The Genetics of CHI: For Parents

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Aims

• Explain in non-medical jargon the genetics of CHI

• Explain what are genes

• Explain the role of proteins

• Discuss the inheritance patterns of the different forms of CHI
Parts of a Cell

- Endoplasmic reticulum
- Free ribosomes
- Mitochondria
- Ribosomes (dots)
- Cell membrane
- Nucleus
The Stuff of Life!

DNA
From DNA to Chromosome
Normal Chromosomes in Humans
From Gene to Protein

Genes Tell the Cells to Make Proteins. If a Protein is Not Formed Properly Then That Protein will Not Do Its Job Properly
Proteins are the Body's Worker Molecules

**Proteins**

- **Hair and Nails**: A protein called alpha-keratin forms your hair and fingernails, and also is the major component of feathers, wool, claws, scales, horns, and hooves.

- **Blood**: The hemoglobin protein carries oxygen in your blood to every part of your body.

- **Muscles**: Muscle proteins called actin and myosin enable all muscular movement—from blinking to breathing to rollerblading.

- **Brain and Nerves**: Ion channel proteins control brain signaling by allowing small molecules into and out of nerve cells.

- **Cellular Messengers**: Receptor proteins stud the outside of your cells and transmit signals to partner proteins on the inside of the cells.

- **Enzymes**: Enzymes in your saliva, stomach, and small intestine are proteins that help you digest food.

- **Antibodies**: Antibodies are proteins that help defend your body against foreign invaders, such as bacteria and viruses.

- **Cellular Construction Workers**: Huge clusters of proteins form molecular machines that do your cells’ heavy work, such as copying genes during cell division and making new proteins.
For Example Insulin is A Protein Made in The Beta-Cell
What Does The Word Mutation Mean?

- A change in the sequence of bases in the DNA
A Mutated Apple!
Summary So Far
The Genetics of CHI
Genetics Of CHI

• 3 Major Types
  
  • **Recessive** (inherited from both parents)
  
  • **Dominant** (inherited from one parent)
  
  • **Focal is unique** (inherited from one parent but also something happens *INSIDE* the focal lesion)
# The Genetics of HH

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<tr>
<th>Gene Location</th>
<th>Symbol</th>
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<tr>
<td>11p15.1</td>
<td>ABCC8</td>
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<td>10q23.3</td>
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Chromosome 11 in CHI

Genes on chromosome 11
ABCC8/KCNJ11
Genes on Chromosomes
Autosomal Recessive Inheritance Pattern

- Dad is a carrier
- Mom is a carrier

Child doesn’t have disease & not a carrier
1 out of 4 chance (25%)

These two don’t have the disease But both are carriers
2 out of 4 chance (50%)

Child has disease
1 out of 4 chance (25%)
An Example of a Recessive Cause of CHI

Chromosome 11

Mother

Father

ABCC8
ABCC8

ABCC8
ABCC8

ABCC8
ABCC8

ABCC8
ABCC8

ONLY THIS CHILD WILL BE AFFECTED

ABCC8
ABCC8

ABCC8
ABCC8

ABCC8
ABCC8

ABCC8
ABCC8
Dominant Inheritance

50% risk
Example of a Dominant Case: Affected Parent

Chromosome 11

Mother
ABCC8  ABCC8

Father
ABCC8  ABCC8

ABCC8  ABCC8  ABCC8  ABCC8  ABCC8  ABCC8  ABCC8  ABCC8
Example of a Dominant Case: Unaffected Parent

Mother

Father

Chromosome 11
CHI: What The Pancreas Looks Like Under The Microscope

Typical diffuse

Typical focal
CHI: Histological subtypes

Diffuse CHI
Genetics of Diffuse CHI

ABCC8/KCNJ11 (autosomal recessive/dominant)

Glutamate dehydrogenase (GLUD 1)

Glucokinase (GCK)

3-Hydroxyacyl-CoA Dehydrogenase (HADH)

Hepatocyte nuclear factor 4 alpha (HNF4A)

Monocarboxylate transporter 1 (SLC16A1)
Focal CHI

Can Be Found Anywhere In The Pancreas
Focal CHI

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Can Be Found Anywhere In The Pancreas
Focal CHI can be found anywhere in the pancreas.
Types Of Focal Lesions

Small Focal Lesion
Types Of Focal Lesions

A Focal Lesion with Tentacles
Types Of Focal Lesions

Giant Focal Lesion
Types Of Focal Lesions
Types Of Focal Lesions

Ectopic Focal Lesion
Types Of Focal Lesions

Ectopic Focal Lesion
Genetics of Focal CHI

• Complicated inheritance

• 2 things must happen for a patient to have a focal lesion
Genetics of Focal CHI: First Step

Mother: ABCC8

Father: ABCC8

Chromosome 11
A bite of the mothers chromosome 11 is missing inside the focal lesion
1. Child Inherits $ABCC8/KCNJ11$ from father

2. Inside focal lesion there is loss of maternal chromosome 11p
Genetics of focal CHI

- Paternally derived leading to CHI

- Imbalance in imprinted genes leading to beta-cell hyperplasia

- SUR1
  - Kir6.2

- IGFII
  - H19
  - p57KIP2

- Imbalanced expression of genes leading to CHI
Summary

• CHI genetics is complicated

• Most cases are due to problems in the genes ABCC8/KCNJ11

• Recessive or dominant

• Focal CHI is inherited in a unique manner with 2 things going wrong