Clinical and molecular characteristics of pediatric patients with multiple endocrine neoplasia (MEN)

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Introduction

- Multiple endocrine neoplasia (MEN) is a rare, autosomal dominantly inherited cancer syndrome caused by mutations in *MEN1* or *RET* gene.
- Identification of the genetic causes of the MEN is critical because genotype provides information on timing of prophylactic surgery in patients with MEN type 2 who have clinically silent tumors.

Objectives

- This study was performed to investigate clinical phenotype and molecular characteristics of children with MEN in a single academic center in Korea.

Subjects and Methods

- This study included 8 pediatric patients with MEN from 7 unrelated families who were diagnosed prior to the age of 18 years between March 2008 and March 2019.
- Clinical and endocrine characteristics were collected by retrospective chart review.
- Molecular analysis of *MEN1* or *RET* was performed according to the clinical phenotype and family history.

Results

Clinical characteristics of patients with MEN

- Eight patients from 7 families were genetically confirmed with MEN, including MEN1 (n = 1), MEN2A (n = 6), and MEN2B (n = 1).
- Subjects 2 and 3 were siblings who were detected by familial screening because their mother was diagnosed with MEN2A with medullary thyroid cancer (MTC) and bilateral pheochromocytoma. Subject 5 was diagnosed by prenatal genetic testing before birth, due to the MEN2A family history of her mother and grandmother.
- Subjects 4, 5, and 6 underwent prophylactic thyroidectomy at age of 5 or 6. The other patients were recommended to undergo prophylactic thyroidectomy.

Table 1. Clinical characteristics of patient with multiple endocrine neoplasia

Subject No.	1	2	3	4	5	6	7	8
MEN type	1	2A	2A	2A	2A	2A	2A	2B
Sex	F	F	F	F	F	F	M	M
Age at Diagnosis, yr	10	9	12	3	0	2	4	6
Presenting features	Hypoglycemia	No symptoms (detected by family screening)						Tongue neuroma
Endocrine tumors	Insulinoma							MTC
Management	Distal pancreatec-tomy	-	-	Prophylactic thyroidectomy			-	Total thyroidec-tomy

Molecular analysis of the *MEN1* and *RET* gene.

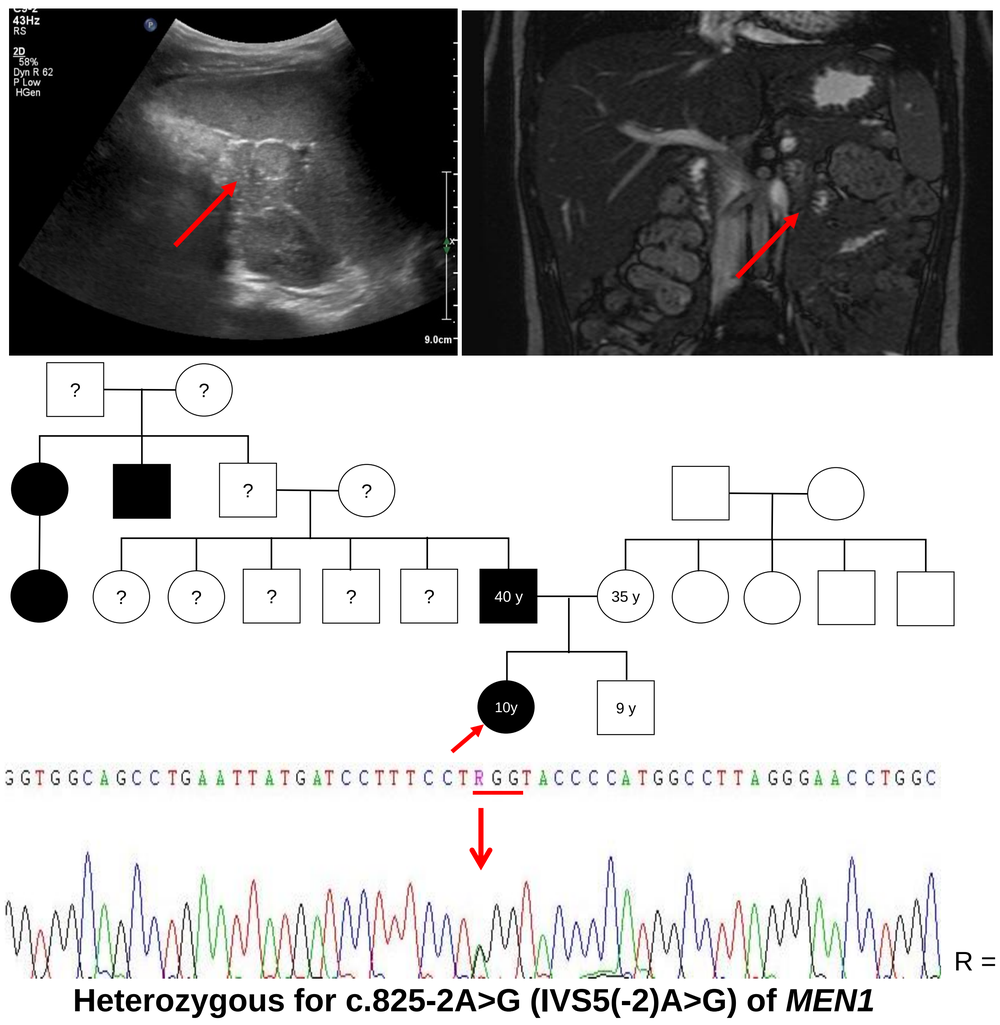
- Five heterozygous, previously reported mutations in *MEN1* or *RET* were identified from 8 patients of 7 unrelated families.

Table 2. Molecular analysis of the *MEN1* and *RET* gene of 8 subjects

No.	Gene	Nucleotide change	Amino acid change	Intron/exon	Inheritance	Reference
1	*MEN1*	c.825-2A>G	Splice site	5	Paternal	[1]
2	*RET*	c.1900T>C	p.C634R	11	Maternal	[2]
3	*RET*	c.1900T>C	p.C634R	11	Maternal	[2]
4	*RET*	c.1891G>T	p.D631Y	11	Paternal	[3]
5	*RET*	c.1900T>C	p.C634R	11	Maternal	[2]
6	*RET*	c.1900T>C	p.C634R	11	Maternal	[2]
7	*RET*	c.1901G>A	p.C634Y	11	Maternal	[4]
8	*RET*	c.2753T>C	p.M918T	16	*De novo*	[5]

Subject 1

- A 10-year-old girl with family history of MEN1 visited the emergency room due to the loss of consciousness. Her initial serum glucose level was 50 mg/dL. Radiologic findings revealed the pancreas tail insulinoma. She was finally diagnosed with MEN1 by molecular analysis of the *MEN1* gene.

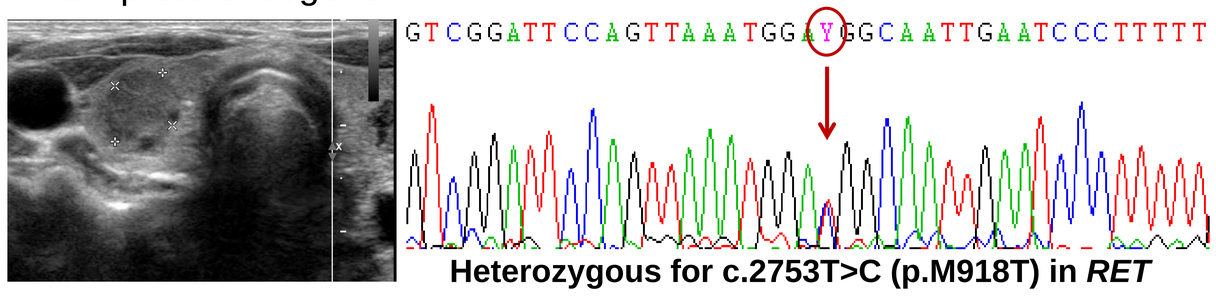


Heterozygous for c.825-2A>G (IVS5(-2)A>G) of *MEN1*

Figure 1. Pedigree of Subject 1 and mutation analysis of *MEN1*

Subject 3

- A 6-year-old boy visited outpatient clinic for evaluation of short stature. Tongue tip nodule was incidentally detected, and biopsy confirmed neuroma. Thyroid ultrasonography showed cystic lesion in both thyroid gland. Initial serum calcitonin was elevated to 296 pg/mL (reference range 0-10). He underwent total thyroidectomy at the age of 7 years. He was diagnosed with MEN2B by mutation analysis of *RET* proto-oncogene.



Heterozygous for c.2753T>C (p.M918T) in *RET*

Conclusions

- Among the studied patients, mutations in exon 11 of *RET* gene were the most frequently identified.
- Genetic screening should be considered in children with family history of MEN for early diagnosis and treatment of hereditary endocrine tumors.
- Patients with any of the hereditary tumor syndromes require lifelong tumor surveillance to facilitate early tumor detection and treatment of associated neoplasms.

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Disclosure statement

The authors have nothing to disclose.