

Mutation-in-Brief

A novel *MEN1* mutation in a Japanese adolescent with multiple endocrine neoplasia type 1

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Introduction

Multiple endocrine neoplasia type 1 (MEN1; OMIM 131100) is an autosomal-dominant hereditary endocrine tumor syndrome. It is characterized by the combined development of anterior pituitary adenomas, adenomas or hyperplasia of the parathyroid glands, and gastroenteropancreatic neuroendocrine tumors (GEPNETs) in a single patient. Germline mutations in the menin gene (*MEN1*) account for the development of MEN1, and most of the *MEN1* mutations are inactivating, which is consistent with the tumor-suppressing role of menin. More than 1000 different germline *MEN1* mutations have been reported throughout the entire length of the coding and noncoding regions without significant clustering. Of all mutations, approximately 23% are nonsense mutations, 41% are frameshift deletions or insertions, 6% are in-frame deletions or insertions, 9% are splice-site mutations, and 20% are missense

mutations (1).

We describe herein a Japanese adolescent with MEN1 carrying a newly identified heterozygous missense mutation (p.Gly42Val) in *MEN1*.

Case Report

A 16-yr-old female initially presented at the age of 9 yr with a hypoglycemic (32 mg/dl) seizure associated with inappropriately elevated insulin concentrations (serum insulin, 13.4 μ U/ml; immunoreactive insulin level/blood sugar = 0.42; normal range, < 0.3). Abdominal enhanced computed tomography (CT) revealed a 2-cm solid mass localized in the pancreatic head (Fig. 1a). A calcium arterial stimulation and venous sampling (ASVS) test was performed for the preoperative evaluation of this tumor. The insulin level in the hepatic venous blood increased from 18.2 to 141.6 μ U/ml (7.78-fold) and 28.9 to 280.9 μ U/ml (9.72-fold) following the injection of calcium gluconate into the superior and the inferior pancreaticoduodenal arteries, respectively. A positive ASVS test result (a greater than 2-fold increase in the insulin level after stimulation) confirmed the presence of insulinoma. The patient underwent the surgical removal of the tumor, and a diagnosis of pancreatic insulinoma was verified by postoperative pathohistology. On further examination, parathyroid function was normal, and there were no pituitary tumors

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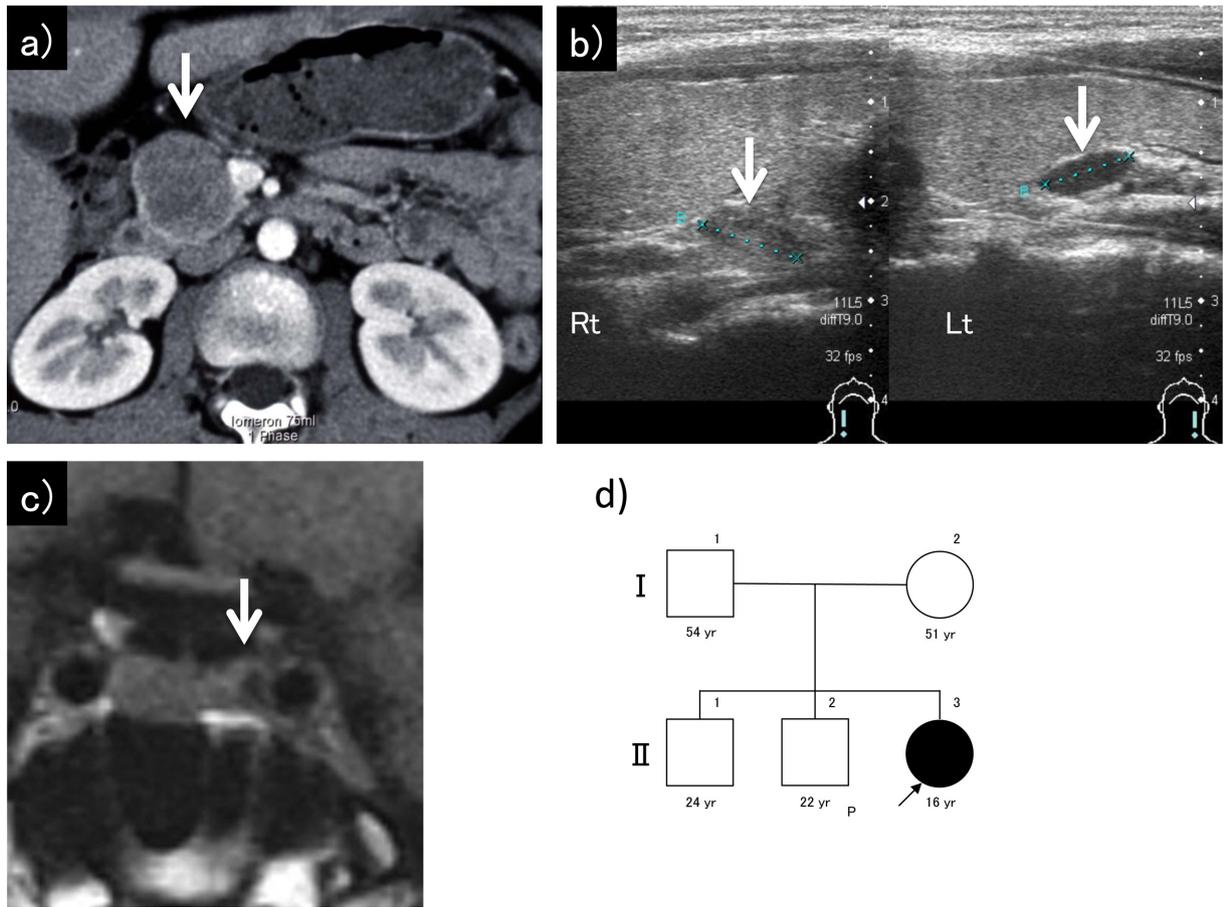


Fig. 1. The three features of the MEN1 triad. (a) Enhanced CT of the pancreas. The CT image shows an insulinoma located in the pancreatic head (arrow). (b) Ultrasonography of the thyroid. The ultrasonographic image shows two nodules, one located posterior to the lower pole of the left lobe and the other located posterior to the lower pole of the right lobe of the thyroid gland (arrow). (c) MRI of the pituitary. The MRI shows a pituitary adenoma on the left side (arrow). (d): A two-generation pedigree of the Japanese family of the patient. The proband (Patient) is indicated as II-3 with a filled symbol. Open symbols indicate unaffected members with MEN1.

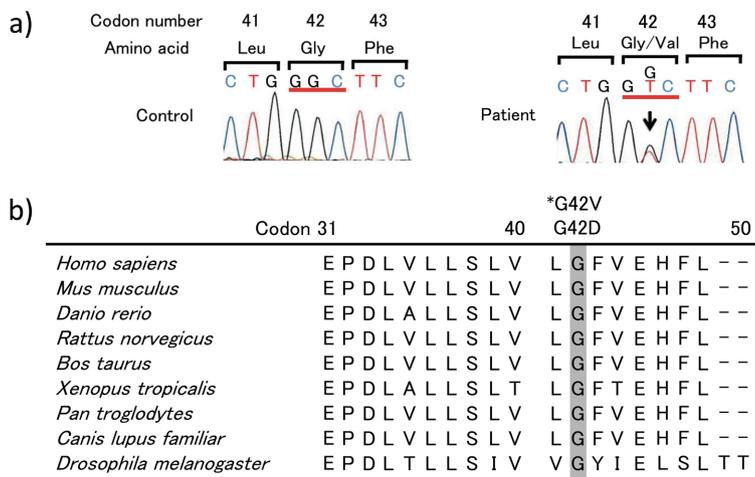


Fig. 2. (a) Identification of a novel mutation in *MEN1*. A heterozygous missense mutation, p.Gly42Val (c.125G>T), was identified in exon 2 (arrow). (b) The glycine at codon 42 in *Homo sapiens* is strictly conserved across various species. The conserved glycine is highlighted in the shaded box. The p.Gly42Val in the patient reported here and the previously reported p.Gly42Asp (3) are indicated as *G42V and G42D, respectively.

identified by magnetic resonance imaging (MRI) screening. At 16 yr of age, she was found to have persistent asymptomatic hypercalcemia (10.5 mg/dl; normal range, 8.5 to 10.3 mg/dl) associated with an inappropriately high serum PTH level (95 pg/ml; normal range, 10 to 65 pg/ml). Ultrasonography of the thyroid demonstrated hypoechoic homogeneous nodules that were 9.8×3.8 mm and 10.5×3.3 mm in size and located posterior to the lower pole of the left lobe and the right lobe, respectively, of the thyroid (Fig. 1b). The patient underwent surgical resection of the nodules, which were diagnosed as parathyroid adenomas by subsequent histopathology. Additional brain MRI scans revealed an 8.0×5.8 mm pituitary tumor (Fig. 1c) that was presumed to be a non-functioning pituitary adenoma because her pituitary hormone profiles were normal. Based on these clinical and biochemical findings, she was diagnosed as having MEN1. Her family members were healthy (Fig. 1d). This patient has been enrolled in the MEN Consortium of Japan database, and her clinical features with insulinoma have been briefly described previously (2).

Genetic Analysis

The patient's family members received genetic counseling. Informed consent for a genetic analysis was obtained from the patient with parental permissions. The ethics committee of Kanazawa Medical University approved this study. Genomic DNA was extracted from white blood cells obtained from the patient. PCR and direct sequencing were performed using standard methods. Analysis of *MEN1* revealed a novel mutation, p.Gly42Val (c.125G>T), in exon 2 (Fig. 2a). This substitution was not found in the dbSNP database (<http://www.ncbi.nlm.nih.gov/snp>) or Human Genetic Variation Database (<http://www.genome.med.kyoto-u.ac.jp/SnpDB/>). p.Gly42 is strictly conserved in various species (Fig. 2b). *In silico* analyses using PolyPhen-2

(<http://genetics.bwh.harvard.edu/pph2/>) and SIFT (<http://sift.jcvi.org>) predicted p.Gly42Val to be likely damaging.

Discussion

We present herein a MEN1 patient with the complete features of the MEN1 triad that sequentially developed in adolescence; the patient carries a newly identified heterozygous missense mutation (p.Gly42Val) in *MEN1*. A different missense mutation at the same codon, p.Gly42Asp, has been described previously (3). p.Gly42 is strictly conserved in various species (Fig. 2a). This amino acid residue is involved in domains that interact with the transcriptional regulatory proteins, such as Smad3 (codons 40 to 278) and nm23H1 (codons 1 to 486) (1). Taken together with the predictions based on *in silico* analyses, a missense mutation at codon 42, i.e., p.Gly42Val and p.Gly42Asp, may affect the functional domains of menin by interfering with the binding of proteins. Although the prognosis of this female patient remains unknown, long-term tumor surveillance is required because Japanese female patients with MEN1 have a high incidence of thymic carcinoid tumors with a high mortality rate (4). Thirteen of 16 reported MEN1 patients who developed GEPNETs before the age of 20 yr had insulinoma (2); therefore, *MEN1* gene analysis should be offered to pediatric patients who present with insulinoma.

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