

Cancer and Genetics Report

A Novel Germline Mutation, 1793delG, of the *MEN1* Gene Underlying Multiple Endocrine Neoplasia Type 1

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Pulmonary carcinoids are rare neuroendocrine tumors which comprise 1–2% of all lung tumors. They usually occur sporadically; however, their association with multiple endocrine neoplasia type 1 (MEN1) syndrome has been documented. We report a case of a Thai woman with a pulmonary carcinoid tumor and a null cell pituitary tumor. Her family history was unremarkable for any MEN-related lesions. Genetic testing revealed a novel deletion mutation at exon 10 (1793delG) of the *MEN1* gene, resulting in a stop codon 26 amino acids downstream. This mutation is predicted to cause a loss of the second nuclear localization signal of the menin protein.

Key words: multiple endocrine neoplasia type 1 – pulmonary carcinoid – pituitary macroadenoma

CASE REPORT AND GENETIC ANALYSIS

Carcinoids are neuroendocrine tumors which originate from enterochromaffin cells (1). They are traditionally classified according to their anatomic site of origin: foregut, midgut or hindgut. Carcinoids can occur either sporadically or as part of familial syndromes. Multiple endocrine neoplasia type 1 (MEN1) syndrome is characterized by the occurrence of neoplasms affecting the parathyroid glands, the pancreatic islet cells and the anterior pituitary gland (2). About 10% of MEN1 cases have been reported in association with carcinoids, especially the foregut type³ (thymic, gastric or pulmonary). Pulmonary carcinoids are rare neoplasms which represent 1–2% of primary lung tumors. They are classified along a spectrum of pulmonary neuroendocrine tumors with clinical behavior and histological differentiation, ranging from the low grade typical carcinoids to the intermediate grade atypical carcinoids to the high grade large cell neuroendocrine carcinomas and small cell carcinomas (4). Unlike thymic carcinoids in MEN1, pulmonary carcinoids occur less frequently in a patient with MEN1 syndrome (<5%) and mainly in females (5).

The proband, a 68-year-old Thai female, was admitted with an asymptomatic lung mass, 7 × 5.9 × 5.1 cm in dimension. Right lower lung lobectomy was performed and its histological findings were compatible with a typical carcinoid tumor. One year

later, severe headache developed. A pituitary macroadenoma, 3 × 2 × 3 cm in size, with apoplexy was found on a magnetic resonance imaging study. Hormonal assessment for pituitary function was normal for free T₄, thyroid-stimulating hormone (TSH), serum cortisol, adrenocorticotrophic hormone (ACTH), insulin-like growth factor-I (IGF-I) and prolactin. Her sex hormone levels were compatible with a menopausal state. Serum calcium and parathyroid hormone levels were in the normal range. Trans-sphenoidal tumor removal was performed and null cell type was confirmed by immunohistochemical study. She was clinically diagnosed with MEN1 syndrome. No other family members developed any MEN1-related lesions (Fig. 1).

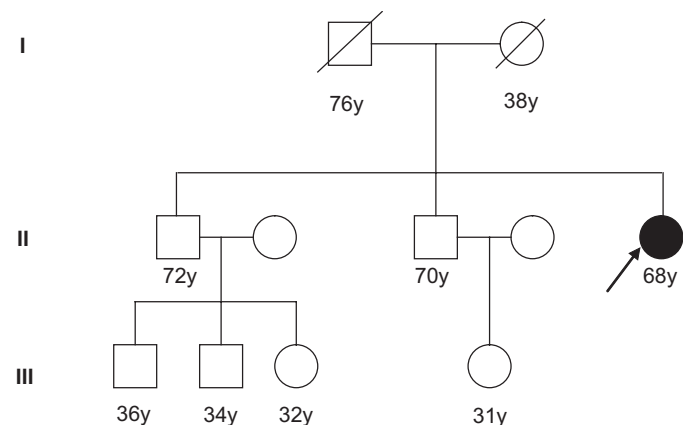


Figure 1. Pedigree of the proband.

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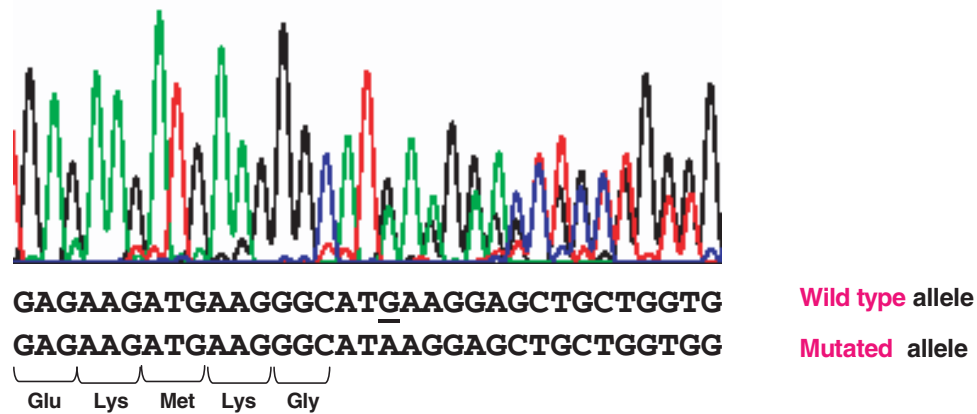


Figure 2. Direct sequencing of the PCR product containing exon 10 of the *MEN1* gene from the patient. The nucleotide sequences of the wild-type allele (upper row) and the mutated allele (lower row) are shown. The deleted G is underlined.

Table 1. Genetic summary

Disorder	Multiple endocrine neoplasia type 1
Ethnicity of patient	Thai
Gene	<i>MEN1</i>
GenBank accession No.	HSU93236, HSU93237
Chromosome assignment	11q13
Type of DNA variant	Germline deletion mutation
Mutation	Deletion of guanine (G) at nucleotide 1793 resulting in a stop codon 26 amino acids downstream
Allelic frequency	–
Method of mutation detection	PCR/direct sequencing
Database searched:	http://archive.uwcm.ac.uk

The *MEN1* gene (Table 1), a tumor suppressor gene, encompasses 9.2 kb of genomic DNA and consists of 10 exons encoding a 610 amino acid nuclear protein termed menin (6). Menin is a 67 kDa protein and interacts with a diverse group of transcription factors and co-regulators, including JunD, NF- κ B, PEM, Smad3 and mSin3A-histone deacetylase, suggesting its role in the regulation of gene transcription, DNA replication and cell cycle control (7–11). The menin sequence has two nuclear localization signals (NLS1 and NLS2) in the C-terminus corresponding to amino acid residues 479–497 and 588–608, respectively (12). Mutation analysis of the *MEN1* gene in our patient revealed a novel heterozygous deletion of guanine (G) at nucleotide 1793 of exon 10 (Fig. 2). This mutation is expected to result in an amino acid change from methionine (Met) to isoleucine (Ile) at codon 561 of the menin protein, producing a stop codon 26 amino acids downstream. The predicted truncated protein lacks the NLS2 locus, which may cause protein instability or loss of function by displacing menin out of the nucleus (13).

Both of the patient's parents died from unknown causes, and two apparently healthy brothers of the patient declined the genetic testing. In conclusion, our study shows a novel

MEN1 gene mutation at exon 10 in a Thai kindred which extends our knowledge concerning the variety of tumor involvement in MEN1 syndrome.

METHODS FOR MUTATION DETECTION

PCR/direct sequencing of exon 10 and the flanking introns was performed with the following conditions and parameters: PCR primer, forward, 5'GAGTTCCAGCCACTGGCCGG3'; PCR primer, reverse, 5'GGTTTGATACAGACTGTACTCGG3'; size of the PCR product = 673 bp. The thermal cycle profile comprised initial denaturation: 94°C, 5 min, 35 cycles of 94°C, 60 s/65°C, 60 s/72°C, 60 s and final extension at 72°C for 10 min. The sequencing primer was the same as the PCR primers.

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