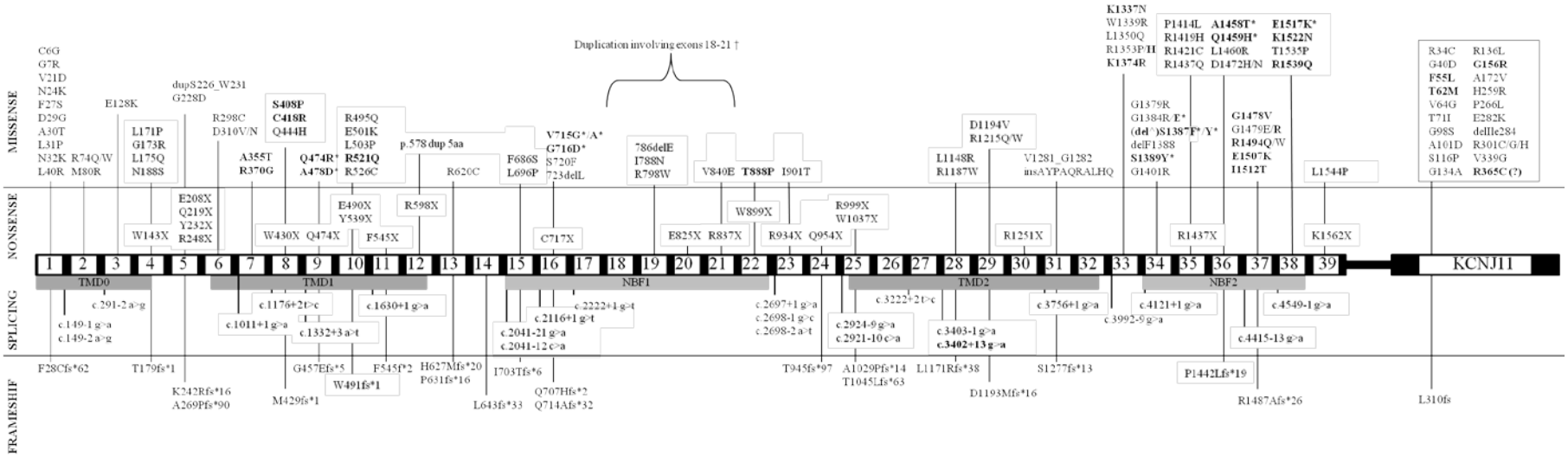
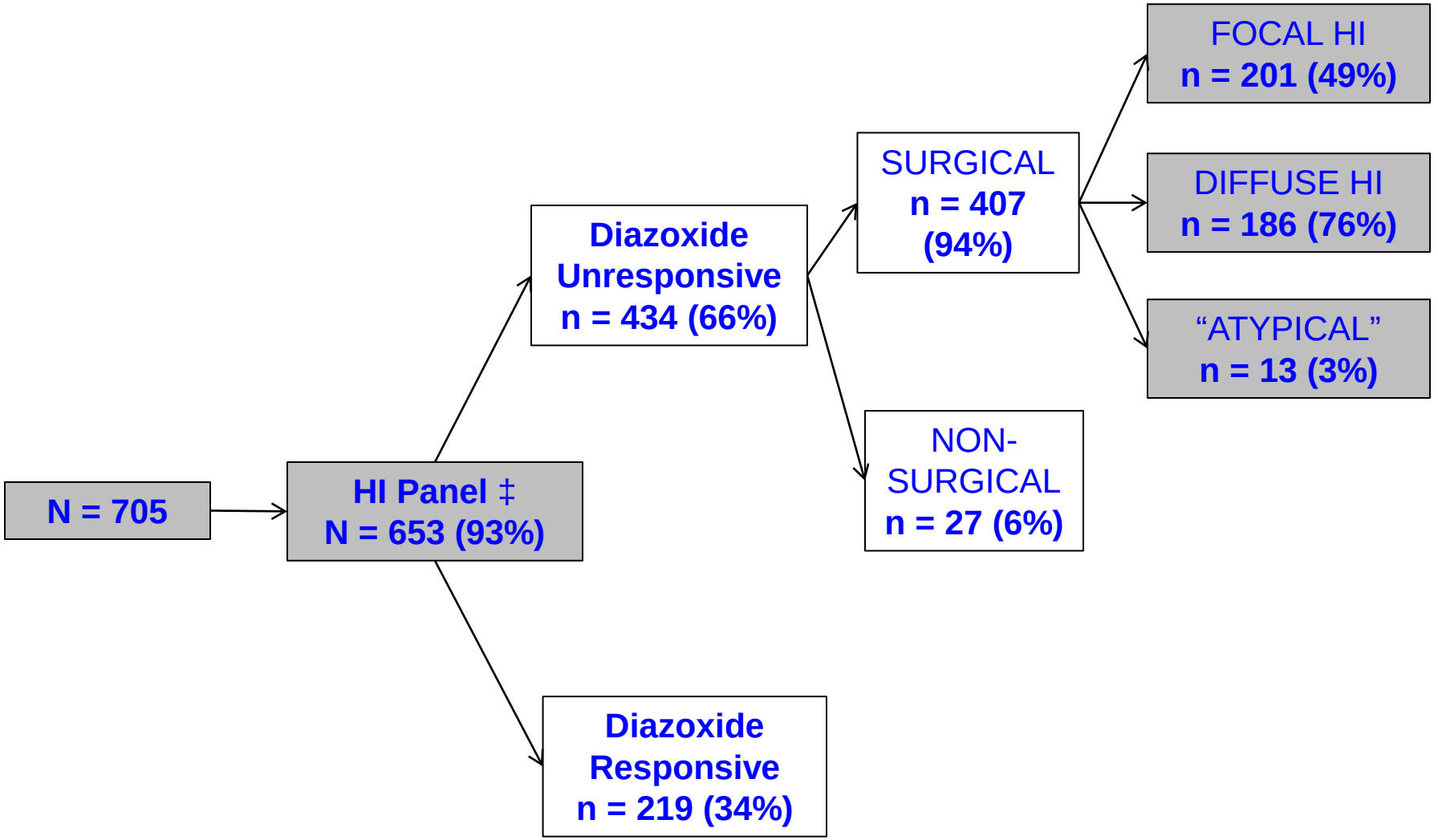
end

185 KATP Channel Mutations in ABCC8 & KCNJ11 Genes



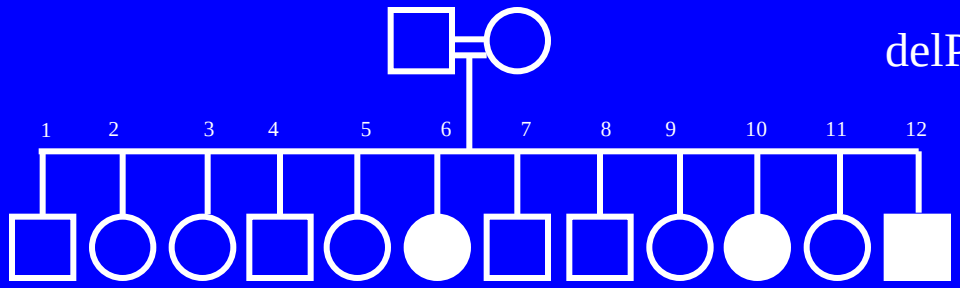
Type of Mutation	*Mode of Inheritance*	*Number in ABCC8*	*Number in KCNJ11*	*Phenotype*
Missense	Recessive	62	17	Diazoxide Unresponsive
	Dominant	12	0	Diazoxide Unresponsive*
		19	5	Diazoxide Responsive
Nonsense	Recessive	44	1	Diazoxide Unresponsive
Splicing	Recessive	24	0	Diazoxide Unresponsive
Frame-shift	Recessive	23	0	Diazoxide Unresponsive
Large Duplication	Recessive	1	0	Diazoxide Unresponsive

CHI Children seen at The Children's Hospital of Philadelphia between 1997-2014

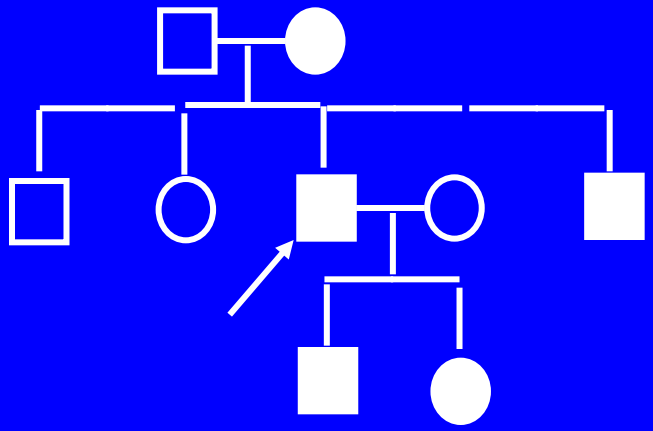


‡Tier 1 = ABCC8, KCNJ11, GCK, GLUD1

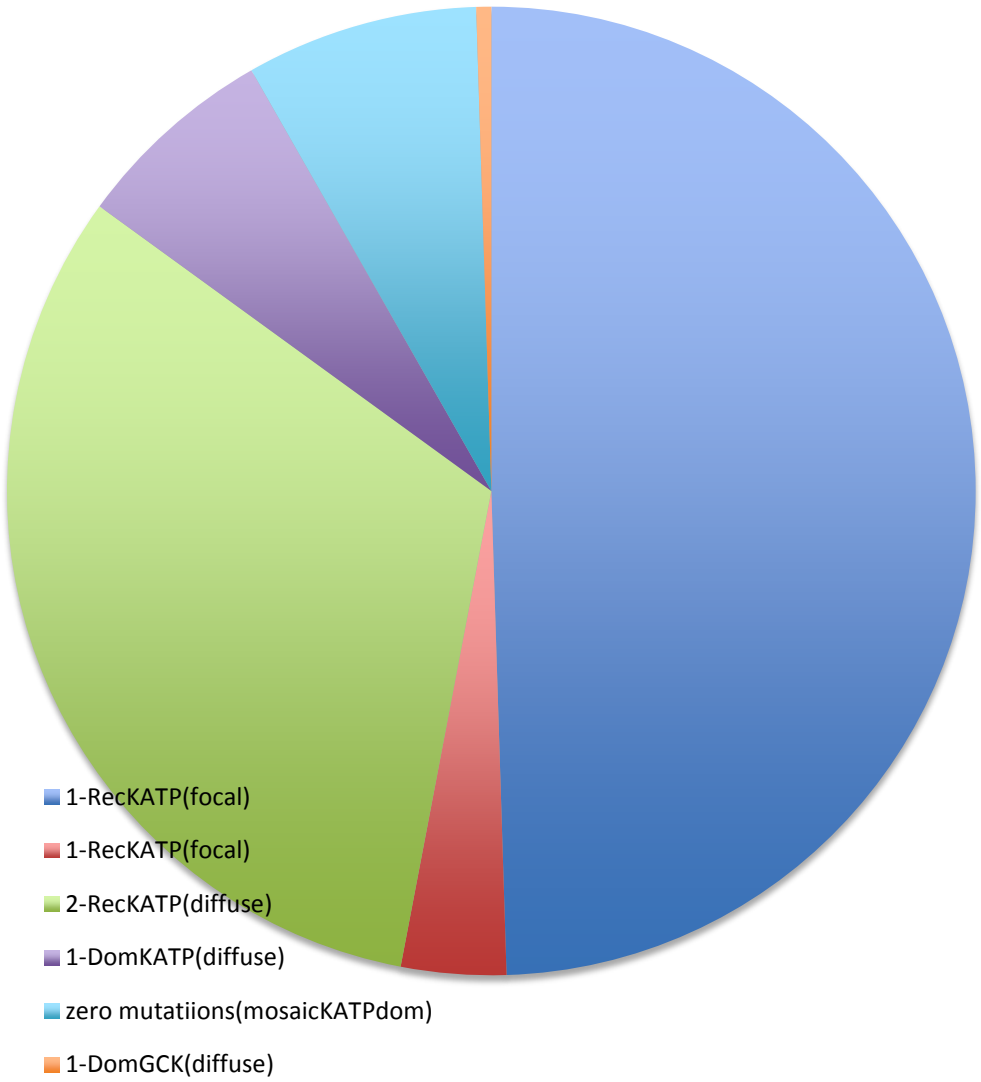
KATP HI mutations: Recessive or Dominant Inheritance

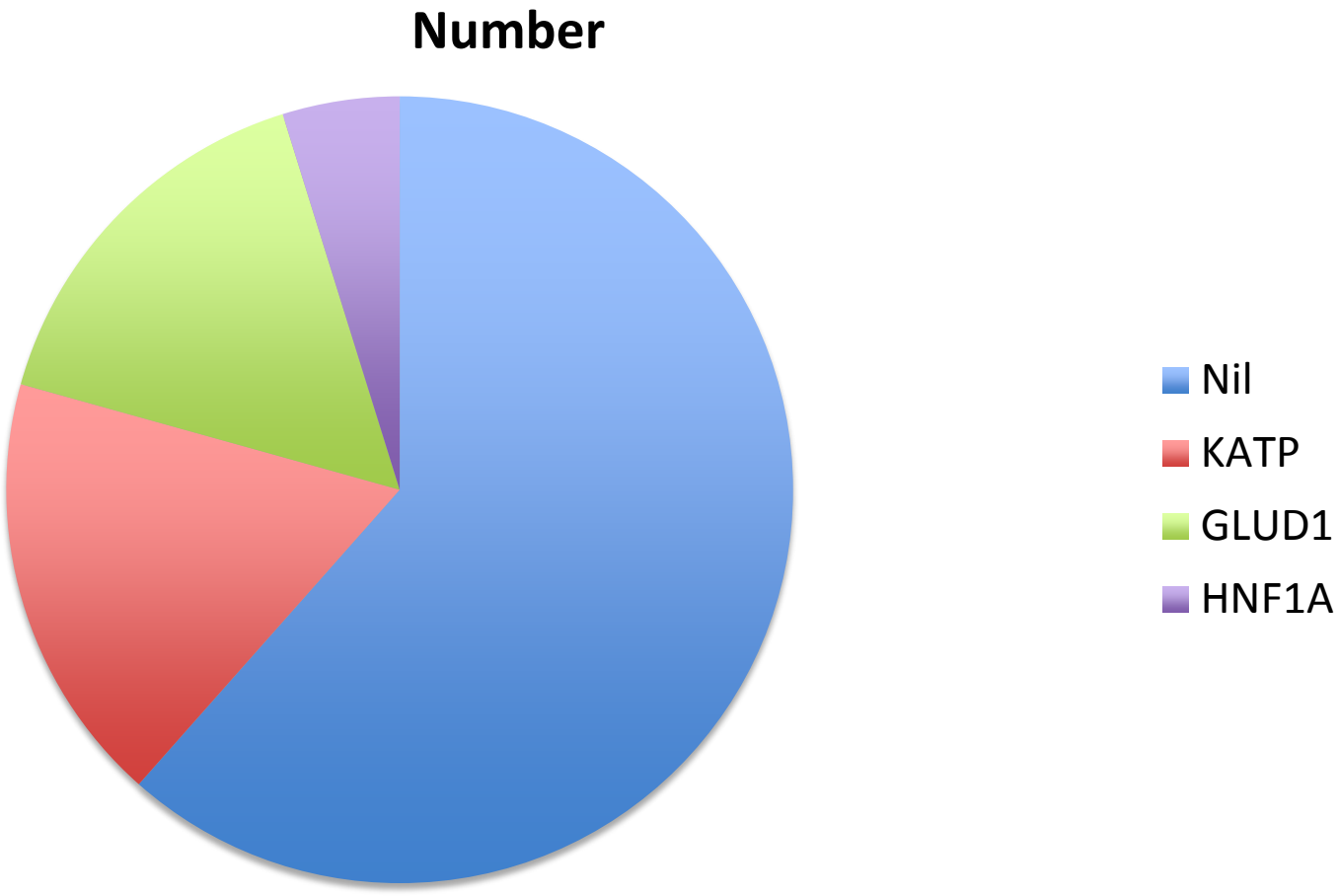


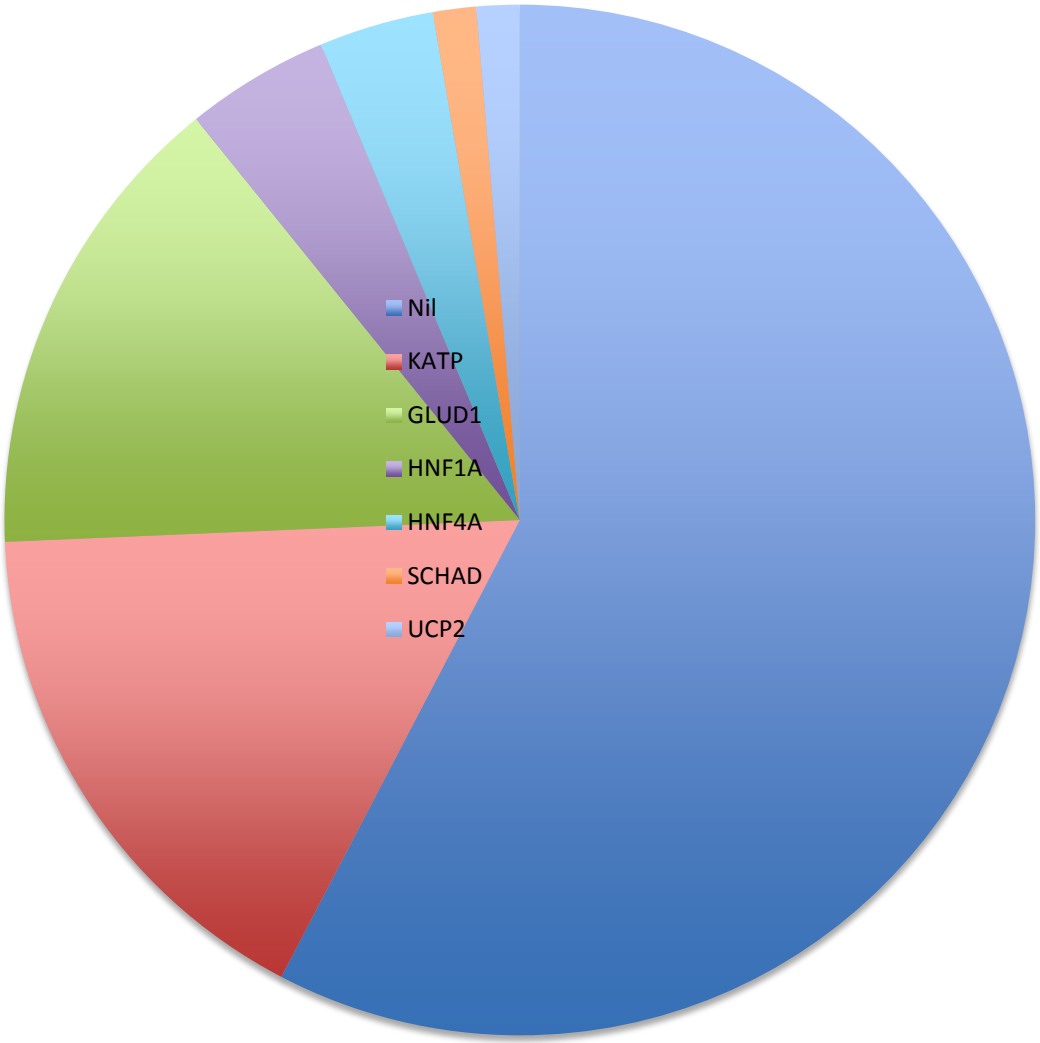
delPhe1388 homozygous



p.delSer1387 heterozygous


1-RecKATP(focal)
1-RecKATP(focal)
2-RecKATP(diffuse)
1-DomKATP(diffuse)
zero mutatiions(mosaicKATPdom)
1-DomGCK(diffuse)


Number
Nil
KATP
GLUD1
HNF1A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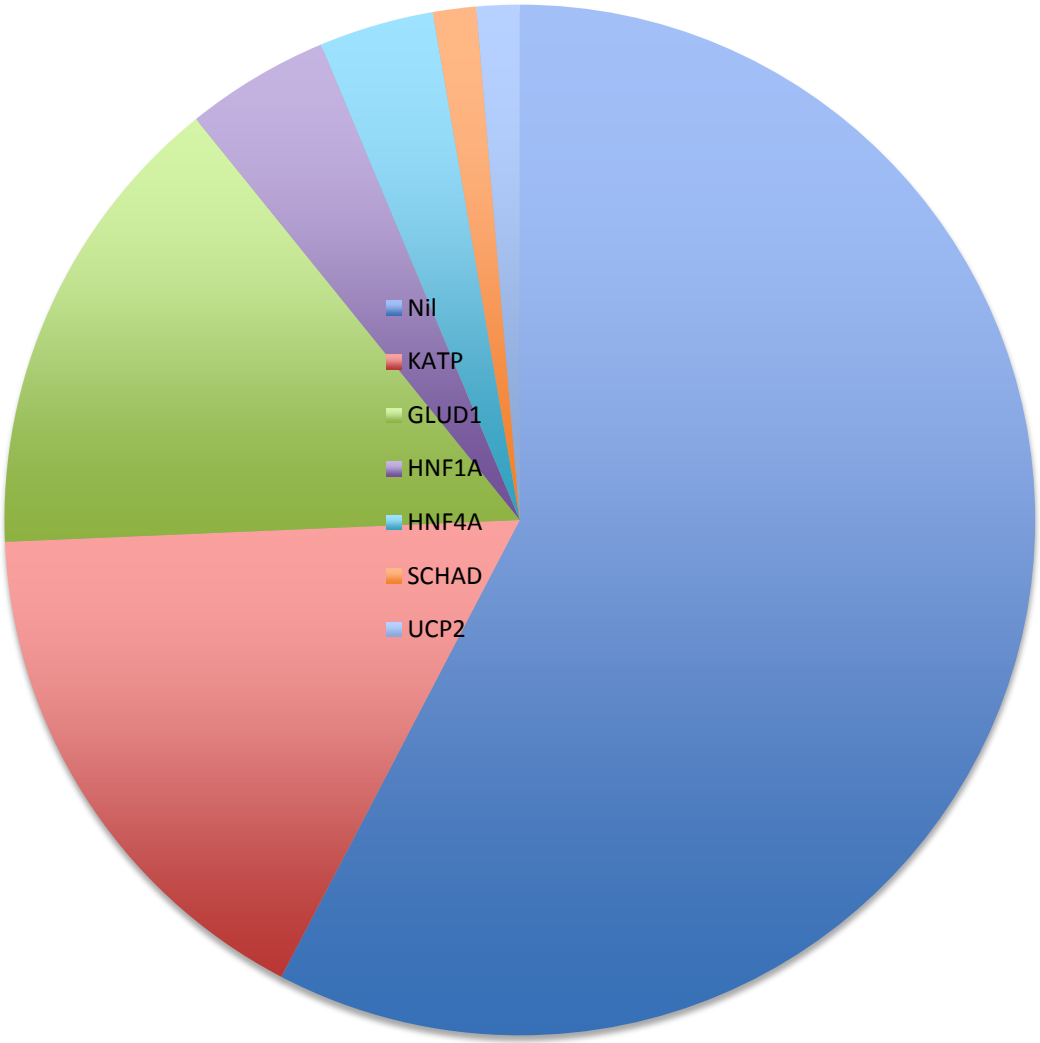
GLUD1
HNF1A
HNF4A
SCHAD
UCP2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Focal HI

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2) LOH of maternal allele on 11p including KATP genes and growth regulatory genes

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