

Mutation-in-Brief

A case of a Japanese patient with neonatal diabetes mellitus caused by a novel mutation in the *ABCC8* gene and successfully controlled with oral glibenclamide

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Introduction

Permanent neonatal diabetes mellitus (PNDM) is a rare form of insulin-dependent diabetes mellitus that presents within the first 6 months after birth and may require lifelong insulin treatment. Approximately 40% of all PNDM cases are caused by activating mutations in either the *KCNJ11* gene or *ABCC8* gene, which encode the Kir6.2 or sulfonylurea receptor (SUR) 1 subunit of the ATP-sensitive potassium channel (K_{ATP} channel), respectively (1–3).

The K_{ATP} channel is expressed on the surface of pancreatic beta cells. In this context, a heterozygous gain-of-function mutation in

ABCC8 or *KCNJ11* causes PNDM.

High-dose oral sulfonylurea has been reported to be an effective treatment agent for PNDM with *ABCC8* and *KCNJ11* gene mutations compared with insulin injection (4). Here we report a patient with PNDM caused by a novel heterozygous missense mutation in *ABCC8* and controlled with oral glibenclamide for more than 3 yr.

Case Report

The present case was a boy born through normal delivery at 40 wk of gestation with a birth weight of 2,784 g. He had no family history of any type of diabetes. At 3 mo of age, he was diagnosed with neonatal diabetes mellitus (NDM) based on an episode of diabetic ketoacidosis and an absence of diabetes-related autoantibodies. Diabetes treatment with multiple daily insulin injections was started immediately and switched to pump therapy when the patient was 2 yr old. At that time, his total daily insulin dose was $0.7 \text{ U} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, and his HbA1c level was 9.2%. Developmental delay and impaired motor

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development without epilepsy were observed, and the patient was diagnosed with intermediate DEND (developmental delay, epilepsy, and neonatal diabetes mellitus) syndrome.

When the patient was 3 yr old, glibenclamide therapy was started at a dose of $0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, and the dose was increased daily by $0.2 \text{ mg} \cdot \text{kg}^{-1}$ to a total dose of $1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. His insulin injections were simultaneously reduced, and they were completely discontinued when the glibenclamide dose reached $1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. Six months after starting the oral glibenclamide therapy, the dose was stabilized at $0.6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$; the HbA1c level had reduced to 5.4%, and it remained at similar levels for 3 yr. He also exhibited remarkably increased spontaneous speech and improvements in muscle tone and motor coordination after the initiation of glibenclamide.

Genetic Analysis

Blood samples were collected from the patient and his parents, and genomic DNA was extracted from peripheral blood leukocytes after obtaining informed consent from the patient's parents. All coding regions of the *ABCC8* gene were amplified by using polymerase chain reaction (Fig. 1). Sequencing analysis revealed a novel heterozygous missense mutation (p.V587G) in exon 12 of the patient's *ABCC8* gene, but this mutation was not detected in his parents. This mutation is located in the sixth transmembrane helix of transmembrane domain 1 at a residue that is highly conservative from humans to zebrafish. By using the PolyPhen-2 tool, the mutation was predicted to be possibly damaging, with a prediction score of 0.971. This mutation was not detected in 100 healthy Japanese individuals or registered in the Human Genome Mutation Database (HGMD Professional, www.hgmd.cf.ac.uk).

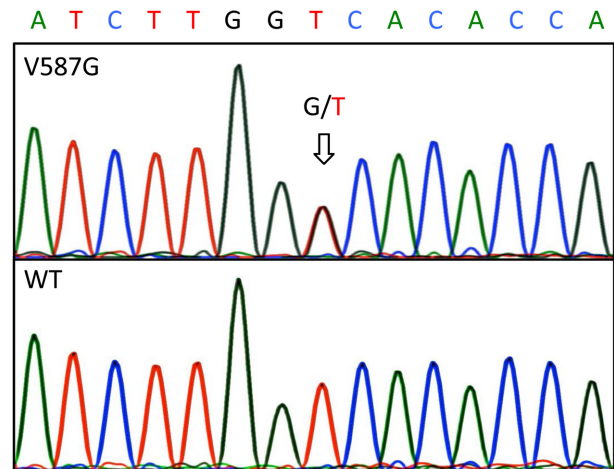


Fig. 1. Polymerase chain reaction-direct sequencing analysis of the *ABCC8* gene in the patient. The chromatogram represents the heterozygous substitution of valine (GTC) in place of glycine (GGC) at position 587 (p.V587G). The arrow pointing downward indicates the mutated nucleotide.

Discussion

Based on the results of the genetic analysis previously described, the *ABCC8* gene mutation was responsible for the boy's PNDM. A previous report revealed that a heterozygous *ABCC8* gene mutation overactivates K_{ATP} channels and inhibits insulin secretion from pancreatic beta cells by increasing the magnesium-nucleotide-dependent stimulatory action of SUR1 on the Kir pore (4).

Several reports indicated that sulfonylurea treatment provides effective glycemic control and improves the developmental and behavioral functions of patients with PNDM and K_{ATP} channel mutations (5), as in our patient. Therefore, patients with NDM should be tested for K_{ATP} channel gene mutations in order to determine if glibenclamide might be useful.

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