GENETICS OF HI

Congenital Hyperinsulinism Family Conference
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OUTLINE OF TALK

- Basics of Genetics
- Genetics of Hyperinsulinism
- Syndromic Causes of Hyperinsulinism
- Considerations in Treatment and Family Planning

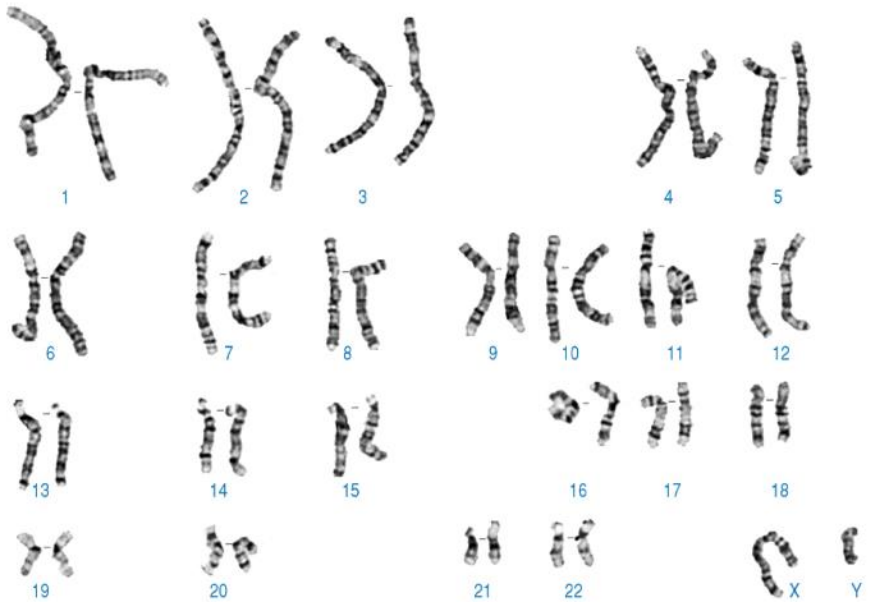
GENES

- Provide instructions for our body's growth, development and functioning
  - Examples: traits for eye and hair color; genes for building pancreas
- Genes are like long sentences made up of a 4 letter code: A, T, G, C
- Most genes come in pairs, one each from biological mother and father

ATTGCCGGCGATATTACGGCGGCGGCG

GENES

- ~20,000 genes
  - We only know what 6000-8000 of them do
- 23 pairs of chromosomes that house our genes



https://biologydictionary.net/dna-structure/

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IT ALL MEANS THE SAME THING

Variant
Mutation
Misspelling
Genetic change

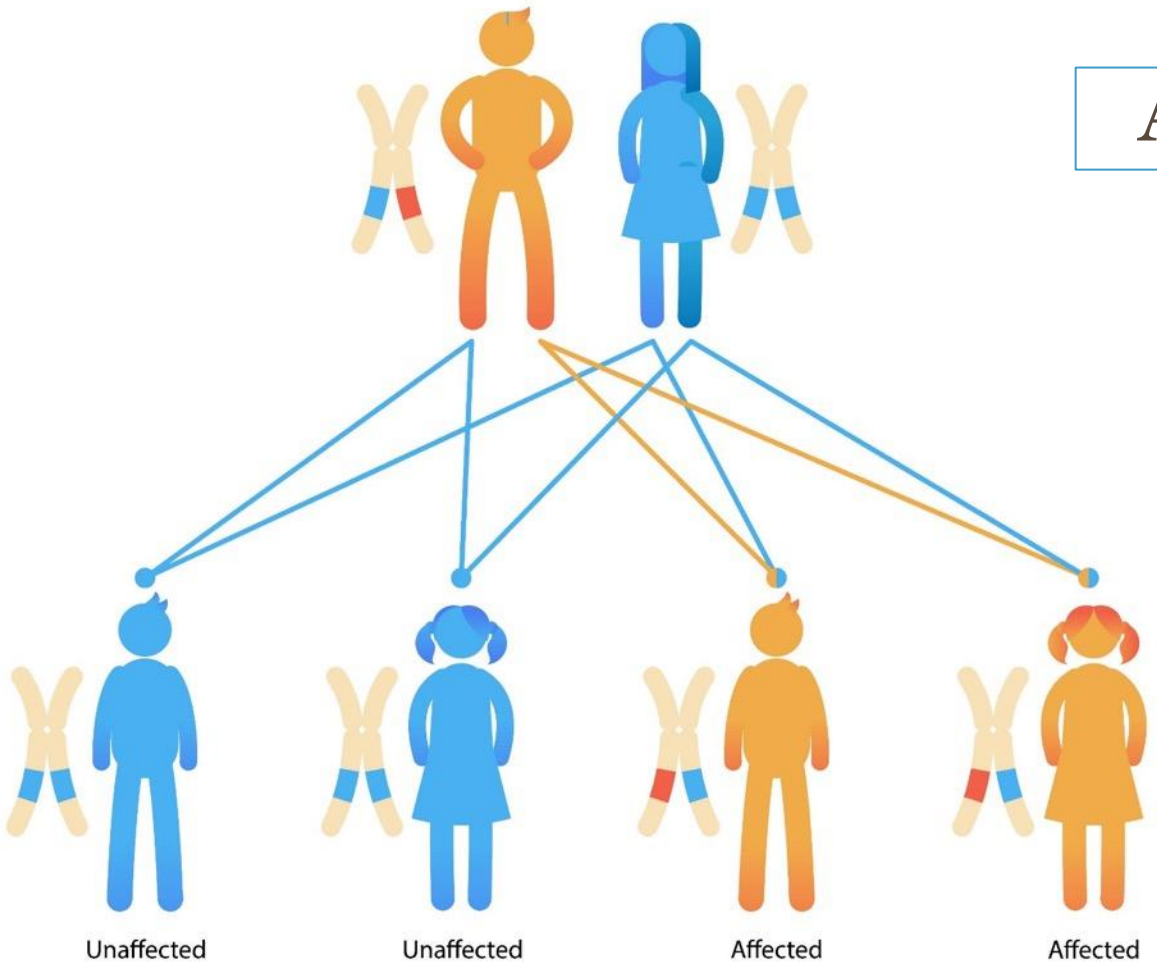
→ Can be further clarified, such as

"pathogenic" or "likely pathogenic" or "disease-causing"

"…of uncertain clinical significance"

"benign"

TYPES OF INHERITANCE



Autosomal Dominant

Parents:
50% recurrence risk

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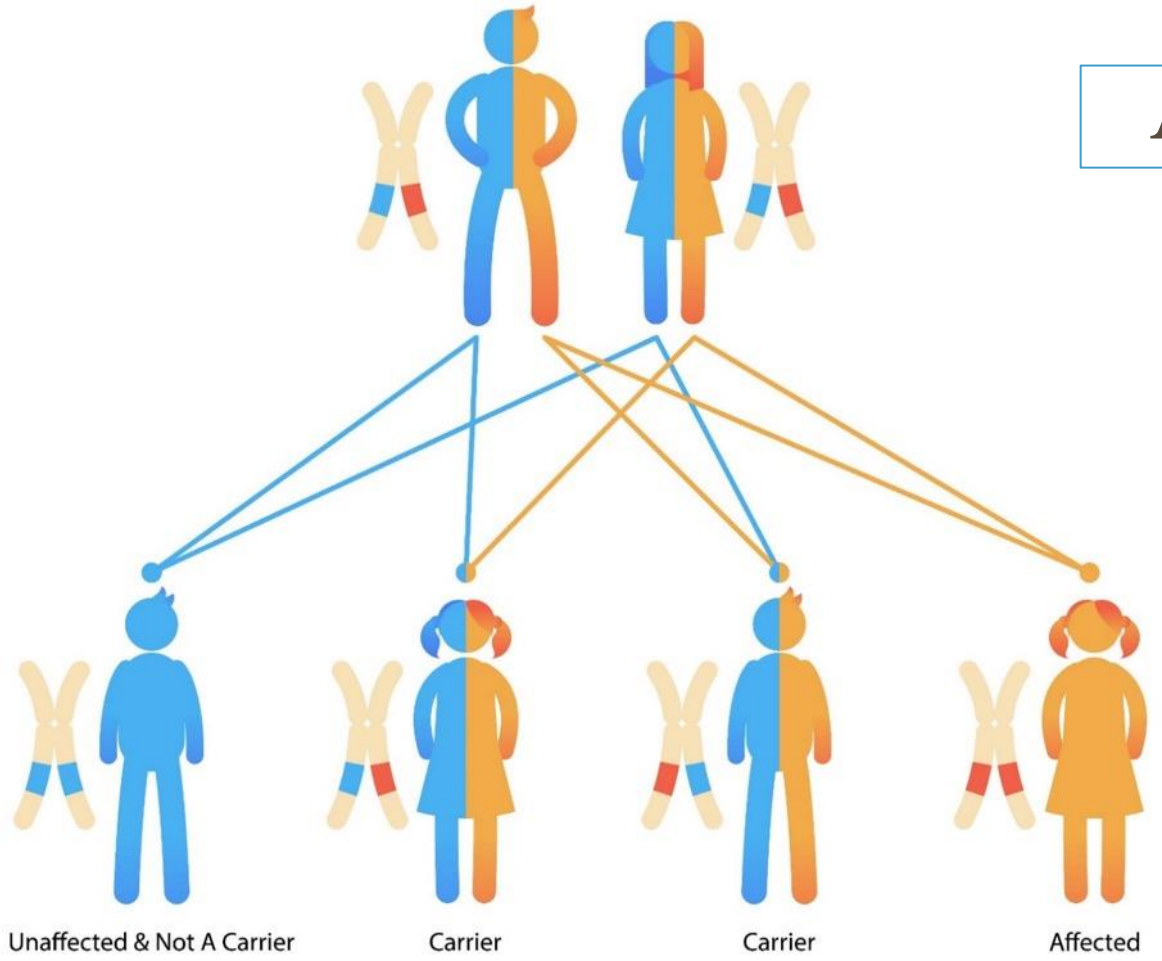
TYPES OF INHERITANCE



Autosomal Recessive

Parents:
25% recurrence risk

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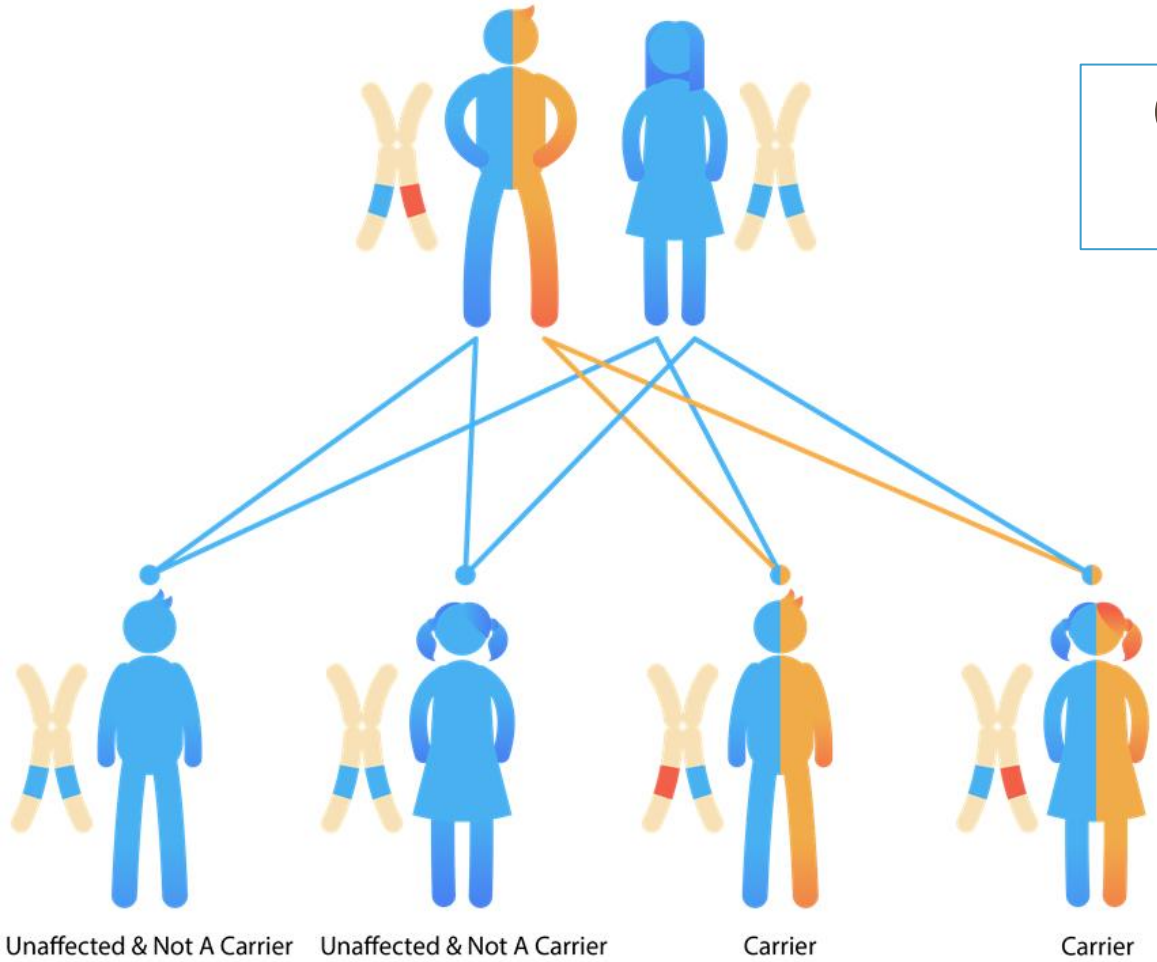
TYPES OF INHERITANCE



Carrier of Autosomal Recessive Disease

Parents:
50% chance for unaffected carriers

For ABCC8 and KCNJ11 genes:
Slight risk of focal HI when father is the carrier
(<0.5% for a child who inherits gene change)

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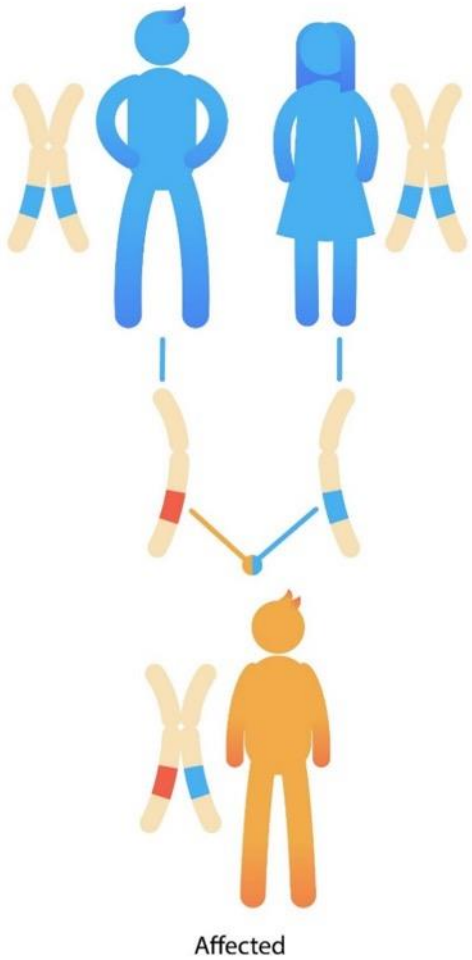
TYPES OF INHERITANCE



De Novo Variants

Parents:
<1% recurrence risk

Affected child:
50% recurrence risk

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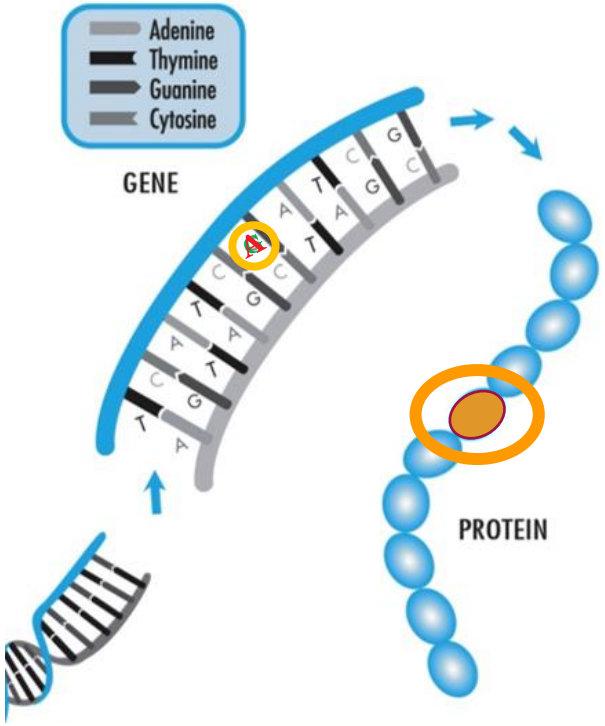
Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
ABCC8, NM_000352.4	AD, AR, 600509	c.88G>A, p.Ala30Thr, Heterozygous	Not listed in ClinVar	0.011% African	Conflicting	UNCERTAIN
ABCC8, NM_000352.4	AD, AR, 600509	c.3572T>C, p.Leu1191Pro, Heterozygous	Not listed in ClinVar	Not Present	Damaging	UNCERTAIN

c.88G>A,
p.Ala30Thr



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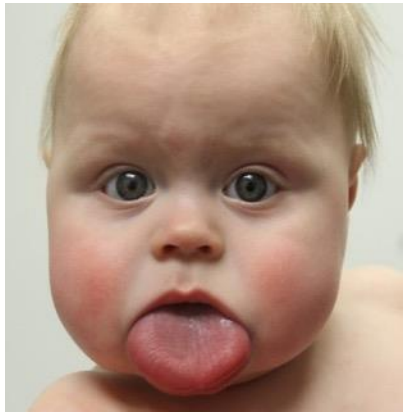
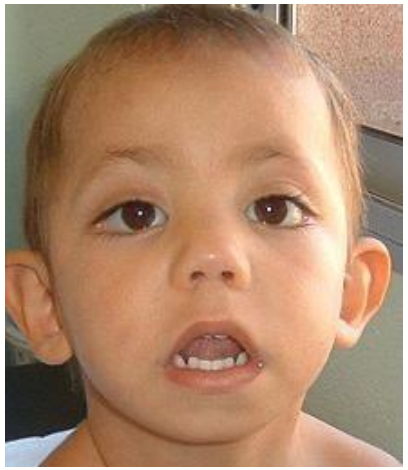
GENETICS OF HYPERINSULINISM - GENES

ABCC8
AKT2
CACNA1C
CACNA1D
CREBBP
EIF2S3
EP300
FOXA2
GCK
GLUD1
GPC3
HADH
HK1
HNF1A
HNF4A
INSR
KCNJ11
KCNQ1
KDM6A
KMT2D
MAFA
MPI
NSD1
PGM1
PHOX2B
PMM2
SLC16A1
SLC25A36
TRMT10A
UCP2

SOME GENES CAUSE HI AS PART OF A GENETIC SYNDROME

- Genetic diagnosis can provide insight into the clinical course
- Clinical features besides HI can give clues towards the diagnosis
- Additional clinical care may need to be included in the care plan





- More common
  - Beckwith-Wiedemann syndrome
  - Kabuki syndrome
  - Sotos syndrome
  - Turner syndrome
- Less common
  - Rubinstein-Taybi syndrome
  - Congenital disorders of glycosylation
  - Simpson-Golabi-Behmel syndrome
  - Costello syndrome

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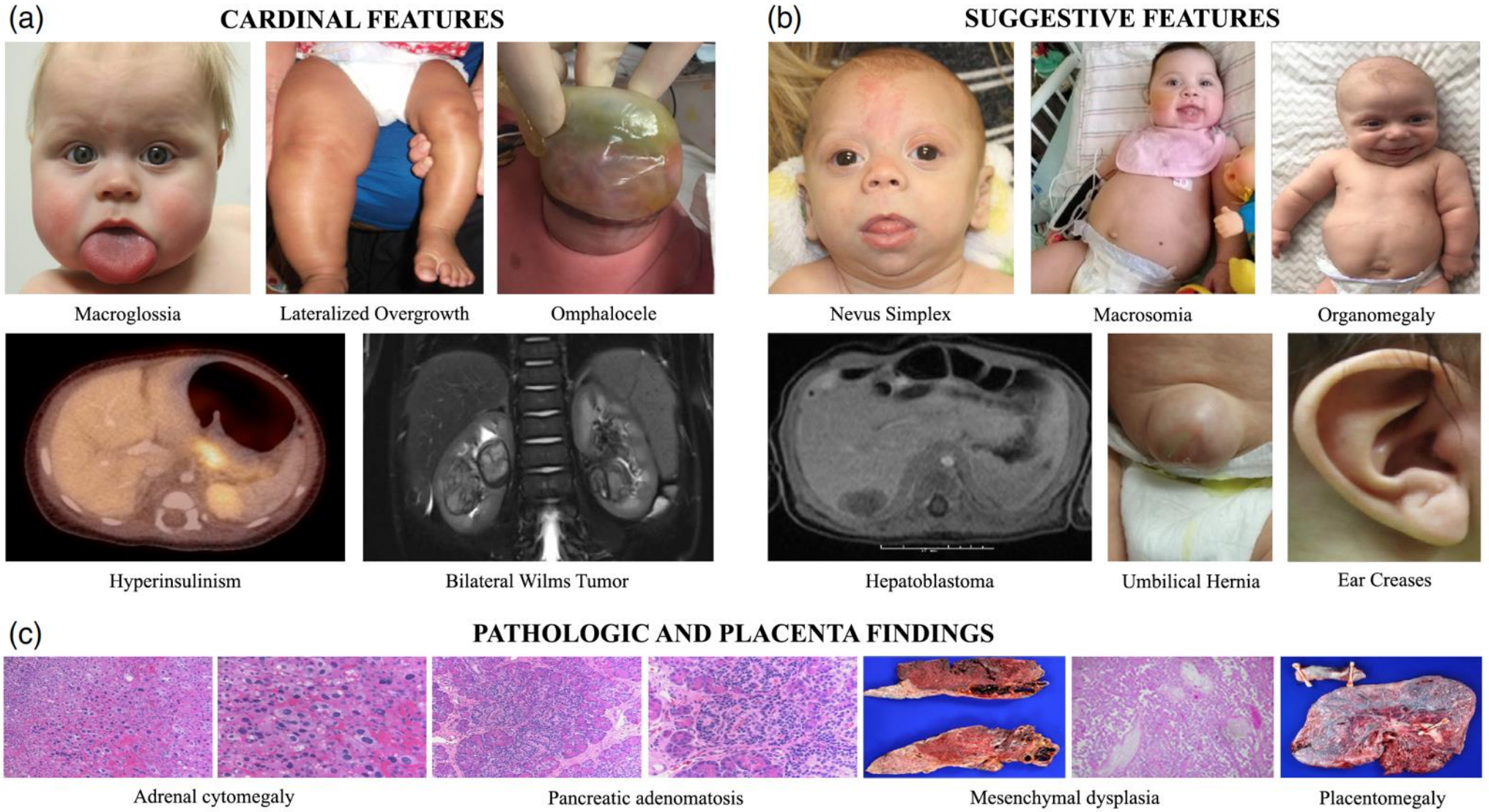
Duffy et al *AJMGC* 2019 Arnoux, Kalish, et al. 2019 Grand et al., 2019 https://www.turnersyndrome.org/medical-information

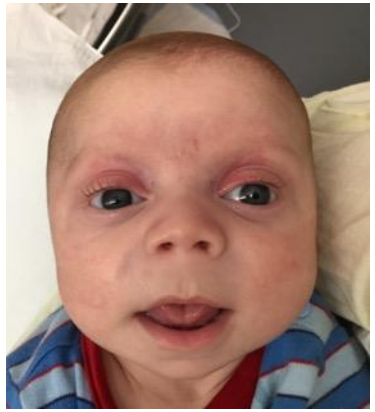
BECKWITH-WIEDEMANN SYNDROME

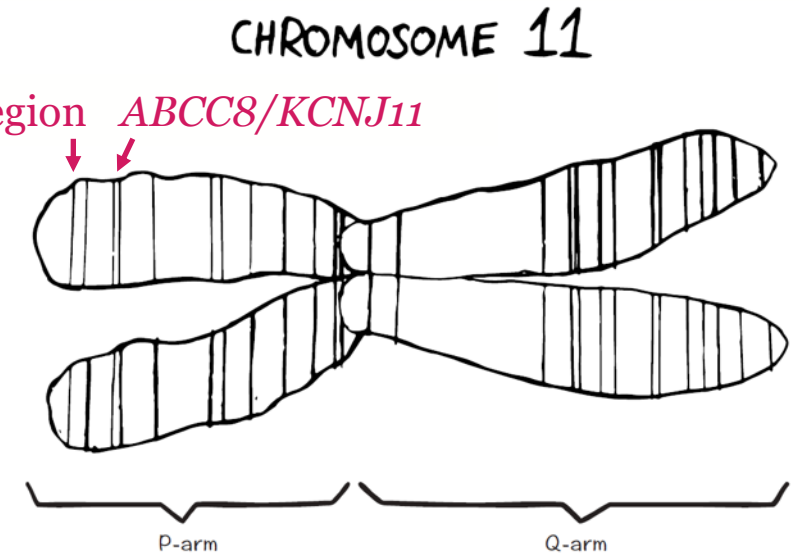


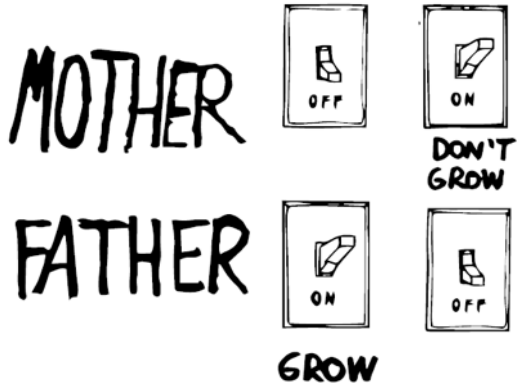
Duffy et al *AJMGC* 2019

BWS AND HI

- Depends on (epi)genetic cause
- Evaluate *ABCC8/KCNJ11* genes
- Diazoxide responsive/unresponsive
- Role of PET-CT
- Subtotal pancreatectomy







https://www.chop.edu/conditions-diseases/beckwith-wiedemann-syndrome/health-resources

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KABUKI SYNDROME OVERVIEW

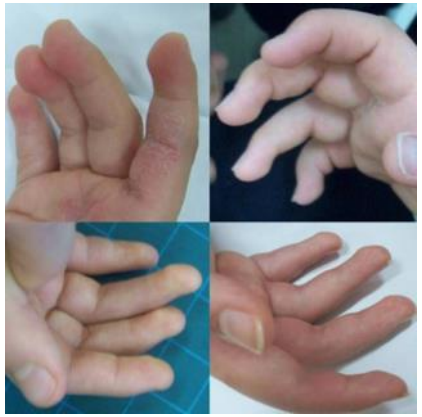
KDM6A, KMT2D

Clinical features

- Long palpebral fissures
- Arched eyebrows
- Prominent eyelashes
- Prominent ears
- Depressed nasal tip
- Dental agenesis
- Developmental delay
- Post natal short stature
- Hyperinsulinism

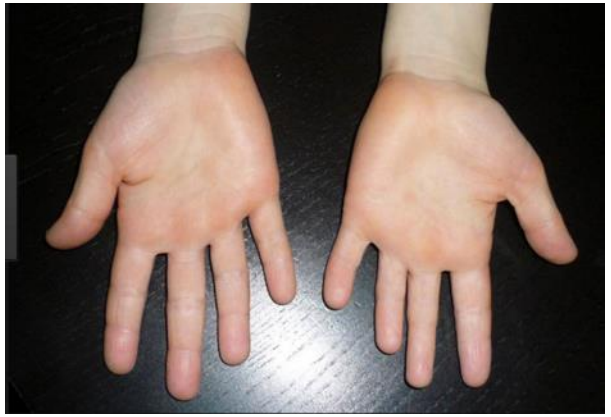
Skeletal features

Fetal finger pads



Clinodactyly

Brachydactyly



Pictures courtesy of Kabuki syndrome network

Arnoux, Kalish, et al., 2019

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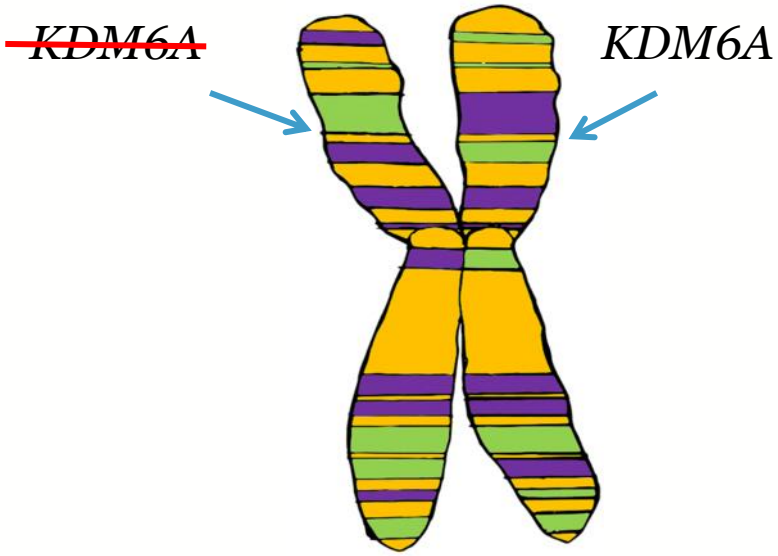
KABUKI SYNDROME AND HI

- HI present from birth
- Usually diazoxide-responsive
- ~6-8% of Kabuki patients reported to have neonatal hypoglycemia
- Managed with diazoxide or with continuous feeds



Meissner et al., 2001

SOTOS SYNDROME OVERVIEW

Overgrowth syndrome characterized by distinctive facial features (frontal bossing), intellectual disability, and prenatal and postnatal overgrowth

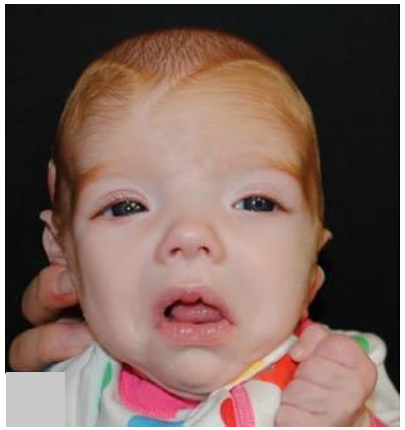
- Features include….
  - Broad and prominent forehead
  - Sparse frontotemporal hair
  - Prominent jaw
  - Malar flushing
  - Down-slanting palpebral fissures
  - Early developmental delay
  - Mild to severe intellectual impairment
  - Prenatal and postnatal overgrowth with height and/or head circumference ≥ 2 standard deviations above mean

- Cardiac defects
- Advanced bone age
- Maternal preeclampsia
- Renal anomalies
- Scoliosis
- Seizures
- Neonatal hypotonia
- Neonatal jaundice
- Joint hyperlaxity

Grand et al., 2019

SOTOS SYNDROME AND HI

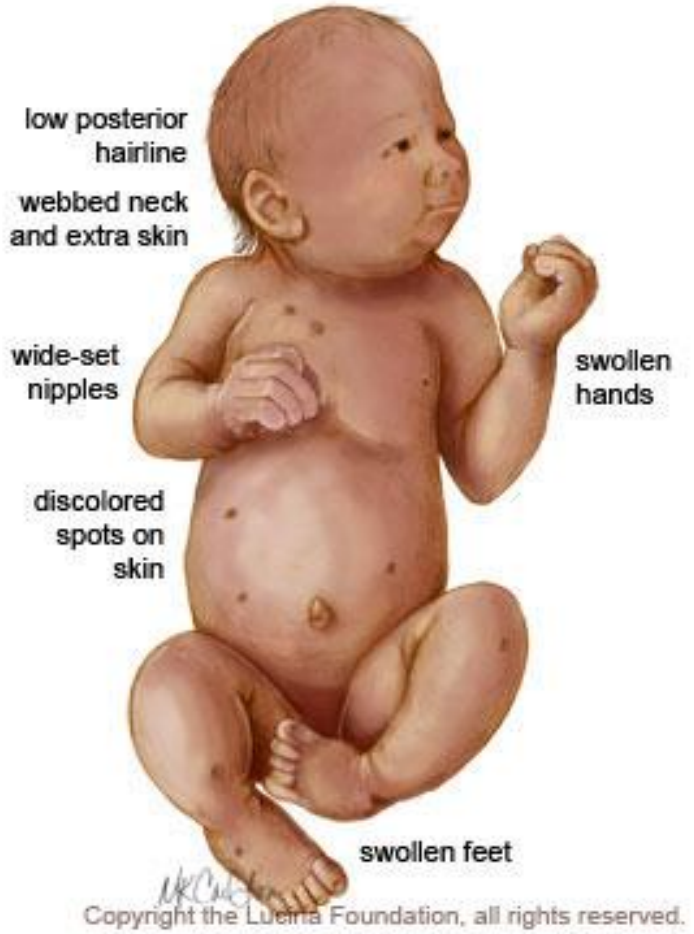
- Typically diazoxide-responsive
- Babies with both HI and Sotos syndrome may not be large at birth
- Mostly transient HI, though several patients with HI until 4 years of age
- Due to mutations in *NSD1*



Grand et al., 2019

TURNER SYNDROME OVERVIEW

- Incidence: ~1:2,500 female live births
- Results from a complete or partial loss of the X chromosome
  - Congenital anomalies
  - Lymphedema
  - Cystic hygroma
  - Short stature
  - Cardiac and renal defects
  - Small for gestational age
  - Down-slanted palpebral fissures
  - Epicanthal folds
  - Low-set anomalous pinnae
  - Micrognathia
  - Narrow palate
  - Endocrine differences
  - Short stature
  - Hypothyroidism
  - Diabetes mellitus
  - Ovarian failure
  - Hyperinsulinism



Gibson et al., 2016
Arnoux, Kalish, et al., 2019

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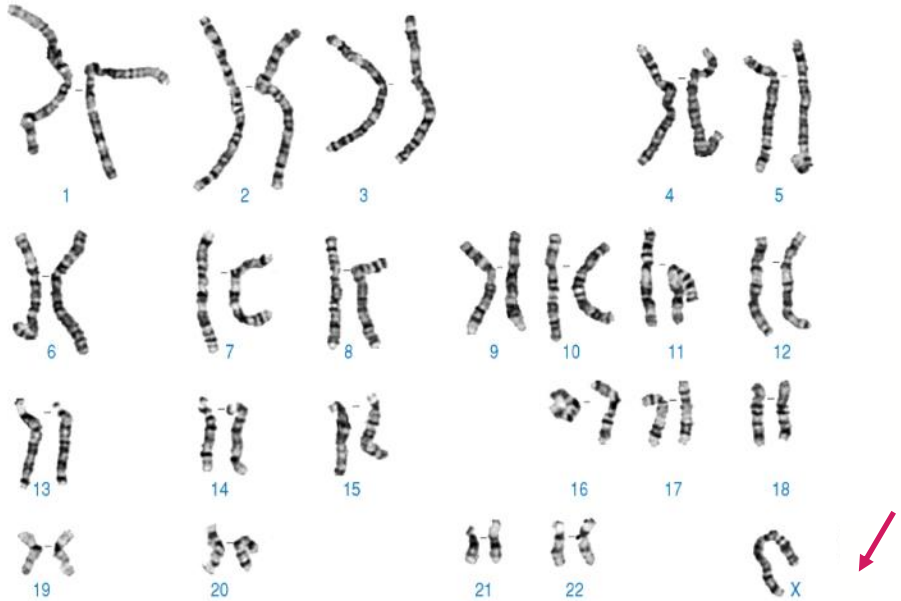
TURNER SYNDROME AND HI

The frequency of congenital hyperinsulinism is increased 35-fold in Turner syndrome girls

- Birth weights tend to be >95th%
- HI presents at birth or in some cases between 3-6 months
- Spectrum of clinical features
- Spectrum of HI management
  - Diazoxide
  - Pancreatectomies



Missing an "X"

Gibson et al., 2016

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CONSIDERATIONS IN TREATMENT

Genetic testing helps with the initial decision tree:

Diazoxide unresponsive

Genetic testing predicts:

Focal HI → PET scan +/-surgery → Possible cure!!

Ex: single ABCC8 gene change from father*

Ex: 2 ABCC8 gene changes, one from each parent

Diffuse HI → NO PET, consider other treatments *(dextrose, medicine, surgery)* → Continued management, may improve with age

CONSIDERATIONS IN TREATMENT

Genetic testing and clinical genetics evaluation for syndromes guides long-term treatment. Examples:

Dietary considerations

Effect of protein on hypoglycemia

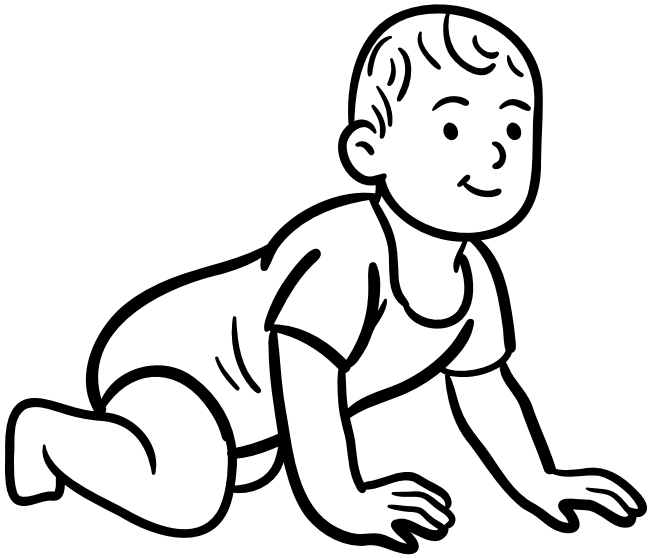
Evaluation of other body systems

Risk for early-onset diabetes

Exercise's impact on hypoglycemia

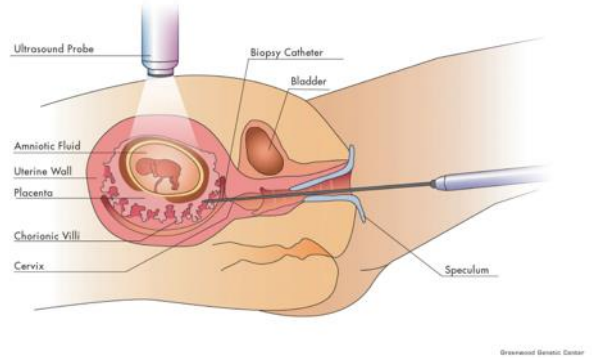
CONSIDERATIONS IN FAMILY PLANNING

Multiple reproductive options available when genetic cause of HI is identified

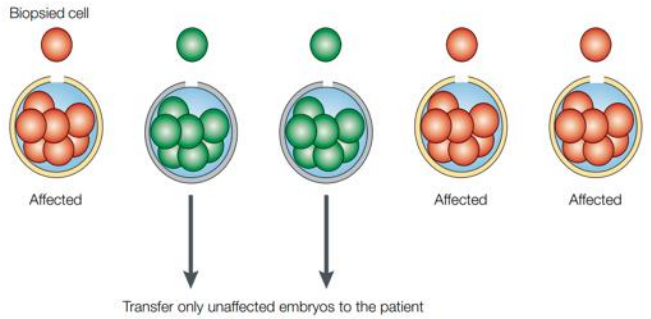


CONSIDERATIONS IN FAMILY PLANNING

- Test newborn at birth and do nothing before or during pregnancy
  - Glucose monitoring/fast before discharge, genetic testing
- Test fetus during pregnancy
  - CVS (~10-11 weeks), amniocentesis (~15 weeks)
  - This just provides information



- Preimplantation genetic testing with *in vitro* fertilization
- Use of egg or sperm donor
- Adoption



- Pros and cons to each option

Braude et al 2002, PMID: 12459724

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CONSIDERATIONS IN FAMILY PLANNING

Interested in learning more?

- Find a local prenatal genetic counselor
  - Assist in carrier testing as needed
  - Review prenatal testing options
- Go to National Society of Genetic Counselors' website:

  www.NSGC.org → "Find a Genetic Counselor"
- Make an appointment in the Congenital Hyperinsulinism Center at CHOP to discuss your genetic testing results
- Evaluation by a clinical geneticist for possible syndromic causes of HI if the cause is not known

CONSIDERATIONS IN FAMILY PLANNING

- What if the genetic cause of HI is **unknown**?
  - No prenatal or embryo testing options available
  - Glucose levels should be monitored during first 48 hours of life
  - Diagnostic fast should be performed prior to discharge, after 48 hours

To Whom It May Concern:

This family has a history of Congenital hyperinsulinism, a hypoglycemia disorder that results from dysregulated insulin secretion. Consequences of hypoglycemia are serious which include seizures and brain damage. Therefore, hypoglycemia must be prevented by early detection and appropriate treatment. Due to the family history, **it is very important to screen the new baby for hypoglycemia and to rule out congenital hyperinsulinism**. Below are the recommendations that are based on the published guidelines from the Pediatric Endocrine Society:

1. During the first 48 hours of life, please monitor blood glucose levels within 1 – 2 hours of birth and before each feed to ensure blood glucose levels remain > 60 mg/dL.
   a. If the blood glucose level is less than 60 mg/dL and the baby is asymptomatic, please give a feeding and repeat the blood glucose. If the hypoglycemia persist or the baby is symptomatic
      - Give 2 cc/kg of D10 IV push.
      - If still hypoglycemic administer continuous IV dextrose at whatever rate is needed to keep the blood glucose greater than 70 mg/dl.

2. If the specific mutation responsible for the hyperinsulinism in the family is known, the recommendation is to obtain a DNA sample for testing for this specific mutation on the baby and to perform a safety fast for 6 – 8 hours with hourly blood glucose monitoring prior to discharge and after 48 hrs of life to determine if the baby is safe to go home while awaiting for the results of the genetic testing. Please confirm final glucose value in the lab. During the fast, the baby may be bottle fed with 1/4 NSS (no sugar containing product).

3. For families in whom the specific mutation is not known, a diagnostic fast to rule out congenital hyperinsulinism should be performed prior to discharge and after 48 hrs of life. A diagnostic fast should also be performed in any baby that has persistent hypoglycemia.

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CONSIDERATIONS IN FAMILY PLANNING

- What if the genetic cause of HI is **unknown**?
  - Depending on when the initial genetic testing was performed

  → consider retesting with newer hyperinsulinism gene panel
  - Evaluation by a clinical geneticist
  - Could consider enrolling in research

CONSIDERATIONS IN FAMILY PLANNING

- What about siblings, future grandchildren, aunts, uncles, etc?
  - When genetic cause of HI is **known** in family:
    - Specific family's member's risk dependent on gene/mechanism (recessive, dominant, epigenetic)
    - Family member can meet with local prenatal genetic counselor

CONSIDERATIONS IN FAMILY PLANNING

- What about siblings, future grandchildren, aunts, uncles, etc?
  - When genetic cause of HI is **unknown** in family:
    - No available genetic testing to offer family members
    - Consider testing in newborn period (glucose checks, fast before discharge) if baby high risk

HK1 GENE

- What about the **HK1** gene?
  - University of Pennsylvania is the only CLIA-certified laboratory currently offering testing of relevant region of HK1 gene
    - They only accept institutional billing, PA Medicaid, or check/credit card (some hospitals may not send to them)
    - https://genetics.med.upenn.edu/cores/genetic-diagnostic-laboratory/test-catalog/congenital-hyperinsulinism-chi/
  - Other labs that list HK1 are looking at a different part of the gene that can cause unrelated health problems, not HI

Questions?

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