## **The Genetics of CHI: For Parents**

#### Khalid Hussain (Khalid.Hussain@ucl.ac.uk)

Department of Endocrinology Great Ormond Street Children's Hospital and The Developmental Endocrinology Research Group, Molecular Genetics Unit, Institute of Child Health, University College London UK.



5th Congenital Hyperinsulinism Family Conference September 17-18, 2013 NH Milano 2 Hotel Segrate, Italy







## 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**



## The Stuff of Life!





## **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



## 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**

| Gene Location | <u>Symbol</u> | <u>Title</u>                                                           | <u>OMIM#</u> |
|---------------|---------------|------------------------------------------------------------------------|--------------|
| 11p15.1       | ABCC8         | ATP-binding cassette, subfamily C,<br>(member 8 sulfonylurea receptor) | 600509       |
| 11p15.1       | KCNJ11        | Potassium inwardly-rectifying<br>channel                               | 600937       |
| 10q23.3       | GLUD1         | Glutamate dehydrogenase-1                                              | 138130       |
| 7p15-p13      | GCK           | Glucokinase (hexokinase-4)                                             | 138079       |
| 4q22-q26      | HADH          | Short Chain L-3-Hydroxyacyl-CoA<br>Dehydrogenase                       | 601609       |
| 20q12-q13.1   | HNF4A/HNF1A   | Hepatocyte Nuclear factor 4/1                                          | 600281       |
| 1p13.2-p12    | SLC16A1       | Monocarboxylate transporter 1                                          | 600682       |

## **Chromosome 11 in CHI**



Genes on chromosome 11

ABCC8/KCNJ11

## **Genes on Chromosomes**



## **Chromosome 11**



#### **Autosomal Recessive Inheritance Pattern**



1 out of 4 chance (25%)

2 our of 4 chance (50%)

1 out of 4 chance (25%)

#### An Example of a Recessive Cause of CHI



## **Dominant Inheritance**



#### 50% risk

### **Example of a Dominant Case: Affected Parent**



#### **Example of a Dominant Case: Unaffected Parent**



### **CHI: What The Pancreas Looks Like under The Microscope**

000

#### **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*)



















### **Small Focal Lesion**



### **A Focal Lesion with Tentacles**



### **Giant Focal Lesion**



#### **Deep Lying Focal Lesions**



### **Ectopic Focal Lesion**



## **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**



### **Focal CHI: Second Step**



### **Genetics of Focal CHI: Summary**



 Child Inherits ABCC8/KCNJ11 from father
Inside focal lesion there is loss of maternal chromosome 11p





• 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

# Thank you

