A Novel Six-nucleotide Insertion in Exon 4 of the MEN1 Gene, 878insCTGCAG, in Three Patients with Familial Insulinoma and Primary Hyperparathyroidism

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Three Japanese patients (a man and his two sons) in a family with clinical diagnosis of familial multiple endocrine neoplasia type 1 (MEN1) suffered from insulinoma(s), primary hyperparathyroidism and pituitary microadenoma. Genomic DNA of the patients was analyzed by sequencing for the MEN1 gene and an insertion of six nucleotides, CTGCAG, in exon 4, resulting in insertion of two amino acids, Leu–Gln, after the 256th amino acid of the menin (256insLQ), was identified. CTGCAG is a palindromic sequence and repeated twice in the wild-type allele (nucleotides 879–890). It is speculated that mutations involving only exon 4 of the MEN1 gene might induce development of insulinoma(s).

Key words: MEN1 – in-frame insertion – multiple endocrine neoplasia type 1 – familial insulinoma – hyperparathyroidism – menin

GENETIC SUMMARY

Disorder: Multiple endocrine neoplasia type 1
Ethnicity of patients: Japanese
Gene: MEN1
GenBank accession number: HSU93236, HSU93237
Chromosomal assignment: 11q13
Type of DNA variant: a germline in-frame insertion mutation
Mutation: 878insCTGCAG, insertion of six nucleotides, CTGCAG, in exon 4 of the MEN1 gene (after the 878th nucleotide in MEN1 cDNA), resulting in insertion of two amino acids, Leu–Gln, after the 256th amino acid (256insLQ)
Allelic frequency: 0/152 normal alleles
Method of mutation detection: PCR/direct sequencing
Data base searched: http://archive.uwcm.ac.uk/uwcm/mg/search/120173.html

CASE REPORT AND GENETIC ANALYSIS

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterized by varying combinations of tumors involving the parathyroids, enteropancreatic neuroendocrine tissues and anterior pituitary. Germline mutation of the MEN1 gene has been reported in more than 80% of familial MEN1 (1–9) and about half of sporadic MEN1 (10). In contrast to MEN2, tumors producing various kinds of hormones may develop in the pituitary and pancreas in patients with MEN1, making the management of patients and mutant carriers difficult, because a genotype–phenotype correlation has not been established.

The proband Japanese patient III-6 (Fig. 1) had an operation for spinal ependymoma (C4-Th5) at the age of 51 years and...
was found to have hypercalcemia (11.5 mg/dl). He was diagnosed as having primary hyperparathyroidism due to parathyroid hyperplasia. Four hyperplastic parathyroid glands were removed, one of which was autotransplanted. Subsequently, he had several hypoglycemic attacks due to insulinomas, which were completely removed by surgery. He also has a non-functioning pituitary microadenoma as detected by MRI of the head.

Patient IV-1 (Fig. 1), a son of the proband, had had repeated episodes of unconsciousness and generalized convolution since he was 8 years old. An insulinoma with a size of 6 × 8 mm was detected at the pancreatic head, which was successfully
removed by surgery at the age of 9 years. Recently, he was found to have hypercalcemia (11.6 mg/dl) due to primary hyperparathyroidism and pituitary microadenoma secreting prolactin, although no further evaluation has been performed yet.

Patient IV-2 (Fig. 1), a younger brother of patient IV-1, had repeated hypoglycemic attacks and was operated on for multiple insulinomas located from the head to the tail of the pancreas at the age of 17 years. Primary hyperparathyroidism was diagnosed at the age of 24 years when he suffered from urolithiasis and hypercalcemia (11.3 mg/dl); enlargement of four parathyroid glands was noted by cervical echography and parathyroid scintigraphy. Non-functioning pituitary microadenoma was detected by MRI of the head.

The three patients were diagnosed as having familial MEN1. They had a common and characteristic feature of insulinoma(s), primary hyperparathyroidism and pituitary tumor. Further, as shown in Fig. 1, a cousin (III-5) of patient III-6 had died of insulinoma although detailed information was not available.

Nucleotide sequences of the exonic regions of the MEN1 gene from nucleotide 88 to 1988 covering the full-length coding region and those of intronic regions at exon–intron boundaries containing at least 38 nucleotides were determined.

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METHODS FOR MUTATION DETECTION

PCR/direct sequencing of exon 4 and the franking introns was performed with the following conditions and parameters:

PCR primer, forward: 5’ CCGCTGAGCAAGCGCAGGGTG3’
PCR primer, reverse: 5’ GTGCAACGGCTCCCGAGCAA3’

Size of PCR product: 256 bp

Thermal cycle profile:

Initial denaturation: 94°C, 5 min
35 cycles of 94°C, 60 s; 58°C, 60 s; 72°C, 10 min
Final extension: 72°C, 10 min

Sequencing primer: the same as the PCR primers

PCR/direct sequencing of regions other than exon 4 was performed as previously described (9).

References


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