

Clinical and genetic characterization of 153 patients with persistent or transient congenital hyperinsulinism

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OBJECTIVE

To examine the molecular and clinical characteristics of Finnish patients with persistent (P-CHI) and transient (T-CHI) congenital hyperinsulinism.

INTRODUCTION

Congenital hyperinsulinism (CHI) is a rare disease characterized by inappropriate insulin secretion from pancreatic beta cells which leads to hypoglycemia. It is the most common cause of prolonged hypoglycemia in neonates. Defects in fourteen genes have associated with CHI. Pathogenic variants in K_{ATP} channel genes *ABCC8* and *KCNJ11* are the most common cause. Previous studies have identified the genetic diagnosis in 38-79% of the patients with P-CHI (1-5). Two *ABCC8* founder mutations have been previously characterized in Finns (6,7).

MATERIAL AND METHODS

- The nationwide study cohort of 95 patients with P-CHI and 58 patients with T-CHI diagnosed in 1972-2015. Only patients who required medication (diazoxide or octreotide) and/or surgery for hyperinsulinism were included. Clinical data were collected from medical records.
- T-CHI was defined as neonatal-onset CHI without a need to increase the diazoxide dose after initial remission, and successful discontinuation of medication within four months.
- Exon sequencing of selected 104 genes which affect glucose metabolism (including ten CHI-associated genes) was performed to all, except for nine P-CHI patients included with previously confirmed genetic data. Pathogenicity was assessed using *in silico* programs.

GENETIC VARIANTS IN P-CHI

- Pathogenic or likely pathogenic CHI-associated gene variants were identified in 68% (n=65) of the patients with P-CHI: six novel and 20 previously reported variants in *ABCC8*, *KCNJ11*, *GLUD1*, *SLC16A1*, *GCK*, and *HNF4A* genes.
- Variants in K_{ATP} channel genes *ABCC8* and *KCNJ11* explained 82% (n=53) and the two Finnish founder mutations 58% (n=38) of the mutation positive cases.
- The recessive founder mutation *ABCC8*/p.Val187Asp explained 37% (n=24) of the mutation positive patients and associated with the most severe phenotype.
- The dominant founder mutation *ABCC8*/p.Glu1506Lys explained 22% (n=14) of the mutation positive cases and associated with diazoxide-responsiveness.
- Thirteen patients (20% of the mutation positive cases) had a paternally inherited K_{ATP} gene variant and a confirmed focal or multifocal CHI.
- Gene defects in *GLUD1* and *SLC16A1* associated mainly with typical phenotypes of hyperinsulinism-hyperammonemia (HI/HA) and exercise-induced hyperinsulinism (EIHI).

GENETIC VARIANTS IN T-CHI

- None of the patients with T-CHI carried a pathogenic CHI-associated variant.

RESULTS

Figure 1. The frequencies of pathogenic or likely pathogenic variants in all patients with P-CHI (A) and the distribution of these variants (B).

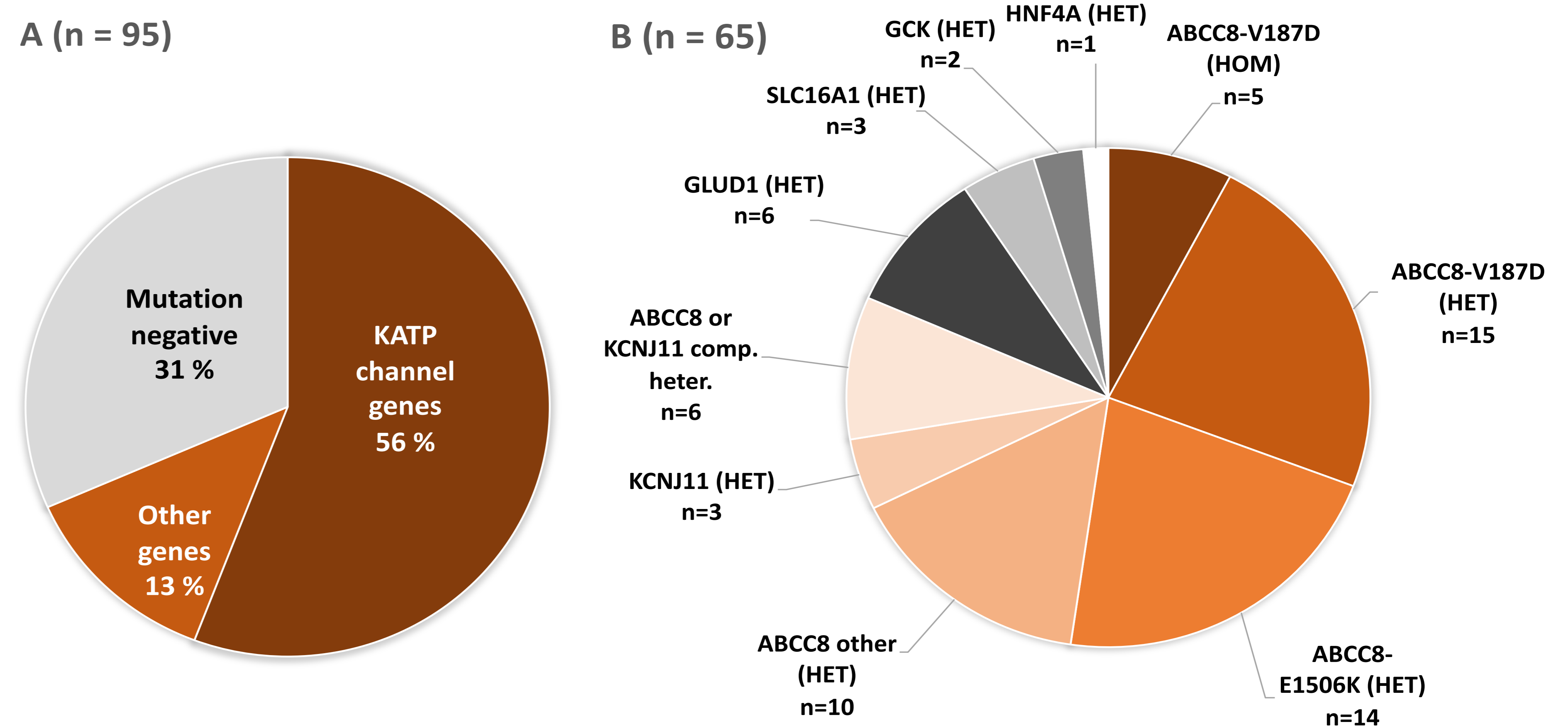


Table 1. Novel CHI-associated variants identified in the study.

No.	Gene	Allele	Protein
1	<i>ABCC8</i>	c.3280_3281del	p.(Lys1094Glufs*19)
2	<i>ABCC8</i>	c.4372C>A	p.(Gln1458Lys)
3	<i>ABCC8</i>	c.4547A>C	p.(Glu1516Ala)
4	<i>KCNJ11</i>	c.539C>T	p.(Thr180Ile)
5	<i>GCK</i>	c.193A>G	p.(Thr65Ala)
6	<i>HNF4A</i>	c.992G>A	p.(Arg331His)

CONCLUSIONS

- The distribution of genetic variants in the Finnish population-based CHI cohort is in line with the previous studies, defects in K_{ATP} channel genes being the most common causes for the disease.
- Pathogenic CHI-associated variants were not identified in patients who were both diazoxide-responsive and able to discontinue medication within four months.
- The results support the principle of focusing genetic testing on patients with an inadequate response or a prolonged need for diazoxide.

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