Clinical manifestations of a sporadic maturity-onset diabetes of the young (MODY) 5 with a whole deletion of HNF1B based on 17q12 microdeletion

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Abstract. We report a sporadic case of maturity-onset diabetes of the young type 5 (MODY5) with a whole-gene deletion of the hepatocyte nuclear factor-1beta (HNF1B) gene. A 44-year-old Japanese man who had been diagnosed with early-onset non-autoimmune diabetes mellitus at the age of 23 was examined. He showed multi-systemic symptoms, including a solitary congenital kidney, pancreatic hypoplasia, pancreatic exocrine dysfunction, elevation of the serum levels of liver enzymes, hypomagnesemia, and hyperuricemia. These clinical characteristics, in spite of the absence of a family history of diabetes, prompted us to make the diagnosis of maturity-onset diabetes of the young 5 (MODY 5). One allele deletion of the entire HNF1B gene revealed by multiplex ligation-dependent probe amplification (MLPA) led us to the diagnoses of 17q12 microdeletion syndrome even though there were negative chromosomal analyses with array comparative genomic hybridization (CGH). 17q12 microdeletion syndrome, which is not rare especially in sporadic cases since 17q12 is a typical hot spot for chromosomal deletion, could have complicated the clinical heterogeneity of MODY5.

Key words: Sporadic maturity-onset diabetes of the young (MODY) 5, HNF1B, 17q12 microdeletion syndrome

Maturity-onset diabetes of the young (MODY) comprises subtypes of diabetes characterized by autosomal-dominant inheritance and early onset insulin secretion defect [1]. To the best of our knowledge, 14 different candidate genes have been identified for MODYs [2]. The first genetically identified case of MODY type 5 (MODY5), with heterozygous mutations of the hepatocyte nuclear factor 1 homeobox beta (HNF1B) gene, was in a Japanese family with renal cysts [3]. Whereas most MODY subtypes are rarely characterized by extrapancreatic dysfunction, MODY5 manifests with variable multi-systemic phenotypes [4]. Although more than 240 HNF1B mutations have been detected up to this point [5], MODY5 is a rare subgroup of MODY that accounts for 2%–6% of all genetically diagnosed MODYs in all populations, including Japanese [6].

We encountered a sporadic case of MODY5 that took more than twenty years to make a precise diagnosis even with the characteristic features of MODY5. Since a family history of diabetes is indispensable for diagnosing MODY, a sporadic case could be easily overlooked. We herein discuss the of 17q12 microdeletion syndrome, which could explain the genetic background for the clinical heterogeneity in MODY5.

Subjects

A 44-year-old Japanese man with poorly-controlled diabetes mellitus had been diagnosed with non-autoimmune diabetes mellitus at the age of 23 when he presented with symptoms of excessive thirst, fatigue, and weight loss (~7 kg per year). He had no relatives with diabetes mellitus, and there was no history of consanguineous marriage in his family. ‘Diabetologists’ had treated him for anti-GAD autoantibody-negative type 1 diabetes for more than twenty years.

Physical and imaging findings

He was 162.1 cm tall and 55.2 kg weight. (average
height and weight for 44-year-old Japanese males (2009) was 171.2 ± 5.6 cm and 69.3 ± 9.1 kg). He had never been overweight as his life-long lowest value of body mass index was 17 kg/m$^2$. Both of his parents were of average build for their age. Imaging findings, including ultrasonography, CT, and MRI of the abdomen revealed a left solitary kidney measuring 10.2 cm × 5.1 cm in size, with multiple small cortical cysts, a regular biliary tree, no sign of hepatic steatosis, and hypogenesis of the pancreatic body and tail, with a slightly atrophic pancreatic head (Fig. 1).

Biochemical analyses

The plasma concentrations of glucose and hemoglobin A1c were 374 mg/dL and 16.0% at diagnosis. Insulin therapy had been introduced at the age of 25 after the failure of the oral hypoglycemic agent, resulting in severe insulin secretion defect without severe insulin resistance; as indicated by the homeostasis model assessment of beta cells (HOMA-β) of 30%, and the homeostasis model assessment of insulin resistance (HOMA-IR) of 0.43 with a fasting glucose level of 97 mg/dL while being treated with insulin glargine. At the age of 39, the insulin secretion potency deteriorated even after insulin therapy as indicated by an increase in serum C-peptide from 0.2 ng/mL to 1.2 ng/mL six minutes after injection of 1 mg glucagon. Serum glucagon concentration was 198 pg/mL (70–174) at the age of 44.

The patient has pancreatic exocrine insufficiency in the absence of apparent symptoms, with the urinary excretion rate of p-aminobenzoic acid after oral ingestion of n-benzoyl-l-tyrosyl-p-aminobenzoic acid (BT-PABA) being 38.5%. He showed asymptomatic elevations of the serum levels of the liver transaminases, γ-glutamyl transferase, and alkaline phosphatase. The serum levels of albumin and bilirubin and the coagulation profile were within the normal range. Both primary biliary cholangitis and autoimmune and viral hepatitis were denied in the absence of detectable autoantibodies against mitochondrial M2 antigen, cell nuclei, hepatitis B or C virus RNA seropositivity, or serum immunoglobulin G or M elevations.

His renal function was preserved at the age of 44; no albuminuria, no proteinuria, estimated glomerular filtration rate (eGFR) was 57.1 mL/min per 1.73 m$^2$. However, he showed chronic electrolyte abnormalities such as hypomagnesemia and hypocalciuria. The hypomagnesemia was as below; serum magnesium level 1.2 mg/dL, the fractional magnesium excretion (FEMg) 15.7% (the mean FEMg in patients with hypomagnesemia of extrarenal origin is 1.4%; range 0.5% to 2.7%) showing excessive urinary magnesium excretion [7]. The hypocalciuria was as below; serum calcium level 9.6 mg/dL, the FECa was low (0.02%; the mean FECa in the presence of normocalcemia is 2% (range 1.5% to 3.0% [8]), and serum parathyroid hormone level was within the normal range.

Genetic and chromosomal analyses

This study was approved by the ethical genome committee of Gifu University (approval number 26–379). After obtaining written informed consent, genomic DNA was extracted from the peripheral blood leukocytes. Exome sequencing of the 4 MODY genes (HNF-1A, HNF1B, HNF-4A, and GCK) revealed no single gene mutations. Multiplex ligation-dependent probe amplification (MLPA) analyses for detecting large genomic rearrangements of the genes were examined by Salsa Multiplex Ligation-dependent Probe Amplification (MLPA) Kit P241 (MRC-Holland, Amsterdam, the Netherlands). The results of MLPA revealed half the copy number variation (CNV) of the HNF1B gene (Fig. 2), indicating a whole-gene deletion of the HNF1B gene and leading to the diagnosis of 17q12 microdeletion syndrome (17q12DS) in spite of the negative results of chromosomal analyses, including G-band, spectral karyotyping (SKY), and comparative genomic hybridization (CGH) with BAC-Array GD-700 (Fuji Film, JAPAN), which placed 22 probes on chr 17q (Fig. 3).

Discussion

We determined this to be a sporadic case of MODY5 based on 17q12DS. The early onset of diabetes and multi-systemic symptoms prompted us to examine MODY [7, 8]; however, the absence of family history made a precise diagnosis challenging. The MODY cases without a family history would be easily misdiagnosed or undiagnosed. Clinical as well as molecular diagnoses are
critical, since optimal therapy may be different. In this case, SGLT2 inhibitors could be introduced due to the low possibility of lethal ketoacidosis as type 1 diabetes was denied.

De novo \textit{HNF1B} mutations comprise 30\%–50\% of all the MODY5 mutations [9, 10]. A whole-gene deletion of \textit{HNF1B} is observed in 50\% of the MODY5 patients as the most frequent molecular alteration of \textit{HNF1B} [4, 6]. All MODY5 subjects with a whole-gene deletion of \textit{HNF1B} are derived from 17q12DS syndrome [6, 11]. 17q12DS comprises around 70\% of sporadic cases of MODY5, although the other mechanisms may be less persuasive [12]. 17q12DS occurs at an incidence of 1.6 per 1,000,000 citizens [10]. Every meiosis cycle contains homologous recombination. During this process, several portions of the chromosome could be a hot spot for microdeletion. Segmental duplications (SDs), which are interspersed lesions longer than 1 kb and with more than 90\% sequence identity, exist in around 5\% of the human genome. Sites with SD, including chromosomal location 17q12 could be the hot spot for nonallelic homologous recombination during meiosis [13]. We emphasize that 17q12 microdeletion related MODY5 should be denoted not rare in sporadic cases.

Representative 17q12DS as Mayer-Rokitansky-Kuster-Hauser syndrome has a missing segment of about 1.4 megabases (Mb) in chromosome 17q12 encompassing 17 genes including \textit{AATF}, \textit{ACACA}, \textit{DUSP14}, \textit{SYNRG}, \textit{DDX52}, \textit{HNF1B}, \textit{LHX1}, \textit{PIGW}, \textit{GGNBP2}, \textit{TADA2A}, and \textit{ZNHIT3} [9, 14]. However, heterogeneity in the deletion length in 17q12DS varies from one exon to a maximum of \(<3.2\) Mbp [12, 15] (The size of human chromosome 17 is 83 Mbp, that of 17q12 is 6.2 Mbp, and that of \textit{HNF1B} gene is 58.6 kbp [16, 17]). The signs and symptoms of 17q12DS vary widely, even among affected members of the same family. For example, the problems with the development or function of the kidneys and urinary system range from severe renal malformations, leading to kidney failure before birth, to absent case. Thus, the diverse clinical heterogeneity of MODY5 in comparison to other MODYs could be explained by the partial symptoms of 17q12DS [18].

In conclusion, 17q12DS is not rare, especially in sporadic cases of MODY5 since 17q12 is a hot spot for chromosomal deletion, and 17q12DS could have complicated the phenotypic heterogeneity of MODY5 [19]. We suggest that an integrated genetic and epigenetic approach would be helpful for a comprehensive under-
standing of MODY5 related to 17q12DS.

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