

## Mutation-in-Brief

# A case of transient neonatal diabetes due to a novel mutation in *ABCC8*

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### Introduction

Neonatal diabetes mellitus (NDM), characterized by hyperglycemia and the need for insulin treatment within the first 6 mo of life, is a rare monogenic form of diabetes with an estimated incidence of 1 in 90,000 neonates (1). Approximately half of NDM cases are transient and resolve at a median age of 3 mo (transient NDM: TNDM), while the remaining cases develop into a permanent form of diabetes (permanent NDM: PNDM; MIM# 606176). Adult onset non-autoimmune diabetes occurs in a significant number of patients with TNDM (2).

Most cases of TNDM (approximately 70%) are caused by abnormalities in chromosome 6q24, including paternal duplications, paternal uniparental isodisomy, and loss of methylation. In a few patients, activating mutations in the genes, which encode the two subunits of the  $\beta$ -cell

ATP-sensitive potassium channel, i.e. *ABCC8* and *KCNJ11*, have been reported to be associated with TNDM. Interestingly, recent studies have shown that familial analysis of TNMD with *ABCC8* mutations revealed that their family members with adult onset non-autoimmune diabetes also have the same mutations (3). Here, we present a Japanese case with TNDM harboring a novel p.Glu350Asp mutation in *ABCC8*. Familial analysis revealed that his non-symptomatic sister and mother, other family members with adult-onset diabetes without neonatal episodes of hyperglycemia, also possessed the same mutation.

### Patient Report

The propositus (III-2) is now an 8-yr-old Japanese male who was born at 40 wk of gestation after an uncomplicated pregnancy and delivery. He was the second child of nonconsanguineous healthy parents. His mother had no history of gestational diabetes. At birth, his weight was 2.974 kg (−0.1 SD). He was referred to us at 2 mo of age because of protracted and intense vomiting followed by Kussmaul breathing (respiration rate was 50/min). Blood examination showed hyperglycemia (serum glucose level was 753 mg/dL), metabolic acidosis (pH 7.26), and

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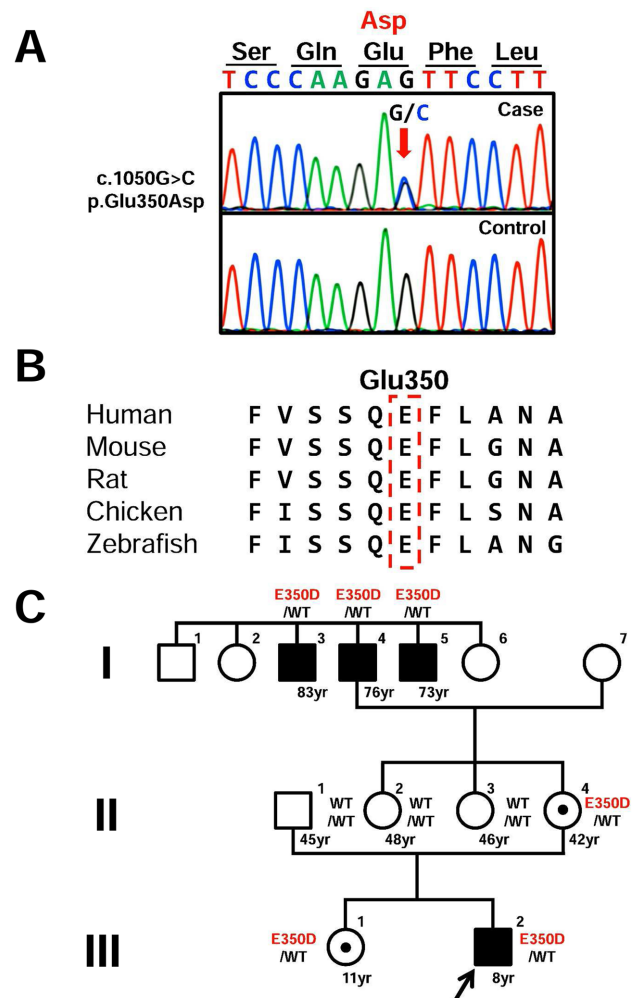
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ketosis (serum total ketone body level, 6982  $\mu\text{M}$ , acetoacetate 1455  $\mu\text{M}$ , and 3-hydroxybutyrate 5527  $\mu\text{M}$ ). Serum C-peptide was low (below 0.5 ng/mL, Ref: 1.0–3.5 ng/mL) and autoantibodies associated with type 1 diabetes were negative. He was diagnosed as NDM and treatment with multiple daily insulin injections (initially 1.0 U/kg/day) was started immediately. Gradually, his insulin requirement decreased, and treatment was stopped at the age of 4 mo. Three months after the discontinuation of insulin, his HbA1c level was 5.5% (NGSP). The patient currently exhibits normal growth and physical development and has not experienced any delays in achieving neurodevelopmental milestones. At his last examination at the age of 8 yr and 1 mo, his height was 121.6 cm ( $-0.8$  SD) and weight was 23.1 kg ( $-0.6$  SD).

### Mutational Analysis

After obtaining informed consent and the approval of the Institutional Review Board of Tokyo Metropolitan Children's Medical Center, genomic DNA was extracted from the patient's peripheral blood leukocytes. Because ketoacidosis is not typically present in patients with 6q24 defects, we first evaluated all coding exons and flanking introns of *ABCC8* and *KCNJ11* by PCR-direct sequencing. We found a novel heterozygous c.1050G>C transition (p.Glu350Asp) in exon 7 of *ABCC8* (Fig. 1A). This mutation was not detected in any of the 100 healthy controls or in the databases, including dbSNP, the 1,000 Genomes Project, Exome Variant Server, NHLBI Exome Sequencing Project, and Human Genetic Variation Database in Japanese. This glutamic acid is a highly evolutionarily conserved amino acid (Fig. 1B), located in the extracellular region of the transmembrane domain 1. No mutations were identified in *KCNJ11*.

Genetic analyses showed that the patient and his non-symptomatic sister and mother (III-1, II-4), his grandfather (I-4), and grandfather's brothers with adult onset diabetes (I-3 and I-5)



**Fig. 1.** Identification of sequence variation in *ABCC8*. (A) Partial sequence of PCR product. The chromatogram represents a heterozygous substitution of aspartic acid (GAC) in place of glutamic acid (GAG) at codon 350. The arrow indicates the mutated nucleotide. (B) Homology study. Glu350 is a highly evolutionarily conserved amino acid among several other species. (C) Pedigree of the patient.

carried the same mutation (Fig. 1C). The patients of I-3 and I-4 received insulin treatment and the patient of I-5 received sulfonylurea treatment with good glycemic control.

## Discussion

Here, we report a case of TNDM with a novel mutation in *ABCC8*. Although the functional consequence of this mutation has not been determined *in vitro*, it may cause disease as this residue is conserved across species according to several databases. To date, more than 500 mutations in *ABCC8* have been reported, but the genotype-phenotype correlation remains unclear. Our finding will improve the understanding of the pathogenesis of *ABCC8* mutations in monogenic diabetes.

Babenko *et al.* reported that heterozygous mutations in *ABCC8* accounted for 12% of cases of NDM and that mutation carriers of *ABCC8* may develop a monogenic form of type II diabetes with variable expression and age at onset, as was observed in our patient and his family (3). Several factors may explain this variability in the family members, such as genetic modifiers and environmental factors.

Several studies have demonstrated that sulfonylurea treatment provides effective glycemic control compared with subcutaneous insulin injection in patients with NDM harboring ATP-sensitive potassium channel mutations (4). Furthermore, transfer to sulfonylurea treatment has been successful for most patients with adult-onset diabetes or maturity-onset diabetes of the young due to *ABCC8* mutation (5). Therefore, identification of *ABCC8* mutations in NDM patients is useful for treatment decisions not only for the patient, but also for family members

with the same mutation.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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