9:10 -9:30 a.m. What is HI?

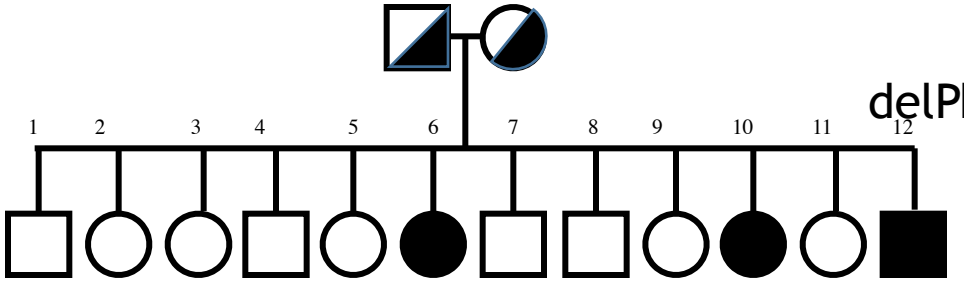
- Understanding the Role of Insulin in the Human Body. Mark Dunne, PhD, Manchester HI Center

- Understanding the Underlying Causes of Hyperinsulinism/The Genetics of Hyperinsulinism. Charles Stanley, MD, *CHOP*

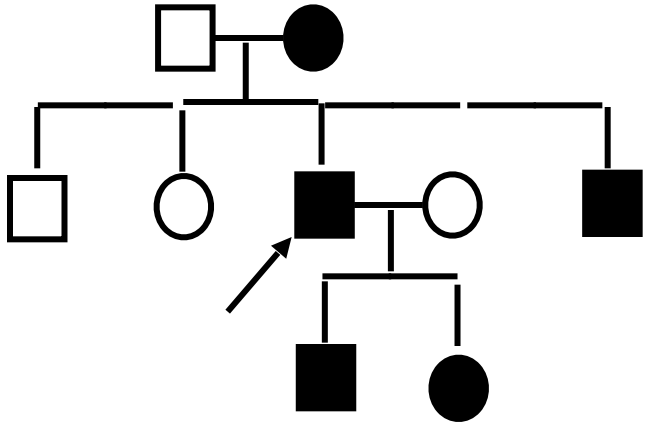
What is Hyperinsulinism (HI)???

- HI is sometimes called: Hyperinsulinemic Hypoglycemia (low blood sugar caused by excessive insulin)
  - hyper = too much …….. insulinemic = blood insulin level
  - hypo = too low……..glycemia = blood glucose level
- Big worry is that a low blood glucose can cause brain injury, since glucose is the essential fuel for the brain
- In HI, the problem is not over-production of insulin, but a failure to turn off insulin adequately during fasting when blood glucose is low
- In certain types of HI, specific foods (commonly, protein) can provoke hypoglycemia
- HI in adults is usually caused by an acquired insulin tumor (insulinoma)
- HI in children is usually caused by a genetic disorder of insulin secretion

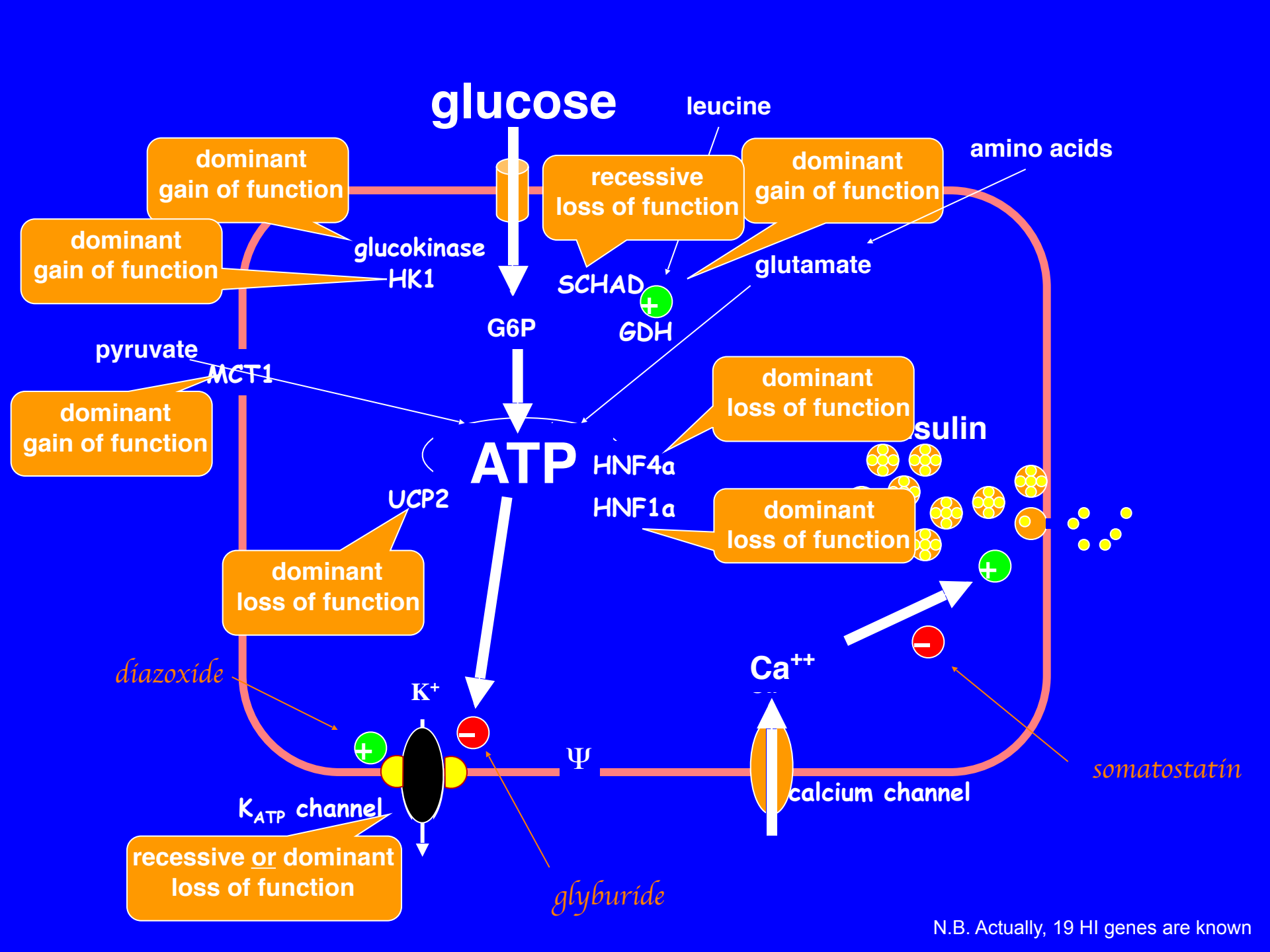
HI is Genetic:
Recessive or Dominant Inheritance



ABCC8
delPhe1388 homozygous

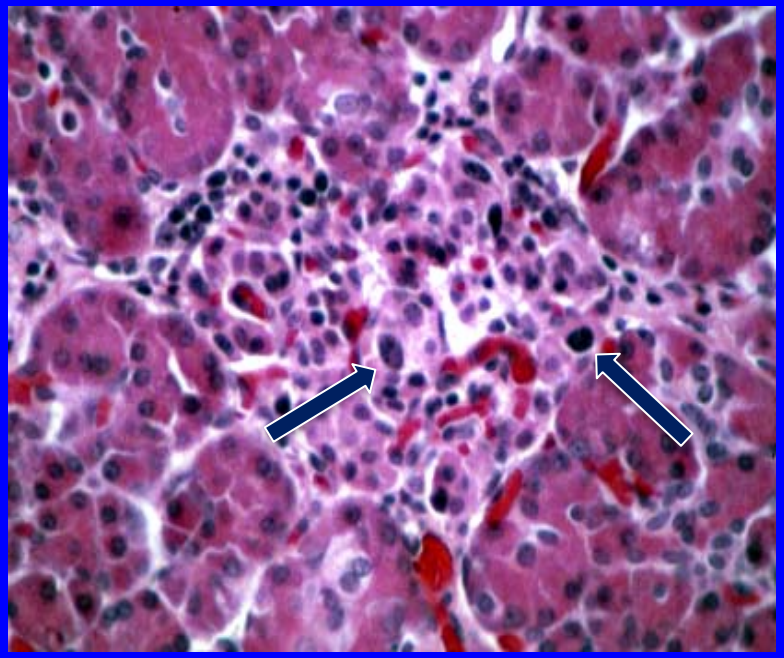


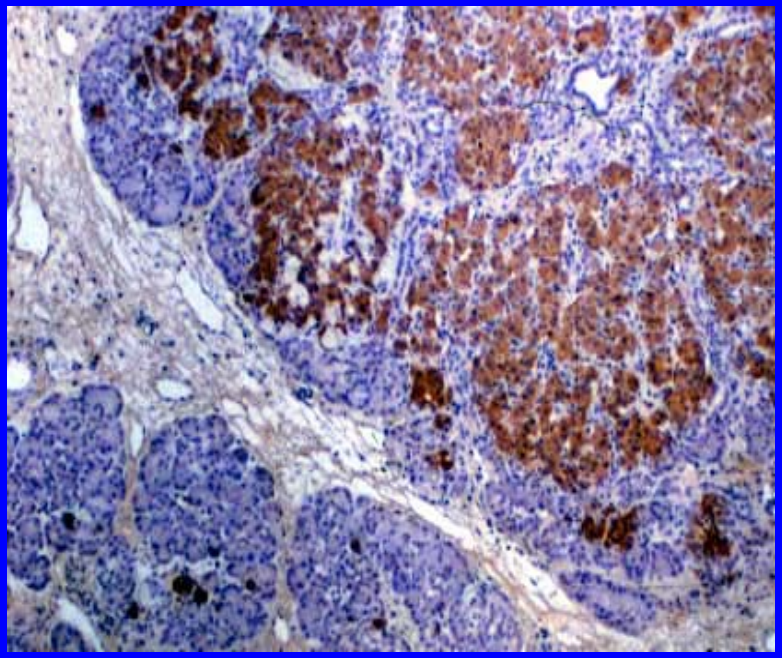
ABCC8
p.delSer1387 heterozygous

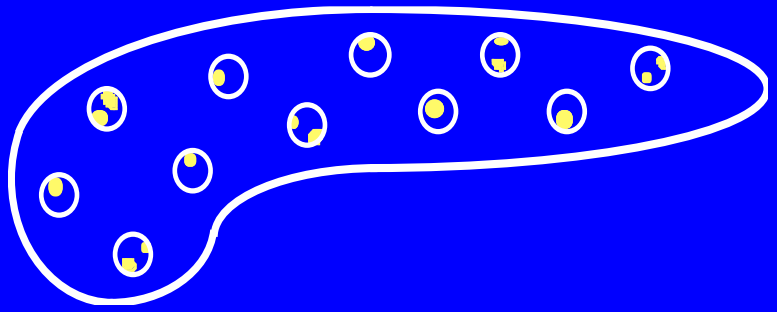


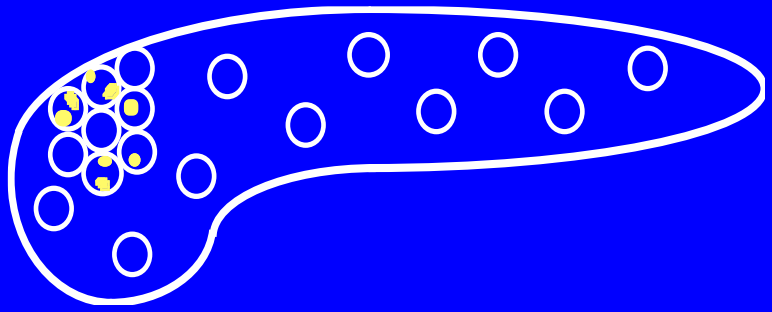
N.B. Actually, 19 HI genes are known

HISTOLOGIC FORMS OF KATP-HI HYPERINSULINISM









Diffuse form

Focal form

Focal HI

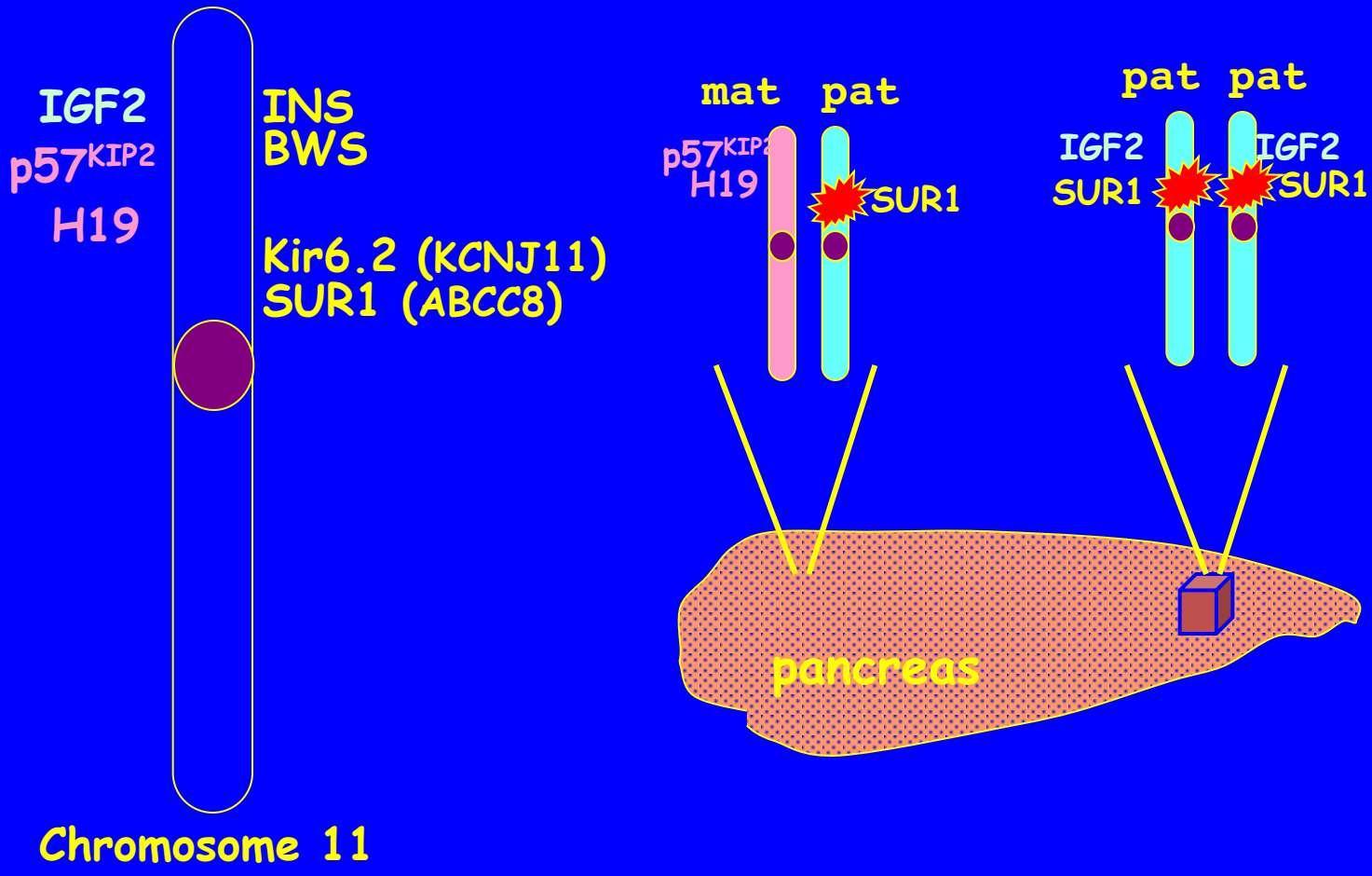
- ~50% of severe congenital HI cases
- Clinically identical to diffuse KATP-HI
- Diazoxide unresponsive
- Potential for cure by surgical resection
- 2-Hit Genetic Mechanism:
  1. *Clonal loss of maternal chromosome 11p region*

     plus

  2. *Duplication of a paternal KATP-channel mutation*

Focal Congenital HI -- Two Hits:

(Maternal LOH & Paternal K_{ATP} Defect)



Rapid Genetic Testing for HI

Univ of Pennsylvania Genetic Diagnostic Lab

Level 1 Congenital Hyperinsulinism **Panel: ABCC8, KCNJ11, GLUD1, GCK**	**5-7 days**
Level 2 Congenital Hyperinsulinism **Panel: ABCC8, KCNJ11, GLUD1, GCK, SLC16A1, UCP2, HNF1A, HNF4A, HADH**	**4-6 weeks**

Predicting Focal-HI by Genetic Testing of Patient and Parents

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

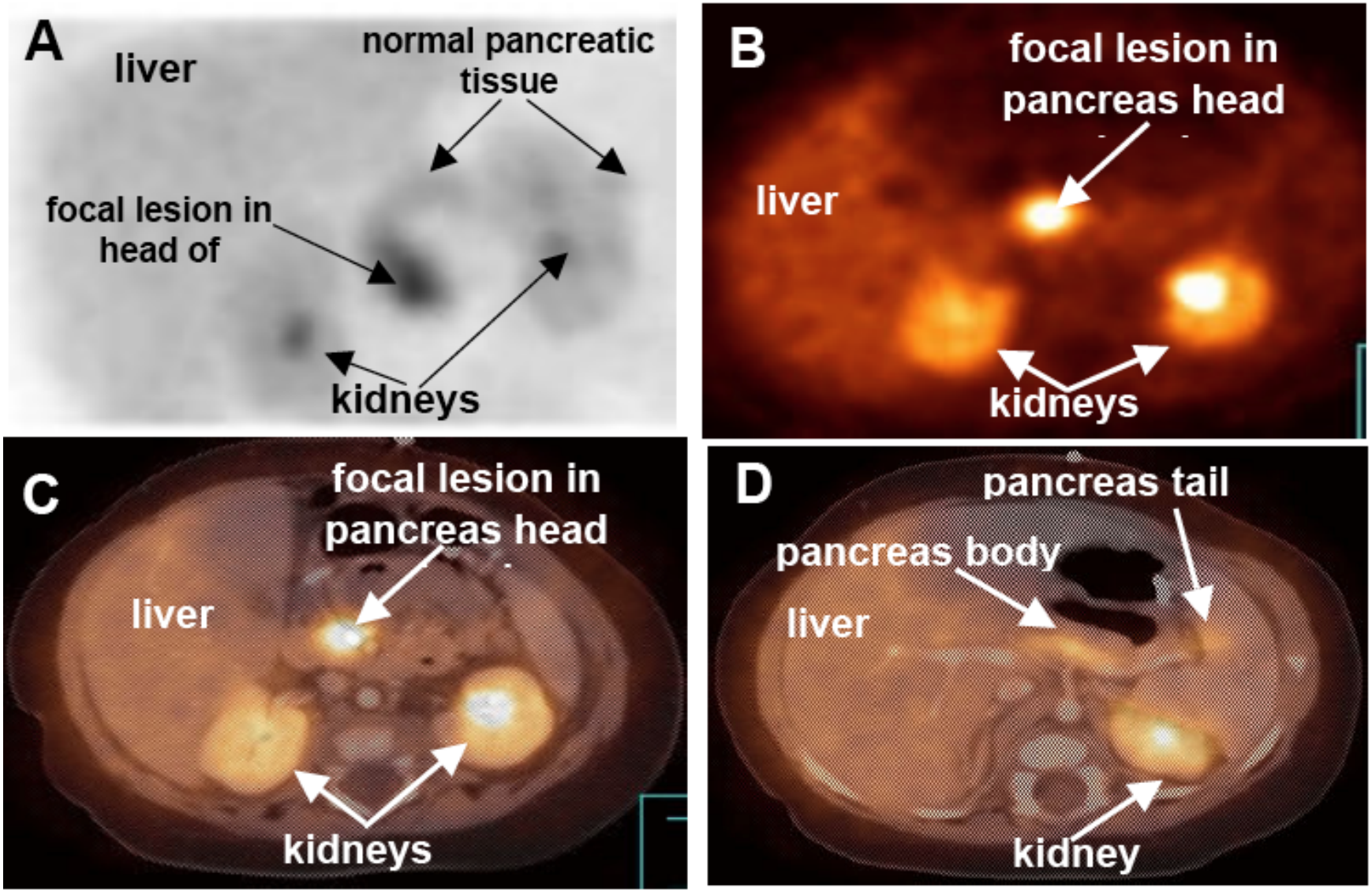
A single heterozygous recessive mutation accurately predicts focal-HI:

Sensitivity: 97%
Specificity: 91%

When paternal inheritance is confirmed:

Sensitivity: 97%
Specificity: 93%

F-DOPA PET images--Focal HI

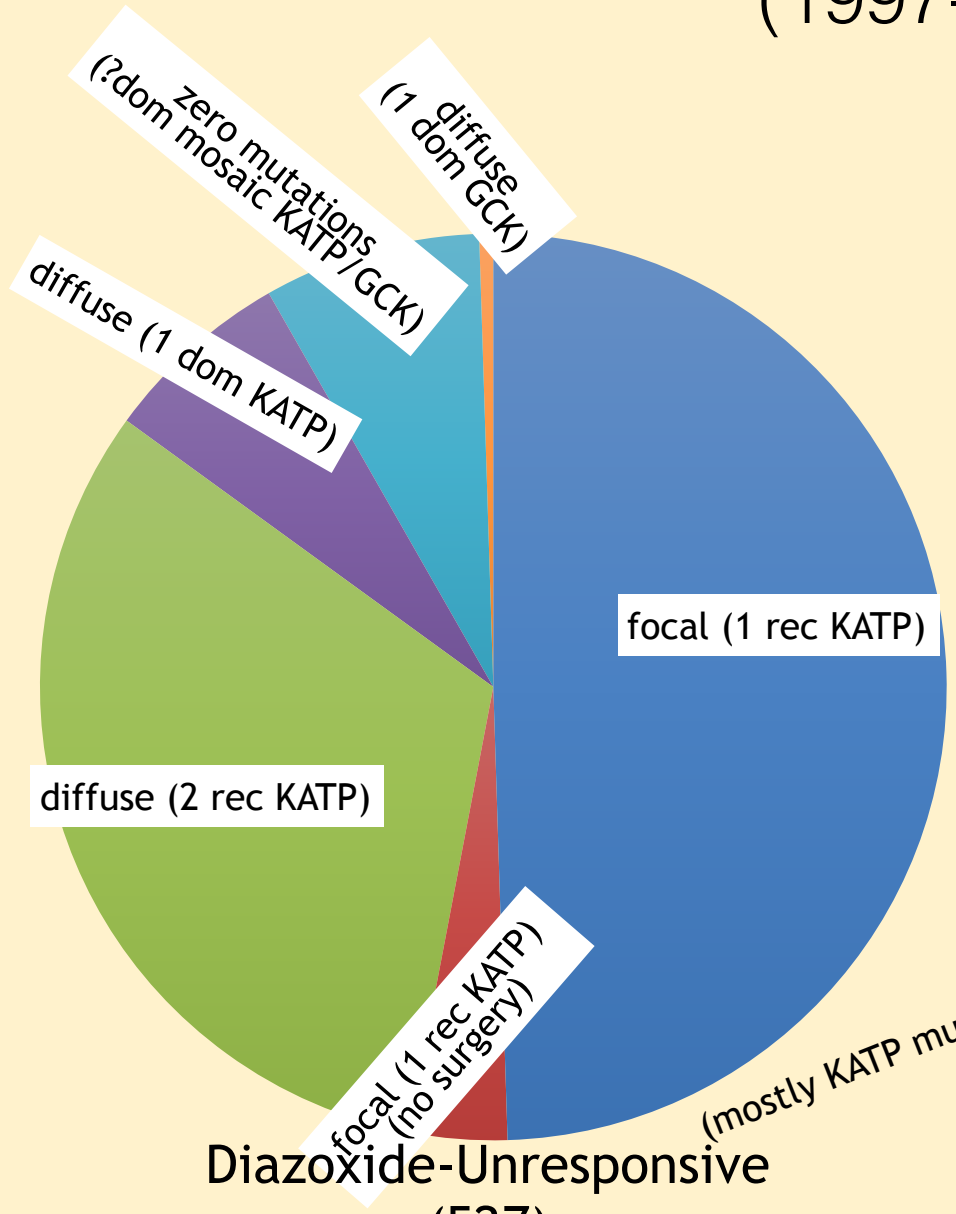


Clinical Features of Congenital Hyperinsulinism

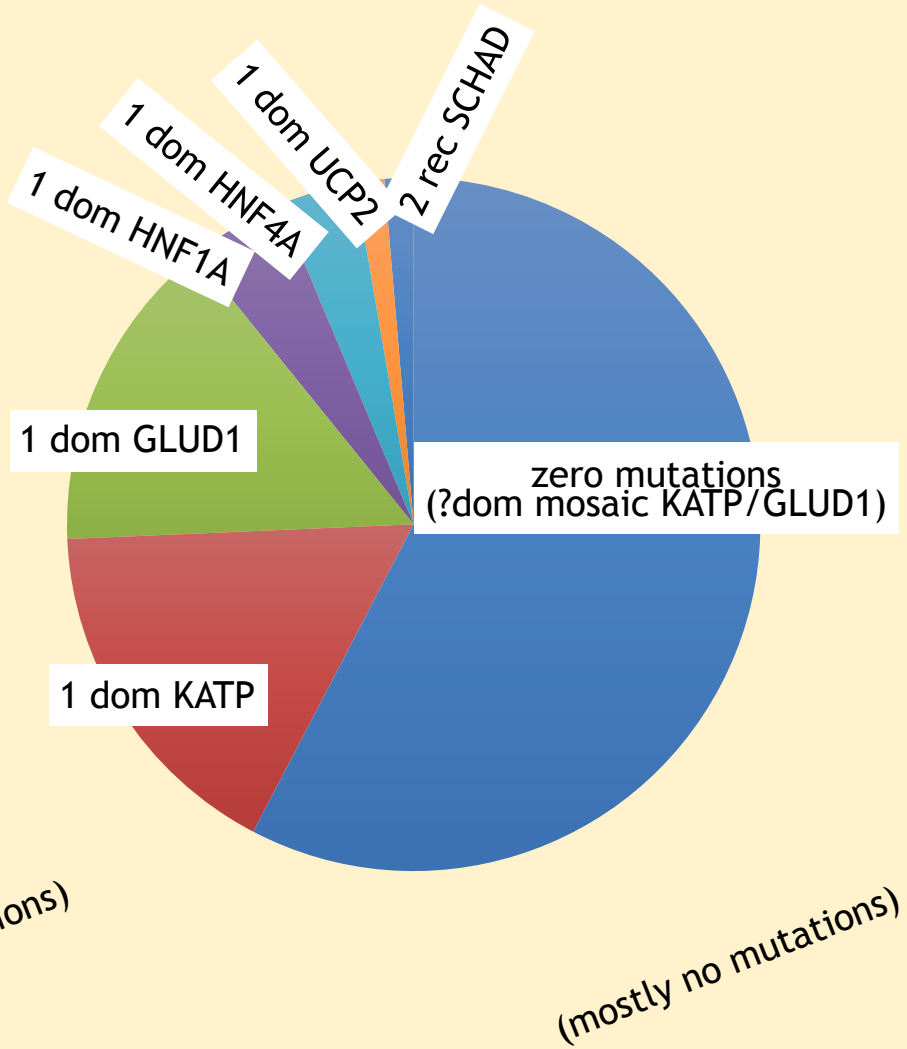
gene	genetics	Sensitivity to stimuli / inhibitors				
		diazoxide	protein	leucine	calcium	exercise
KATP (ABCC8 = SUR1) (KCNJ11 = Kir6.2)	rec	-	+	-	+	-
KATP (ABCC8 = SUR1) (KCNJ11 = Kir6.2)	dom	+/-	+	-	+	-
GDH (HI-HA)	dom	+	+	+	-	-
GCK	dom	-	-	-	-	-
SCHAD	rec	+	+	+	-	-
MCT1	dom	?	-	-	-	+
HNF4a & HNF1a	dom	+	+?	+?	+?	-
UCP2	dom	+	-	-	-	-
HK1	dom	+	-	-	-	-

KEY: Most common Less Common Rare

Mutations in 882 Children with Congenital HI (1997-2018)



Diazoxide-Unresponsive (527)



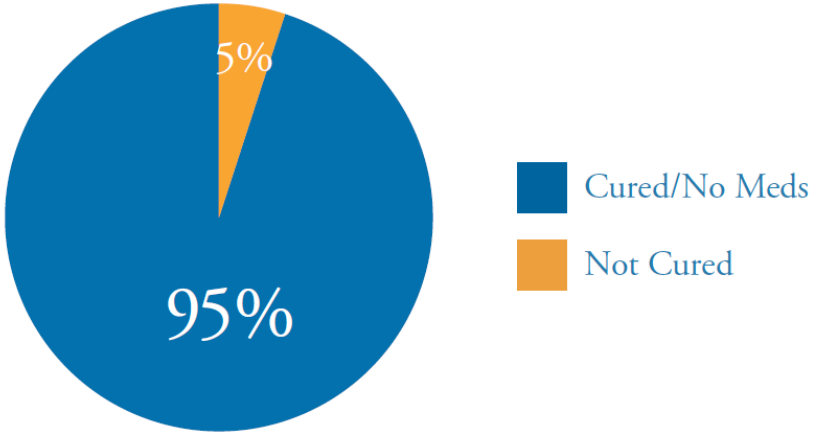
Diazoxide-Responsive (355)

Why are there “Missing Mutations”?

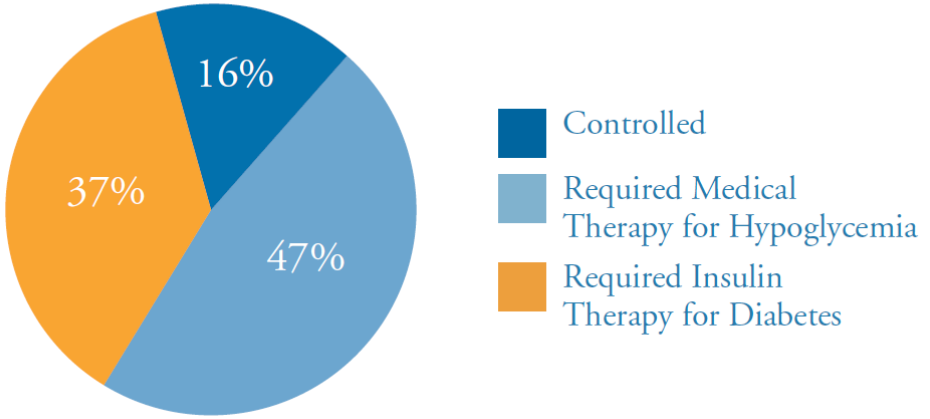
- In some HI patients, standard genetic testing cannot find any disease-causing mutation.
- Especially true for diazoxide-responsive patients (over 50%)
- Possible reasons:
  1. Novel Gene: i.e., a new HI gene that hasn’t been discovered yet
  2. De Novo Embryonic Mutation: i.e., an embryonic dominant HI gene mutation in pancreatic islets, not inherited from a parent and not present in patient’s blood cells (also called a “somatic“ mutation)
  3. Syndromic HI: e.g., a genetic disorder affecting tissues in addition to islets that are not included in HI gene testing (Beckwith Syndome, Turner Syndrome, Kabuki Syndrome, etc.)

Surgical Outcomes of CHOP Focal vs Diffuse HI (since 2008 with Genetic Testing & F-DOPA PET)

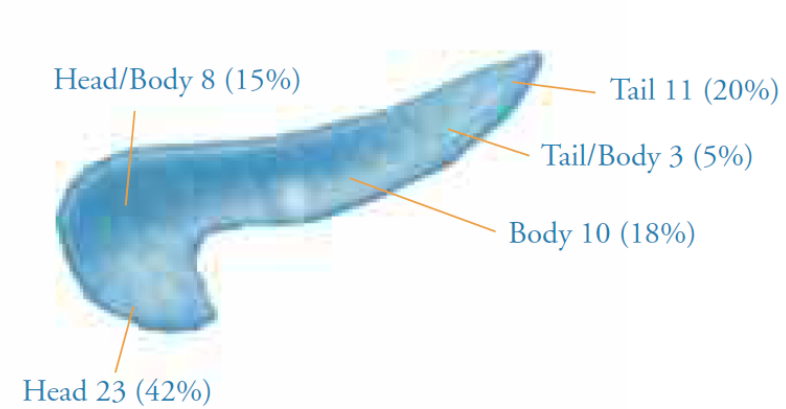
Outcomes of Focal Patients (55 cases)



Outcomes of Diffuse Patients (43 cases)



Location of Focal Lesions



HI and Genes (summary)

- 9 different genes are associated with HI
- Genetic testing is important for predicting:
  - best type of management (diazoxide responsiveness, potential for surgically-curable focal lesion)
  - risk of recurrence (family members & future offspring)
- Genetic test results need to be available within less than one week and should include simultaneous testing of parents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Pan Chen
Kara Boodhansingh
Arupa Ganguly
Diva DeLeon
Mark Yudkoff
Itzak Nissim
Michael Bennett
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Thank You
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