GENOTYPE AND PHENOTYPE OF 99 VIETNAMES PATIENTS WITH CONGENITAL HYPERINSULINISM

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Background

• Hyperinsulinemic hypoglycemia (HH) is a consequence of unregulated insulin secretion by pancreatic β-cells and is a major cause of hypoglycemic brain injury and mental retardation.

• Congenital HH (CHH) is caused by mutations in genes involved in regulation of insulin secretion, Eight of which have been identified (*ABCC8*, *KCNJ11*, *GLUD1*, *CGK*, *HADH*, *SLC16A1, HNF4A* and *UCP2*). Severe forms of congenital HH are caused by inactivating mutations in *ABCC8* and *KCNJ11,* which encode the two components of the pancreatic β-cell ATP-sensitive potassium channel (sulfonylurea receptor SUR1 and the inwardly rectifying ion channel KIR6.2).

Objectives

Our aim is to identify mutations in *ABCC8* and *KCNJ11*, *HNF4A* and *GLUD* genes, and to describe genotype & phenotype correlations of Vietnamese patients with CHH.

Methods

• A case series study including phenotype, genotype characteristics in 99 patients with CHH from 1/2007 to 3/2016 at National Children's Hospital, Hanoi, Vietnam.

• Genomic DNA was extracted from peripheral leukocytes using standard procedures.

• All exons of *ABCC8, KCNJ11, HNF4A & GLUD1* was amplified & directly sequenced.

• Medical records were reviewed to identify phenotypes.

Results

❖ **Mutations** were identified in **50/99 cases (50.5%): *ABCC8*: 44/99 (44.4%); *KCNJ11*: 5/99 (5.1%); *HNF4A*: 1/99 (1.0%).**

❖ **Mutations of *ABCC8***: 25/44 cases were homozygous or compound heterozygous; 19/44 cases were paternal/maternal heterozygous. 24 causative different mutations of *ABCC8* were identified including **12 novel mutations** and 12 reported mutations.

Results

❖ **Mutations of KCNJ11**

➢ 3 Novel paternal inheritance mutation **c.482C>T, c.512C>A, c.820G>C** in *KCNJ11* gene was identified in two unrelated cases.

➢ Homozygous mutation **c.185delC** in *KCNJ11* was identified in 2 siblings.

❖ **Mutation of *HNF4A*:**

Novel & maternal inheritance mutation **c.659T>C** in *HNF4A* gene was identified in 1 case.

Table 1. Mutations of *ABCC8* & frequency

Genotype with *ABCC8* mutations	Number of families
c.3403-1G>A	12
c.3403-1G>A/c.3403-1G>A	1
c.3403-1G>A/c.2995C>T	1
c.2057T>C	2
c.2057T>C/c.2057T>C	1
c.4160_4162del	2
c.1467+5G>A/c.2800C>T	1
c.2041-21G>A	1
c.2041-21G>A/c.3978del	1
c.2041-21G>A/c.2041-21G>A	1
c.2056T>A/c.2057T>C	1
c.2057T>C/c.3403-1G>A	2
c.2057T>C/c.2995C>T	1
c.2995C>T	3
c.3293A>G	1
c.3403-1G>A/c.4462C>T	1
c.4415-13G>A	1
c.4610C>T	1
c.655C>A/c.892C>T	2
c.1106A>G/ c.4611G>A	1
c.1183A>T	1
c.2056T>A/c.2057T>A	1
c.3293A>G	1
c.4061A>G *	1
c.4135G>A	1
Deletion of exons 22-26	1

* Maternal inheritance; other heterozygote cases were paternal inheritance. Red color is novel mutation

Results

❖ **Phenotype & Genotype correlation:**

➢ 49 cases without identified mutations, 1 case with novel mutations in *KCNJ11*; 1 case with mutation in *HNF4A,* & 1 case with maternal mutation in *ABCC8* were responsive with diazoxide.

➢ 47 cases were not responsive with diazoxide including:

▪ 4 cases with mutations in *KCNJ11*

▪ 43 cases with homozygous or compound heterozygous or paternal heterozygous mutations in *ABCC8.*

❖ **Treatment for cases with unresponsive diazoxide:**

▪ 18 cases were preformed near total pancreatectomy by laparoscopy.

▪ 2 cases with paternal heterozygous mutations in *ABCC8* needed focal pancreatectomy by laparoscopy.

▪ 27 cases needed octreotide injection.

Conclusions

❖ Understanding genetic basis of CHI provide novel insights into β-cell physiology.

❖ Management & genetic counseling:

▪ Genetic analysis for mutation in genes involved in regulation of insulin secretion can help in genetic diagnosis of diffuse or focal CHI and help in treatment.

▪ Prenatal diagnosis of CHI can help immediate medical management at the time of birth.

References

• Flanagan SE et al. 2009. Human Mutation 30(2): 170–180

• Banerjee I et al. 2011. European Journal of Endocrinology 164: 733–740

• Nessa A et al. 2016. Frontiers in Endocrinology 7 article 29

Conflicts of interest: None declared; **E-mail address: dungvu@nhp.org.vn (D.C. Vu).**

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