HYPERINSULINISM RESEARCH

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

500 SURGERIES.

20 YEARS OF BREAKTHROUGHS.

Join us to

CELEBRATE OUR CONGENITAL HYPERINSULINISM CENTER

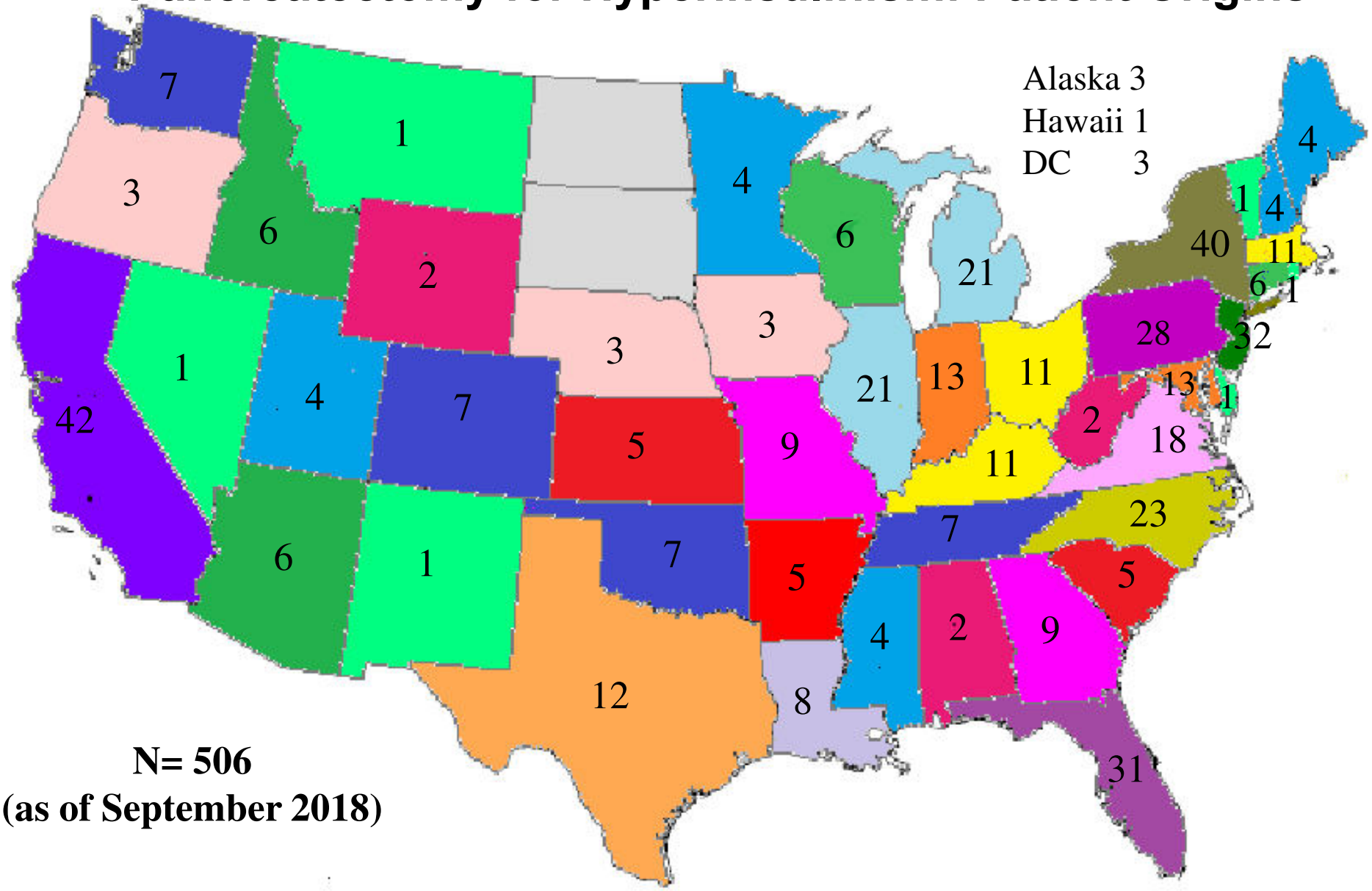
You'll hear from clinicians and patient families about what the center means to them — and about the breakthroughs that are on the horizon.

THURSDAY,
SEPT. 13, 2018
11 A.M.

ATRIUM, MAIN BUILDING
CHILDREN'S HOSPITAL OF PHILADELPHIA

Children's Hospital of Philadelphia®
Congenital Hyperinsulinism Center

Pancreatectomy for Hyperinsulinism: Patient Origins



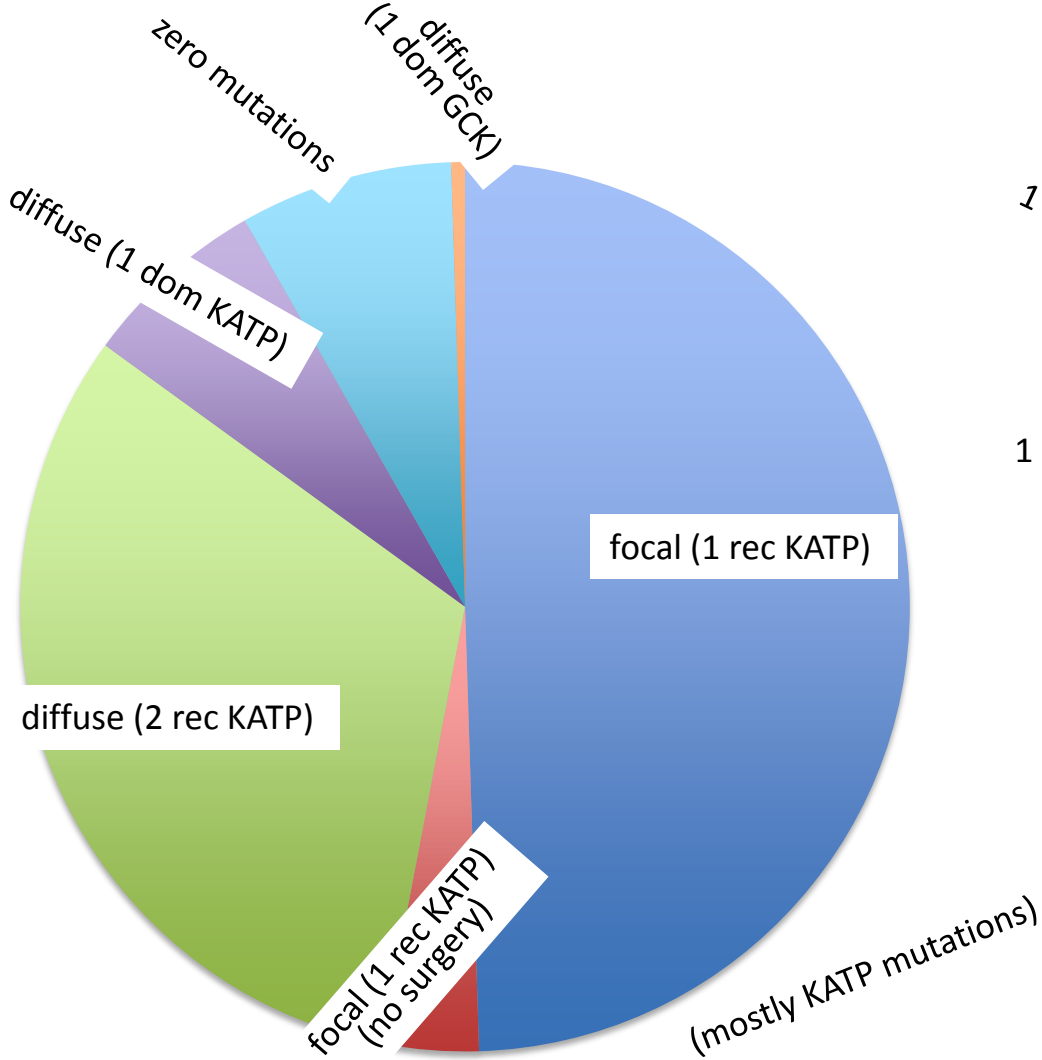
N= 506
(as of September 2018)

Argentina 1 Australia 1 Brazil 1 Canada 19 Colombia 1 Curacao 1 Ecuador 2 Iceland 1 Iran 1 Israel 2 Japan 1
Kuwait 1 Panama 1 Paraguay 1 Saudi Arabia 1 Singapore 1 UAE 1 Venezuela 1

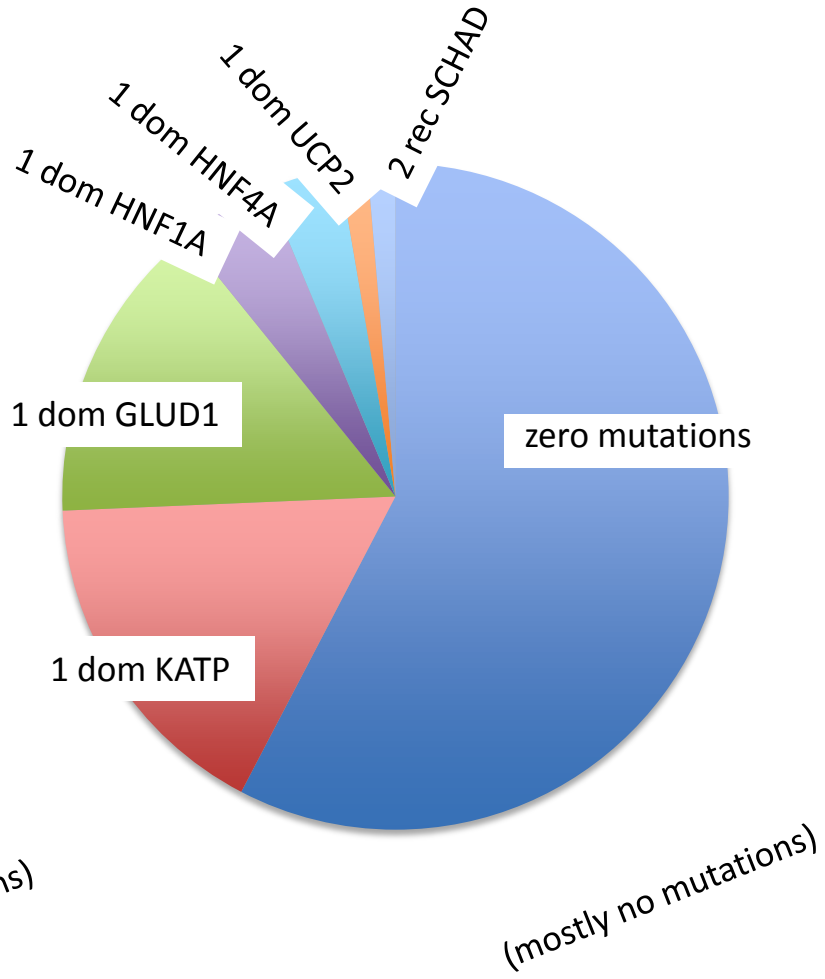
Translational research program

- Novel molecular mechanisms of disease
- Mechanistic studies in pancreatic islets
- New modalities of treatment/management of hypoglycemia and hyperglycemia in patients with hyperinsulinism

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



Diazoxide-Unresponsive
(527)



Diazoxide-Responsive
(355)

CHOP HI Research.
Using Genetic Testing to Improve Patient Care

- Example: Results of CHOP HI Center genetic series show that we can predict which infants have focal HI: a single paternal recessive KATP mutation predicts focal HI (>95% accuracy)

- BUT….Important obstacles for using genetic results:
  - Obstacle #1: Because 70% of KATP mutations are novel, we can't predict whether a new variant is disease-causing vs. benign; dominant vs. recessive; diazoxide-responsive vs. unresponsive.
  - Obstacle #2: 3 distinct types of KATP mutations:
    1) HI bi-allelic recessive mutations cause diazoxide-unresponsive diffuse HI
    2) mono-allelic paternal recessive mutations cause diazoxide-unresponsive focal HI
    3) mono-allelic dominant mutations cause diazoxide-responsive or unresponsive diffuse HI
  - Obstacle #3. Many children with HI (especially diazoxide-responsive cases) do not have a detectable mutation

CHOP HI Research.
(1) Using Genetic Testing to Improve Patient Care

Studies in progress to characterize novel KATP mutations by two methods:

1. In-vitro: studies with Dr. Show-ling Shyng (Portland, OR) to examine the function of novel missense KATP mutations by expression in COS cells (Golgi processing, Rb efflux, electrophysiology):

   Recessive = non-trafficking. Dominant = trafficking, but low activity]

2. In-vivo: studies by Dr. Stanley & Dr. De Leon to test whether mutation carriers (parents) are normal (recessive mutation) or abnormal (dominant mutation) using 24-hour fasting studies and provocative tests (oral protein, oral glucose)

- Preliminary observations suggest that oral protein challenge test of the carrier parent may be an easy, rapid way to determine whether a novel missense variant in ABCC8 or KCNJ11 is a dominant disease-causing mutation (e.g., predict whether a single paternal missense mutation means diffuse or focal HI)

CHOP HI Research.

(2) The problem of "missing" mutations in diazoxide-unresponsive "atypical HI" (LINE HI) (Boodhansingh, Li, Ganguly, Bhati, Stanley, DeLeon)

- Hypothesis: *the 9% of diazoxide-unresponsive children with NO mutation may have embryonic ("mosaic") mutations*

- Testing 12 cases with LINE HI ("atypical HI")
  - Functional studies of isolated islets from atypical vs normal regions
  - Use of both conventional Sanger and Next-gen Sequencing of isolated islets or whole pancreas cDNA and genomic DNA to identify "missed" dominant mutations in GCK or ABCC8
  - Verify detection of mosaic mutations in peripheral blood DNA

- Preliminary observations:
  - In most LINE HI cases we can detect very low-level mosaicism (4-8%) for dominant mutations of either ABCC8 or GCK in isolated islets and/or pancreas, but the mutations cannot be detected in peripheral blood)
  - Implication: children with "missing" mutations very likely have embryonic, mosaic mutations in a known dominant HI gene, rather than in an undiscovered HI gene:
    - GCK & ABCC8 for diazoxide-unresponsive HI
      - (2 GCK mutations detected in peripheral blood)
    - ABCC8, KCNJ11, GLUD1 for diazoxide-responsive HI
      - (2 GLUD1 mutations detected in peripheral blood)

CHOP HI Research.
(3) The problem of "missing" mutations in diazoxide-responsive HI (Boodhansingh, Ganguly, Stanley, DeLeon)

- Hypothesis #2: *although many of the 60% of diazoxide-responsive children with NO mutation probably have mutations in known dominant genes, some might have mutations in <u>novel</u> genes*

- Testing of 7 families cases with dominant HI (one or two affected children plus one affected parent)
  - Phenotype testing of affecteds (fasting, oral glucose, oral protein)
  - Whole exome/genome sequencing of trio (patient and both parents)
  - Analyzing sequences for novel rare variants in potential candidate genes (~200-400 / case)

- Preliminary findings:
  - We have identified 3 candidate novel genes in two families
  - Work is in progress to validate the findings and to design functional expression assays to verify the mutations

CHOP HI Research.

(4) Mechanism(s) of HI in Syndromic Forms of HI: Beckwith-Wiedemann Syndrome and Turner Syndrome (Boodhansingh, Ganguly, Stanley, DeLeon, Kalish)

Monogenic HI

- Most common:
  - KATP Channel Defects
  - GLUD1
  - GCK
- Rarer genes:
  - SCHAD
  - UCP2
  - MCT1
  - HK1
  - HNF4A
  - HNF1A
  - CACNA1D
  - PGM1
  - KCNQ1
  - KMT2D
  - KDM6A

Syndromic HI

- Beckwith-Wiedemann
- Kabuki (KS1, KS2)
- Turner
- Sotos
- Congenital Disorders of Glycosylation (CDG)
- Perlman
- Simpson-Golabi-Behmel
- Costellos
- Timothy

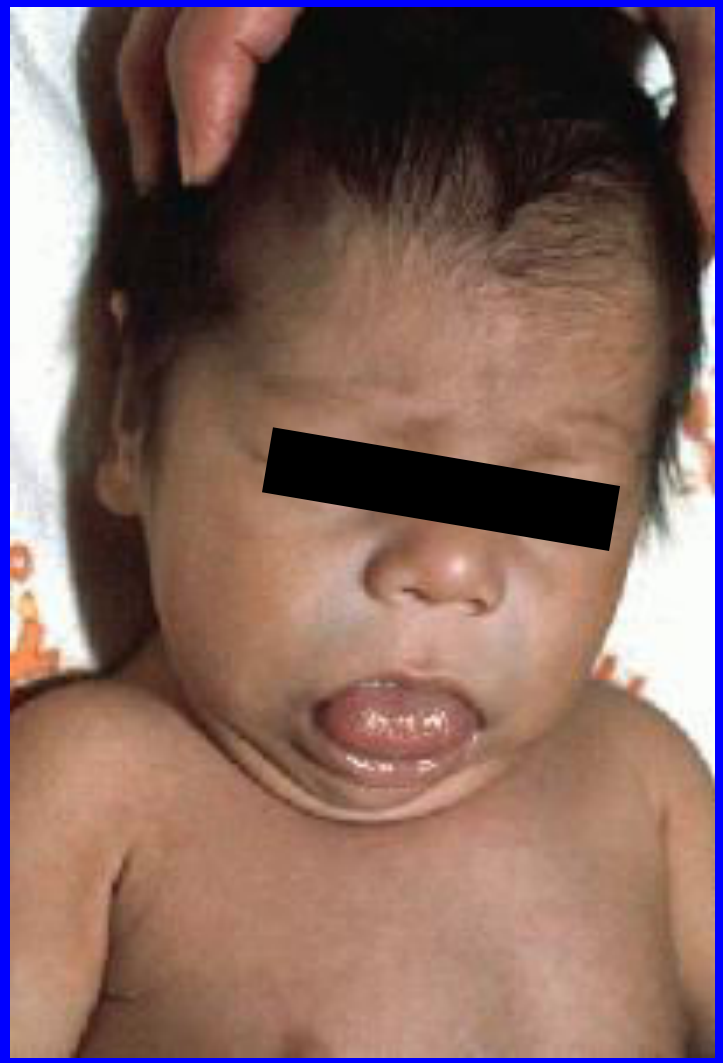
Neonatal Hypoglycemia

- Transitional Hypoglycemia (HI)
- Perinatal-Stress HI

Hyperinsulinism in Beckwith-Wiedemann Syndrome

- **Features: macrosomia, macroglossia, hemihypertrophy, omphalocele, ear pits**
- **Locus: BWS imprinted locus on 11p (distal to KATP)**
- **Hyperinsulinism in 50% of BWS, usually transient, often responsive to diazoxide and resolves within first few months**
- **However ~5 % have persistent HI that does not respond to diazoxide**

Question: what is the molecular basis for severe HI in BWS?



Congenital hyperinsulinism in children with paternal 11p uniparental isodisomy and Beckwith–Wiedemann syndrome

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Kalish JM, et al. J Med Genet 2015

CHOP HI Research.

(3) Mechanism(s) of HI in Syndromic Forms of HI: Beckwith-Wiedemann Syndrome and Turner Syndrome

(Boodhansingh, Ganguly, Stanley, DeLeon, Kalish)

Original Paper

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Congenital Hyperinsulinism in Infants with Turner Syndrome: Possible Association with Monosomy X and *KDM6A* Haploinsufficiency

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CHOP HYPERINSULINISM CENTER

THANK YOU

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Children's Hospital of Philadelphia℠
Congenital Hyperinsulinism Center

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Our patients and their families

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Questions

"I'm the Blood Sugar Fairy.
If you can see me, yours is too low."