CookChildren's

Cook Children's HI Center

Paul Thornton

Medical Director Cook Children's Hyperinsulinism Center

Cook Children's HI Center

- Formed in Oct 2010
  - Mission: To provide excellence in medical care to patients with HI in the Southern United States, using a family centered care model.
  - Located in Fort Worth Texas
  - Cook Children's Medical Center is a 400 bed not for profit stand alone children's hospital

CookChildren's℠

HI Team Physicians

- Pediatric endocrinologist
- Pancreatic surgeon
- Histopathologist
- Neonatologist
- Neurologist
- Gastroenterologist

CookChildren's

HI team support staff

- HI Nurse
- Social Worker
- Psychologist
- Nutritionists
- Speech and language therapists
- Feeding therapists
- Child life specialist
- Family advisory council and support group

CookChildren's

Clinical activities

- In patient service is located in our unique 100 private bed room NICU with special twin, triplet and quadruplet rooms
- Surgeries are performed in our main campus.
- Outpatient clinic is located in our new Endocrinology department but we also see patients in satellite clinics nearer home for the more routine interim visits.

CookChildren's

Scholarly activity

- Education of physicians
  - Talks in all the major children's hospital in Texas
  - Talks in Ca, NM, La, Mi, Fl, Ga
  - Talks to PESTOLA
- Book Chapters
- Presentations at the major and local meetings

CookChildren's

Research

- Several IRB approved protocols
  - HI Database
  - Neurological outcomes study
  - Genotype – Phenotype study
  - PET Study under review
  - PET IND application

CookChildren's

Advocacy

- Work with “HI Kids” to improve access to quality HI care for children in Texas and to increase awareness of this disease in the medical community
- Work with “CHI”
- Work with individual families who are not in centers of excellence to help them through the process of dealing with physicians not familiar with this disease

Cook Children's

Surgeries

- Operate on patients with known diffuse disease
  - 2 mutations and AD HI
- Patients whose insurance (primarily medicaid) is not accepted by or will not allow transfer to CHOP
- Families who can not make the trip to CHOP

Cook Children's

Transient HI

- Worked with the local neonatologists to implement policies for fasting all neonates who have hypoglycemia lasting > 48 hours or requiring IV fluids to resolve.
  - We are seeing approximately 15-20 patients a year with THI just in our local catchment area

Genetics 101

- Objectives
  - Explain why our children have HI
  - Explain why it is not your fault
  - Explain why it may not a good idea for your children to date other children in HI clinics

Why are we all different

- Nearly everyone is different
- We have characteristics similar to our families
- These characteristics may be passed from generation to generation
- Genetic information
- Chromosomes
- Genes
- DNA

Cook Children's

What are genes

- Genes carry information
- Some traits we have are carried on one gene
  - Red Hair
- Some traits need many genes
  - Height
- Some diseases are caused by many genes
  - Down Syndrome

CookChildren's

How do genes cause disease

- Genes primarily make proteins
- Proteins have important functions
  - KATP channel made of 2 proteins
  - Responsible for making sure the right amount of insulin is released into the blood by the beta cell
  - If underactive or not there
    - Hyperinsulinism

Hyperinsulinism

- The secretion of insulin is very complex and there are many steps involved
- Each step is regulated by proteins
- Each proteins has the potential to be made incorrectly
- Thus there are many forms of hyperinsulinism
- Each type of HI will cause different problems and require different treatments

Different forms of HI

- There are 4 common forms of HI known, 4 more rare types and many more not yet characterized
- The beta cells in KATP HI patients can not tell if the glucose is low or high so they just keep making insulin
- The beta cells in GDH HI make insulin when you eat protein as well as sugar
- The beta cells in Exercise induced HI make insulin when you exercise as well as when you eat sugar

So why does my child have HI

- Because they have a broken gene involved in the secretion of insulin
- Genes are broken either by:
  - A mutation in the DNA: GATT → GATA
  - A deletion of some DNA
    - GATTAGTA →GATA
- Broken genes
  - May be inherited
  - May be acquired

Cook Children's

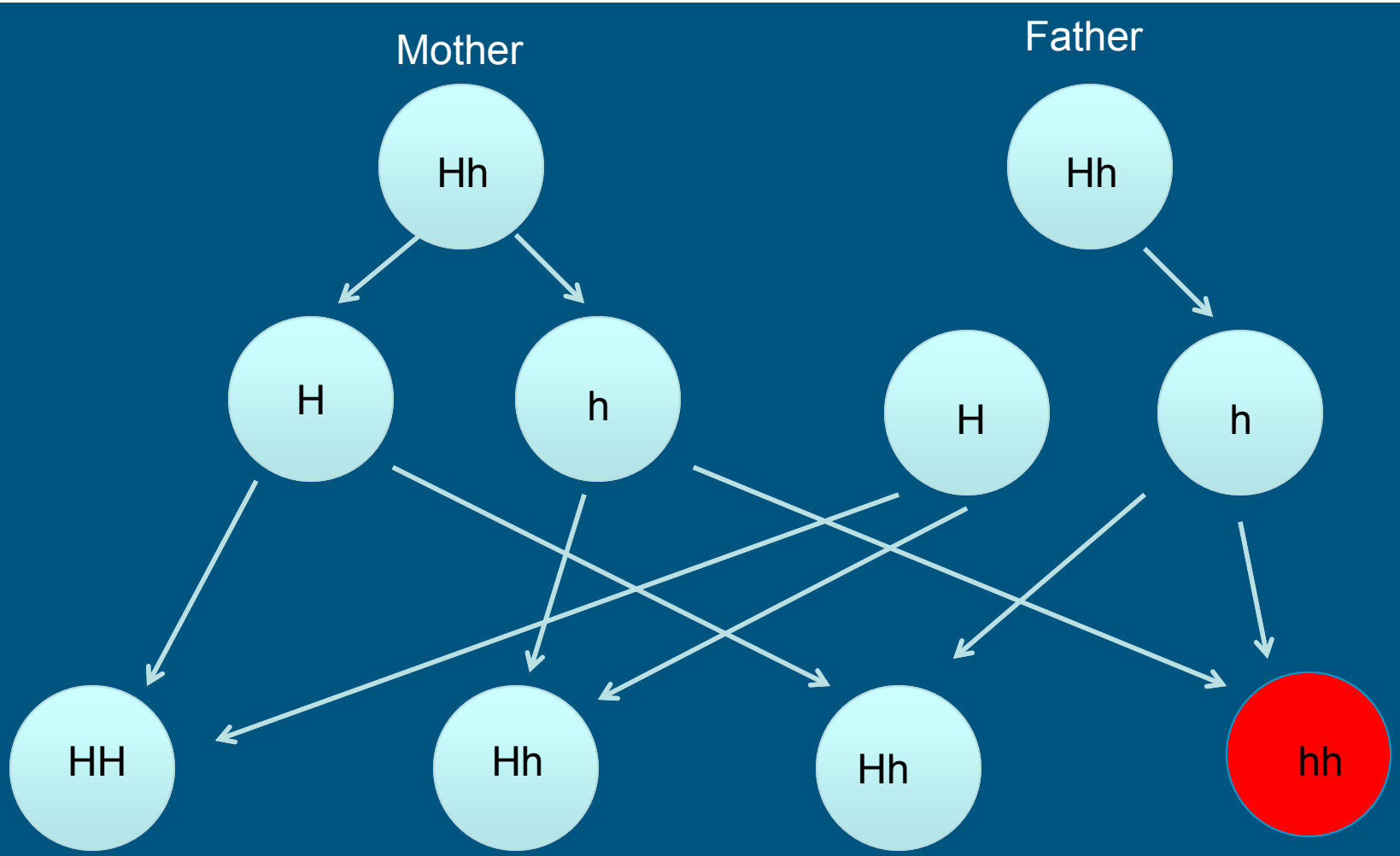
So why is it not my fault

- We can not control our own genes
- There are different ways we pass mutations to our children
  - From generation to generation
    - Dominant mutations
  - No one in the family has the disease then one of the children has it
    - Recessive mutation
    - Spontaneous dominant mutation

Mendelian genetics

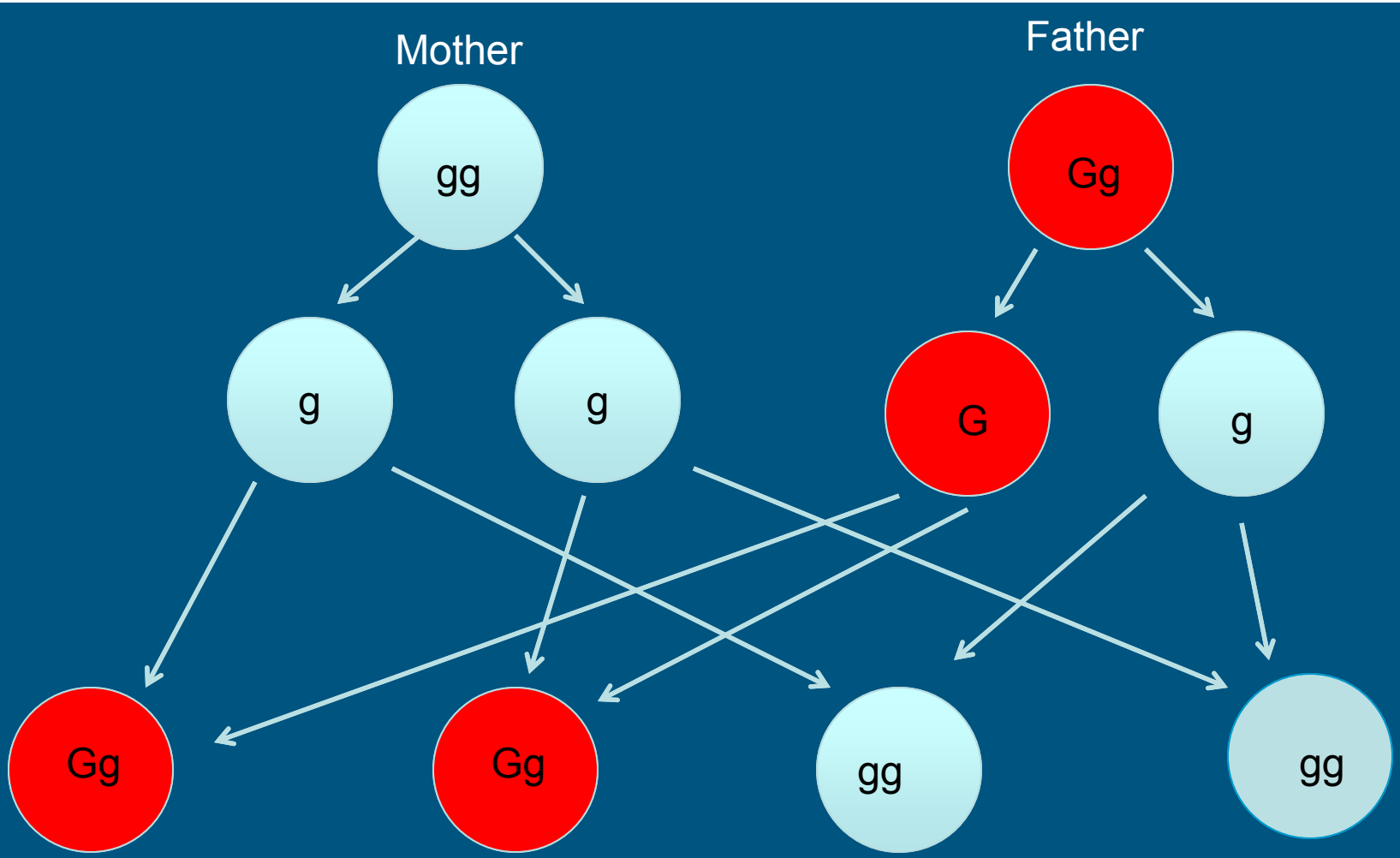
- A scientific description of how hereditary characteristics are passed to off spring
  - Dominant and recessive factors
- Each child has two copies of each gene
  - One from mother and one from father
- Most diseases require the child two have two broken genes
  - Neither mother or father have the disease because they only have one broken gene
  - The parents are called “carriers”

Example of recessive disease



CookChildren's

Example of dominant disease



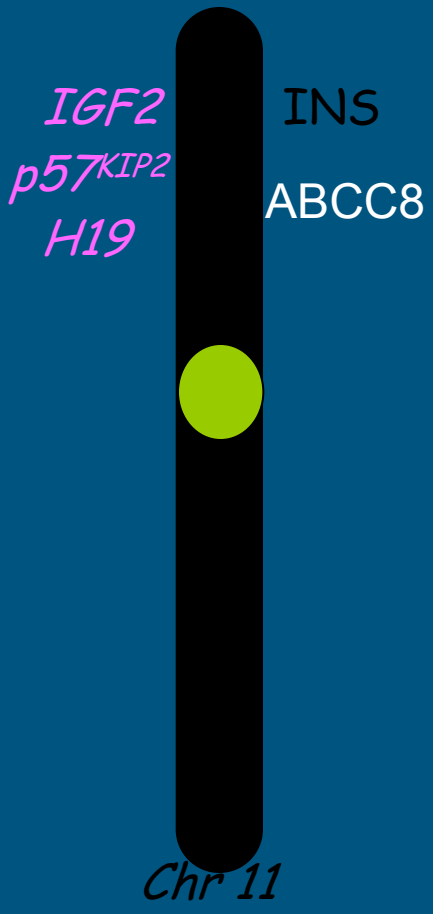
CookChildren's

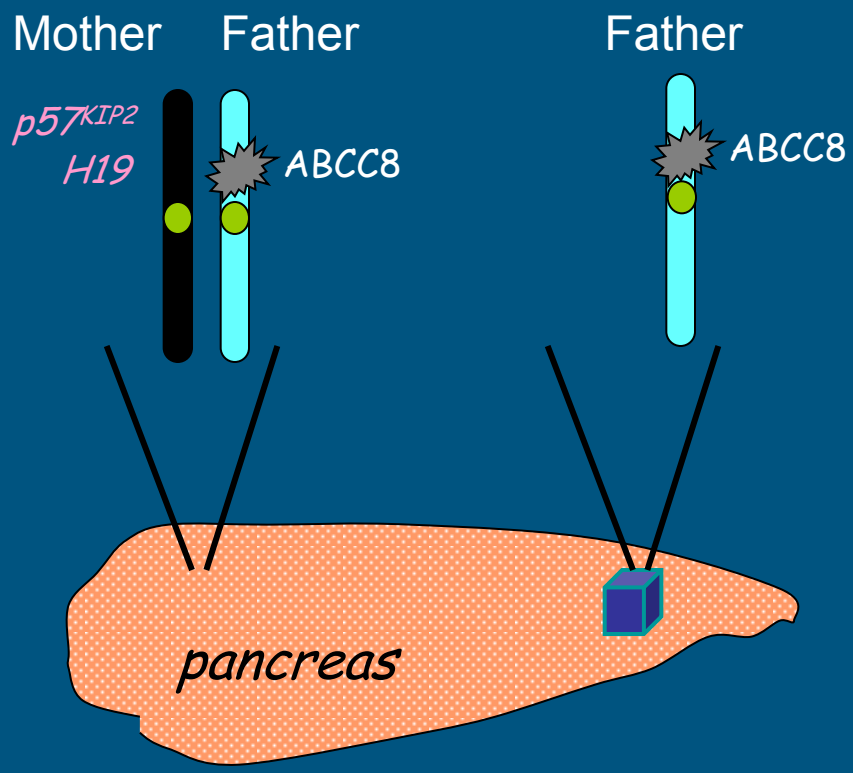
So what about Focal HI

- Focal HI which is caused by recessive mutations in ABCC8
- Only father carries mutation so the child looks like a “carrier”
- BUT
  - In the pancreas, during development of the early fetus, one cell looses the mothers ABCC8 good gene and only has the fathers broken gene.
  - These cells grow to become a focal lesion

Focal K_{ATP} HI: Two hit hypothesis of Knudson

(Maternal LOH & Paternal KATP Defect)





CookChildren's

So why should my kids not date the other kids in the HI clinic (Statistically speaking)

- In the population 1 in every 100 people carries a gene for HI
  - The chances of marrying another carrier is 1:10,000 and the chances of a having a baby with Diffuse CHI is 1:40,000
  - If you have HI then the chances are 1:100 of marrying a carrier and 1:200 of having an affected child
- In the HI clinic 1: 2 siblings will be a carrier and so the chances of marrying a carrier is 1:2 and the chances of having an affected child is 1:2
- If 2 affected kids marry there is 100% chance that the kids will be affected.

Conclusions

- Hyperinsulinism is a genetic disease
- There are many forms of HI
- There are many ways to inherit HI
- Each form has its own complexities
- The disease is not wonderful BUT OUR KIDS ARE

Cook Children's