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Case Report

ABCC8 haploinsufficiency in a mother-daughter pair with young-onset diabetes with and without neonatal hypoglycemia

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Highlights

- *ABCC8* haploinsufficiency can lead to variable phenotypes in a family.
- *ABCC8* haploinsufficiency can cause hyperinsulinemia-remission-diabetes sequence.

Abstract. The ATP-binding cassette transporter subfamily C member 8 (ABCC8) regulates insulin secretion from β-cells. Loss- and gain-of-function variants of *ABCC8* have been implicated in neonatal hyperinsulinemic hypoglycemia and young-onset diabetes, respectively. Although some patients with *ABCC8* variants have been reported to exhibit both neonatal hypoglycemia and young-onset diabetes, the molecular and clinical characteristics of this atypical phenotype remain unknown. Here, we report a girl and her mother with a heterozygous truncating *ABCC8* variant (c.2857C>T, p.Gln953Ter). The girl showed a large birth weight and mild neonatal hypoglycemia. She developed diabetes at 10 yrs of age and was treated with insulin. Her mother had a normal birth weight and no history of hypoglycemia. The mother had gestational diabetes during each of her five pregnancies. She was subsequently diagnosed with diabetes at 35 yrs of age and treated with oral hypoglycemic agents. This study provides evidence that *ABCC8* haploinsufficiency leads to variable phenotypes in a family. These phenotypes include the hyperinsulinemia-remission-diabetes sequence and young-onset diabetes without apparent neonatal hyperinsulinemia.

Key words: ABCC8, neonatal hypoglycemia, young-onset diabetes mellitus

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Introduction

The ATP-binding cassette transporter subfamily C member 8 (ABCC8) regulates insulin secretion from β-cells (1). Previous studies have shown that loss-of-function variants of *ABCC8* typically lead to neonatal hyperinsulinemic hypoglycemia, while gain-of-function variants result in neonatal or young-onset diabetes (1). To date, however, some patients with *ABCC8* variants have been reported to have both neonatal hyperinsulinemia and young-onset diabetes (1–3). These patients carried protein-truncating or missense variants, indicating that the hyperinsulinemia-remission-diabetes sequence is a rare clinical consequence of loss-of-function mutations in *ABCC8*. This biphasic phenotype is assumed to reflect an increased Ca^{2+} influx, resulting in chronic insulin hypersecretion and subsequent progressive β-cell apoptosis (2). However, given the limited number of previous reports, further studies are needed to clarify the molecular basis and clinical characteristics of this atypical phenotype of *ABCC8* abnormalities. Here, we report a girl and her mother with *ABCC8* haploinsufficiency, who exhibited young-onset diabetes with and without neonatal hypoglycemia.

Case Report

The proband was a Japanese girl (**Table 1**, **Fig. 1**). She was born at term as the fourth child of a non-consanguineous couple. Her birth weight was +2.75 SD. Shortly after birth, she developed hypoglycemia and received intravenous glucose injections for a few days. She did not require any further medical intervention. Her growth and development were uneventful. At 10 yrs of age, she visited our hospital for the evaluation of glycosuria detected during a routine health check at school. Blood examinations revealed normal levels of C-peptide despite mildly elevated levels of glucose and glycosylated hemoglobin A1c (HbA1c) (**Table 1**). She was not obese. Autoantibodies for GAD, IA-2, and insulin were negative. She was suspected of having maturity onset diabetes of the young (MODY) or slowly progressive type 1 diabetes and was treated with insulin. Her HbA1c levels ranged from 7.3 to 9.1%, under incomplete compliance to insulin therapy. At the latest visit at 13 yrs of age, she was in good health condition.

The mother of the proband was born with normal body weight (**Table 1**). Allegedly, the mother showed no symptoms related to neonatal hypoglycemia, although detailed clinical data of this individual were unavailable. She was diagnosed with gestational diabetes during her first pregnancy at 21 yrs of age and was treated with glimepiride until delivery. Subsequently, she developed hyperglycemia during the four subsequent pregnancies and was treated with oral hypoglycemic agents. She had normal blood glucose levels during the interval between pregnancies. At 35 yrs of age, she showed sustained hyperglycemia after a stillbirth. She was diagnosed with

Table 1. Clinical findings of the proband and her mother

	Proband (III-4)	Mother (II-2)	Reference value
At birth			
Birth weight	3,685 g (+2.75 SD)	2,900 g (–0.80 SD)	
Birth length	51.0 cm (+1.84 SD)	No data	
Treatment	Intravenous glucose infusion	None	
At diagnosis			
Age	10 yrs	21 yrs	
Diagnosed by	Routine health check at school	Urine examination during pregnancy	
Height	145 cm (+0.36 SD)	168 cm (+1.89 SD)	
Body weight	35.9 kg (+0.08 SD)	No data (within normal range)	
Random blood glucose	**177 mg/dL**	No data	70–139 mg/dL
HbA1c	**8.7%**	No data	4.6–6.2%
Serum C-peptide	1.28 ng/mL	No data	0.61–2.09 ng/mL
Urine C-peptide	26.9–36.5 μg/d	No data	29.2–167.0 μg/d
Insulin therapy	Basal and bolus (total 1 U/kg/d)	None	
Other therapy	None	Glimepiride	
At the latest visit			
Age	13 yrs	46 yrs	
Height	153 cm (−0.51 SD)	168 cm (+1.89 SD)	
Body weight	50.8 kg (+0.29 SD)	64 kg (+1.33 SD)	
HbA1c	**8.3%**	**8.0%**	4.6–6.2%
Serum C-peptide	1.00 ng/mL	No data	0.61–2.09 ng/mL
Insulin therapy	Bolus (0.5 U/kg/d)	None	
Other therapy	None	Metformin, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter-2 inhibitor	

HbA1c, glycosylated hemoglobin A1c. Abnormal hormone values are boldfaced.

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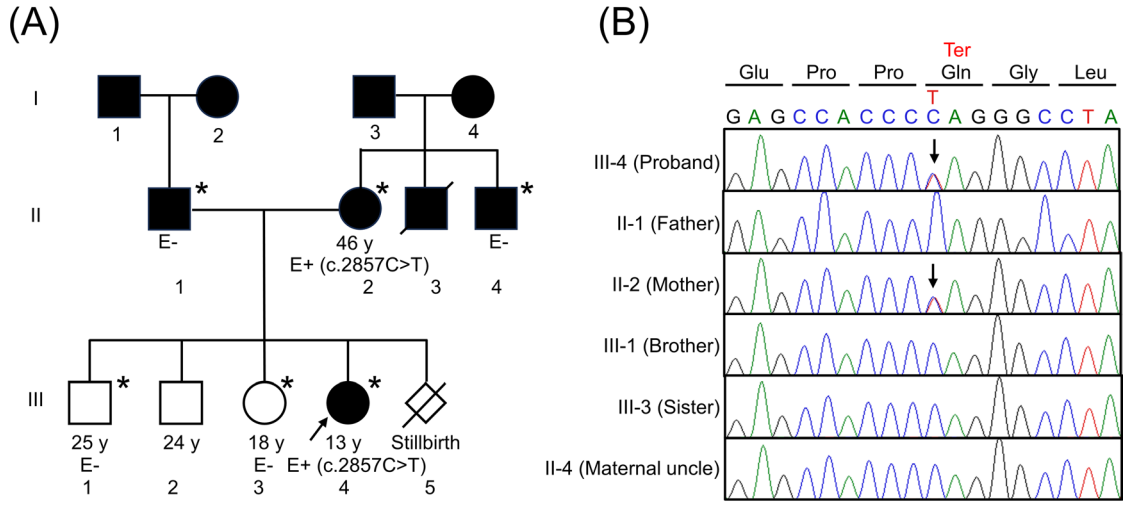

Fig. 1. Clinical and molecular findings of the family. (A) Pedigree of the family. Black squares and circles indicate individuals with diabetes. Asterisks indicate documented evaluation. The E- and E+ symbols indicate the negative and positive results of genetic testing for *ABCC8*, respectively. (B) Chromatographs of *ABCC8*. The c.2857C>T (p.Gln953Ter) variant was shared by the proband and her mother, but was not found in other examined family members. Black arrows depict the mutated nucleotide.

diabetes and prescribed oral hypoglycemic agents. Her HbA1c levels ranged from 5.8% to 8.0% under treatment.

The proband had a family history of diabetes (**Fig. 1**). Her father was diagnosed with diabetes in his twenties and treated with oral hypoglycemic drugs. Allegedly, the parental grandparents and maternal uncles also had adult-onset diabetes. One of the maternal uncles (II-3) had diabetes and hypertension and died from cerebral hemorrhage at 36 yrs of age. The siblings of the proband were unaffected. The affected individuals in this family were not obese, except for the paternal grandmother and two maternal uncles.

Molecular analyses

This study was approved by the Ethics Committee of the National Center for Child Health and Development (No.2019-100). Written informed consent was obtained from the participants or their parents. The proband was subjected to mutation screening for 12 major causative genes of monogenic diabetes (*ABCC8*, *GATA6*, *GCK*, *GLUD1*, *HNF1A*, *HNF1B*, *HNF4A*, *INS*, *INSR*, *KCNJ11*, *NEUROD1*, and *PDX1*) using a custom-made next-generation sequencing (NGS) panel (Kazusa Research Institute, Kisarazu, Japan). We searched for rare variants that were assessed as damaging by multiple *in silico* analyses. As a result, we identified a heterozygous nonsense substitution in *ABCC8* (c.2857C>T, p.Gln953Ter) (**Fig. 1**). This variant was previously identified in a few patients with neonatal hyperinsulinemia (4–7). No rare variants were detected in any of the tested genes.

Sanger sequencing confirmed the presence of the *ABCC8* variant in the proband. The variant was shared by her mother, but not by her father, siblings, or maternal uncle (**Fig. 1**). The variant of the proband was assessed as "pathogenic" according to the ACMG guidelines (PVS1 + PM2 + PP4) (https://www.broadinstitute.org/videos/variant-classification-using-acmgamp-interpreting-sequence-guidelines).

Discussion

We identified a heterozygous nonsense variant of *ABCC8* in a girl and her mother with young-onset diabetes. The position of the premature stop codon of the variant satisfies the condition of nonsense-mediated mRNA decay (8), and therefore, the mutated mRNA is likely to be degraded before being translated into a protein. These results provide evidence that the *ABCC8* haploinsufficiency represents one of the genetic causes of young-onset diabetes. Notably, the p.Gln953Ter variant has been identified in a few patients with neonatal hyperinsulinemia, but without diabetes (4–7). Furthermore, the UK Biobank study has shown that the variant was present in two of 185,509 diabetes-free adults (9). These data imply that the penetrance of young-onset diabetes in individuals with *ABCC8* haploinsufficiency is low. Indeed, previous studies have suggested that only a small subset of patients with neonatal hyperinsulinemia due to *ABCC8* variants develop diabetes in later life (2, 10).

The proband of this study manifested a large birth weight and mild postnatal hypoglycemia which are indicative of hyperinsulinemia (10), whereas her mother lacked these clinical features. Subsequently, the proband was suspected of having MODY or slowly progressive type 1 diabetes, and the mother was diagnosed with gestational diabetes. Molecular analysis confirmed the presence of an apparent pathogenic variant of *ABCC8* (MODY12) in both individuals. These cases represent a new example in which *ABCC8* haploinsufficiency

produced a biphasic phenotype in an individual, and diverse phenotypes in one family. Furthermore, our results, in conjunction with previous findings on cases with *ABCC8* truncating variants (11, 12), imply that neonatal hyperinsulinemia is a common but inconsistent feature of *ABCC8* haploinsufficiency. In this context, the clinical features of the proband can be ascribed to both *ABCC8* haploinsufficiency and poor glycemic control in the mother during pregnancy. Furthermore, since the father and a maternal uncle of the proband had diabetes despite lacking the *ABCC8* variant, other genetic or environmental factors may also have contributed to the development of diabetes in this family.

In summary, the results of this study indicate that *ABCC8* haploinsufficiency leads to variable phenotypes, including a biphasic phenotype, as well as young-onset diabetes without apparent neonatal hyperinsulinemia. Further studies are necessary to clarify the factors involved in the phenotypic diversity of *ABCC8* variants.

Conflict of interests: The authors declare no conflict of interest.

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