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Mutation-in-Brief

A Case of Novel Mutation of *HNF1B* in Maturity-onset Diabetes of the Young Type 5 (MODY5)

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Introduction

Maturity-onset diabetes of the young (MODY) is both a genetically and clinically heterozygous type of diabetes mellitus characterized by early onset (often before 25 yr of age) and absence of pancreatic β-cell autoimmunity markers (1). To date, mutations in several distinct genes have been implicated in MODY (1, 2). Among the different types of MODY, MODY5 is caused by mutations in the gene encoding the transcription factor hepatocyte nuclear factor (HNF) 1β. It is known that several abnormalities in kidney, pancreas, and genital tract formation are found in MODY5 patients (1–4).

Here we report clinical characteristics and a novel mutation in *HNF1B* in a Japanese patient with MODY5.

Case report

An 11-yr-old, nonobese girl was admitted to our hospital because of urine glucose in a school health examination. There was no family history of diabetes. On physical examination, her height was 144.8 cm and body weight was 35.3 kg (BMI 16.8 kg/m^2; 10th percentile). Laboratory evaluation showed that her fasting glucose level was 425 mg/dl and blood C-peptide and insulin levels were 1.9 ng/ml and 5.3 μU/ml, respectively, despite the elevated blood glucose level. Urine ketone bodies were positive; however, ketoacidosis was not observed (pH of venous blood 7.40). Serum BUN and creatinine were 13 mg/dl and 0.67 mg/dl, respectively. Other biochemical findings were also within normal limits. Her HbA1c level was 14.3% (NGSP). Islet cell antibodies (ICAs) and glutamic acid decarboxylase (GAD) antibodies were not detected in the serum. Urinary C-peptide concentrations measured on two different days were definitely low (22. 8 μg/d and 19.5 μg/d, normal range 20.1–155 μg/d) despite elevated blood glucose levels. Abdominal computed tomography revealed hypogenesis of the head of the pancreas (Fig. 1A), and hydronephrosis of the left kidney and agenesis of the right kidney (Fig. 1B). Since her capacity for insulin secretion was thought to be decreased, insulin therapy was started at this time at each meal. Her most recent insulin requirement and HbA1c level were 0.5 units/kg and 6.9% (NGSP), respectively. Renal function is now normal.

Based on diabetes without autoantibodies in addition to renal and pancreatic anomalies, she was suspected to have MODY5. Thus,

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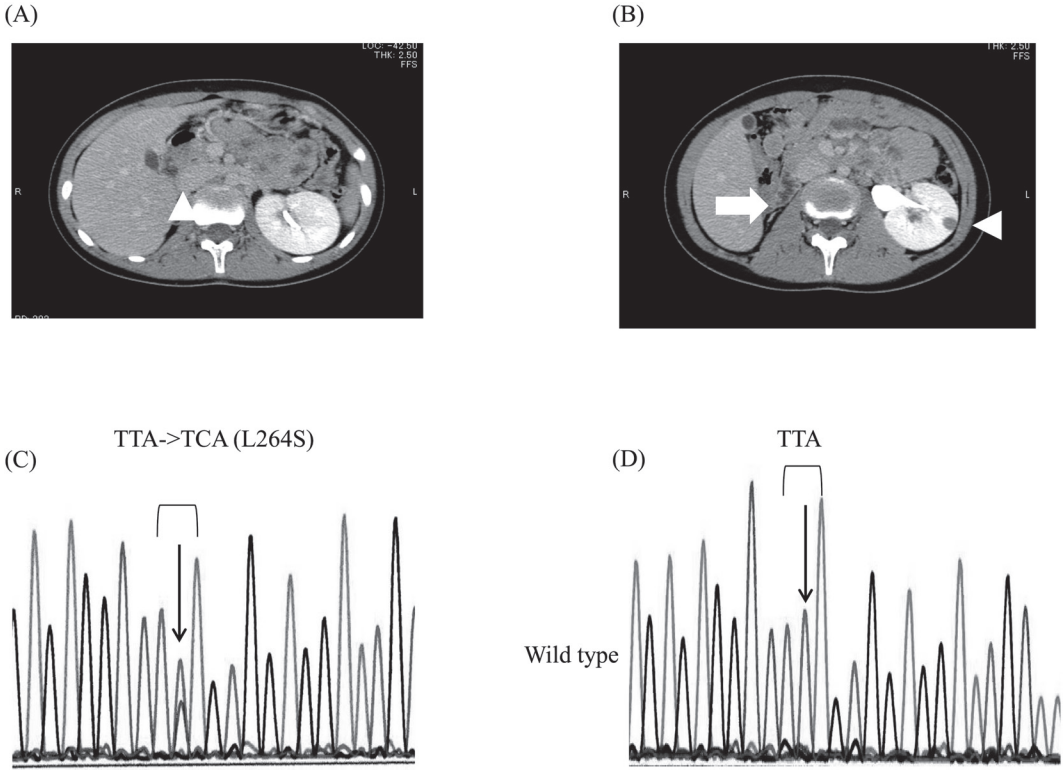

Fig. 1 (A) Hypogenesis of the head of the pancreas (arrowhead). (B) Agenesis of the right kidney (arrow) and hydronephrosis of the left kidney. (C) Sequence of the *HNF1B* gene in the patient. The patient had a heterozygous mutation (c.578T->C, p.L264S). An arrow indicates the mutation site. (D) Wild type sequence.

HNF1B was amplified and sequenced directly. As a result, a heterozygous mutation of leucine (TTA) by serine (TCA) at codon 264 (c.578T>C) was identified (p.L264S) (Fig. 1C, D). Analysis of 100 normal chromosomes of healthy controls was unable to identify this amino acid change. This mutation was not detected by single nucleotide polymorphism (SNP) in the Japanese SNP (JSNP) and SNP database (dbSNP). DNA from her father and mother was not available.

Since HNF-1β plays a critical role in normal kidney development, renal involvement becomes evident before onset of diabetes in some patients with MODY5. Renal diseases include multicystic dysplastic kidneys, noncystic renal parenchymal disease, oligomeganephronia, or atypical familial juvenile hyperuricemic nephropathy (2, 3, 5). Therefore, pediatric diabetic patients without autoantibodies for pancreatic β-cell should be screened for renal diseases.

We identified a novel mutation of p.L264S. The functional consequence of L264S was not determined; however, this mutation might be the cause of MODY5 for the following reasons. First, this leucine at codon 264 is located in the homeodomain and well conserved in different species. Second, the PolyPhen-2 tool, which predicts the possible impact of an amino acid substitution on the structure and function of a human protein (http://genetics.bwh.harvard.edu/pph2/), demonstrated that substitution of this amino acid might affect the normal protein function.

Recently, Yorifuji *et al*. (5) reported that 5 patients had whole or partial deletion of *HNF1B* in 6 Japanese patients with MODY5, and

suggested that diabetes in patients with deletion is severe. Therefore, examination for deletion of *HNF1B* is important for the diagnosis of MODY5.

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