A Japanese woman was treated for insulinoma when she was 29 years old. Ten years later, hyperparathyroidism and non-functioning adrenal tumor were found and she was diagnosed as having multiple endocrine neoplasia type 1 (MEN1). No other family members have developed MEN-related lesion(s). Genomic DNA of the patient was analyzed by sequencing for the MEN1 gene and a novel, three-base in-frame deletion resulting in deletion of an amino acid Leu259 was identified. Her two children showed a wild-type sequence at this codon.

Key words: MEN1 – in-frame deletion – multiple endocrine neoplasia type 1 – 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 deletion mutation
Mutation: Deletion of three successive nucleotides CTG (Leu, wild-type) of the MEN1 gene resulting in deletion of an amino acid Leu259 (L259del)
Allelic frequency: 0/130 normal alleles
Method of mutation detection: PCR/direct sequencing
Database 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). Analysis of the MEN1 gene is now postulated to belonging to Group 1 cancer predisposition testing by the American Society of Clinical Oncology (ASCO) (9).

A Japanese woman (Fig. 1, III-1) underwent distal pancreatectomy due to insulinoma when she was 29 years old. Ten years later, she was admitted to a hospital because of severe hyperglycemia. Hypercalcemia and high intact PTH (parathyroid hormone) level were found. Under diagnosis of primary hyperparathyroidism, four hyperplastic glands of the parathyroid were surgically removed and 80 mg of the tissue were autotransplanted. During examination, a nodular lesion with a maximum diameter of 21 mm in the right adrenal gland was...
L259del novel MEN1 mutation

detected by computed tomography. Her cortisol and ACTH (adrenocorticotropin) levels were normal and 1 mg dexamethasone suppressive. Under diagnosis of non-functioning adrenal tumor, this lesion is currently being followed up. She was clinically diagnosed as having MEN1.

As shown in Fig. 1, no family members developed MEN1-related lesion(s), although no information was obtained on paternal family members because of parental divorce when the patient was 4 years old.

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 in both orientations, in the peripheral blood cells from the patient (9). A novel, heterozygous and germline mutation of the MEN1 gene in exon 4, L259del, in-frame deletion of three successive nucleotides CTG (Fig. 2), resulting in deletion of an amino acid Leu259 of the menin, was identified. The L259del is considered not to be a rare polymorphism but to be a pathological mutation because the L259del was not found in 130 independent normal alleles and because Leu259 is conserved among all the species sequenced to date and sequences of amino acids 189–313 were completely identical among human, rat and mouse homologues (11).

From limited information on the family, the patient was clinically diagnosed as having sporadic MEN1. It is unclear whether the mutation is de novo because genetic testing for her parents was not performed. With informed consents and assents, carrier testing for the mutation of her sons aged 15 and 7 years was performed. They were negative for the L259del mutation.

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′CCCTGAAGCAGGCACAGGGTG3′
PCR primer, reverse: 5′CTGCCCAGGGTCCCACAGCAA3′
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, 60 s.
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 described previously (9).

Acknowledgments

This work was supported in part by grants-in-aid from the Sagawa Foundation for Promoting Cancer Research, and the Kudo Foundation.
References


Cancer Genetics Report is a new section for JJCO and presents a brief report focusing on genetic analysis of a case which merits publication. Specifically:

1. Typically, the section reports a previously undescribed germline mutation or polymorphism of a gene which is associated with a cancer. A case report with known mutation or polymorphism may also be considered, if the report can be expected to contribute substantially to the advancement and/or accumulation of our knowledge in the field of clinical cancer genetics.
2. Nucleotide sequence of the mutation or polymorphism must be defined on the genomic DNA.
3. Method of the mutation/polymorphism detection should be described explicitly, such as PCR conditions and primer sequences.
4. Whenever appropriate, a pedigree (family tree) must be presented. The pedigree should be drawn according to the “Recommendations for Standardized Human Pedigree Nomenclature”, Am. J. Human Genet. 56:745-752, 1995. The summary of the Nomenclature is available at wwwinfo.ncc.go.jp/jjco/pedigree.pdf
5. Privacy and right of a patient and of any other relevant family member(s) should be strictly protected in the study, and it is the responsibility of author(s) to obtain an appropriate informed consent and approval from Institutional Review Board (IRB).

A manuscript for Cancer Genetics Report should be prepared according to the Instructions to authors for regular papers, except: 1) Running Head and Mini-abstract are not required, 2) Abstract should be non-structural and up to 100 words, 3) a genetic Summary should be provided describing Disorder, Ethnicity, Gene and its GenBank, EMBL or DDBJ accession number and Chromosomal assignment, Type of DNA variant, Mutation, Allelic frequency, and Method of mutation detection, URL(s) of mutation database(s) searched and/or to which the record of the mutation is deposited by the authors, etc., 34) Text may have minimum sections, but a Methods section is mandatory and 4) Two sets of the manuscript with original figures should be sent to the Editorial Office with a covering letter signed by all coauthors.