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Characteristics of the Germline *MEN1* Mutations in Korea: A Literature Review

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Purpose: Multiple endocrine neoplasia type 1 (MEN-1) is an autosomal dominant disease caused by the *MEN1* germline mutation. We reviewed previous reports in order to summarize the characteristics of germline *MEN1* mutation in Korea.

Methods: We retrieved the relevant literature regarding *MEN1* germline mutation in Korea using the Pubmed (http://www.pubmed.org/) and Koreamed (http://www.koreamed.org/) databases from 2000 to 2012. We evaluated the pedigree of the patients in order to exclude the same, repeated families. We collected all data on the types of mutations and clinical characteristics.

Results: There were nine studies with 12 cases of *MEN1* mutations in Korea. Two cases were sporadic MEN-1. C.196_200dupAGCCC was reported in three families. There were six cases of frameshift mutation, three cases of missense mutation, two cases of nonsense mutation, and one case of splice site mutation. Five mutations were novel mutations not previously reported.

Conclusion: We summarized the characteristics of germline *MEN1* mutations in Korea. Genetic testing of *MEN1* is rare in Korea; however, it will be useful in preclinical diagnosis and genetic counseling.

Key Words: Multiple endocrine neoplasia type 1, Germ-line mutation

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INTRODUCTION

Multiple endocrine neoplasia type 1 is an autosomal dominant inherited tumor syndrome characterized by the presence of parathyroid, entero-pancreatic and pituitary tumors. *MEN1* gene is a tumor suppressor gene which is composed of 10 exons. The *MEN1* gene translates 610 amino acids, MENIN protein.(*1*)

In contrast to the *RET* gene of MEN-2, the germline mutation of *MEN1* gene is reported to have no mutational hot spots. Therefore all exons should be searched to detect mutations. There are no genotype-phenotype correlations in *MEN1* mutations which makes it difficult to predict mutational type.(*1*)

Until now there have been some studies about the *MEN1* mutation in Koreans including somatic mutation in parathyroid tumors,(*2*) but most of these studies were case reports. The germline *MEN1* mutation test is not popular in Korea and only 38% of Korean MEN-1 patients were reported to have had a genetic study.(*3*) In this study we reviewed previous Korean reports to summarize the characteristics of germline *MEN1* mutations in Korea.

METHODS

We searched journals from the Koreamed database (http://www.koreamed.org) using the keywords 'MEN1' and the Pubmed database (http://www.pubmed.org/)

using the keywords 'MEN1 KOREA' from 2000 to 2012. The journals without mutational data were excluded. After reviewing the journals, the clinical characteristics and mutational data were summarized. We checked the pedigree of the cases to rule out people from the same family. The mutational types were rechecked using sequencing data graphs and renamed according to the standard recommended nomenclature.(*4,5*)

RESULTS

We found 12 journal articles about *MEN1* mutation in Korea. Among them, 3 articles had no mutational data. Total 9 articles reported *MEN1* mutation. Eight articles were case reports and one article reported 4 cases of MEN-1. After comparison of pedigree, there was no repeated case. A total of 12 cases of *MEN1* mutations in Korea were reported (Table 1).

Two cases were sporadic MEN-1. Eleven cases had

Table 1. Clinical characteristics of MEN-1 cases in the literature review

Case	Sex	Age	Familial	Pedigree	Parathyroid tumor	Entero-pancreatic tumor	Pituitary tumor	Other
1	N/R*	N/R	Familial	Yes	(-)	Multiple somatostatinoma	Prolactinoma	
2	N/R	N/R	Sporadic		Multiple	Multiple non-functioning	Microadenoma	
3	N/R	N/R	Familial	Yes	Multiple	Multiple gastrinoma	Prolactinoma	
4	N/R	N/R	Sporadic		Tumor	Insulinoma	Prolactinoma	
5	M	42	Familial	Yes	Single	Gastrinoma/glucagonoma	Prolactinoma	
6	F	22	Familial		Tumor	Multiple insulinoma	Prolactinoma	
7	M	70	Familial		Tumor	VIPoma	(-)	
8	M	52	Familial	Yes	Multiple	Non-functioning	(-)	Adrenal mass
9	F	26	Familial	Yes	Multiple	Multiple insulinoma	(-)	
10	F	50	Familial		Multiple	Non-functioning	Non-functioning	Leiomyoma
11	F	42	Familial		Ectopic	(-)	(-)	Papillary thyroid cancer
12	F	23	Familial	Yes	Single	Multiple insulinoma	Non-functioning	

*Not Reported.

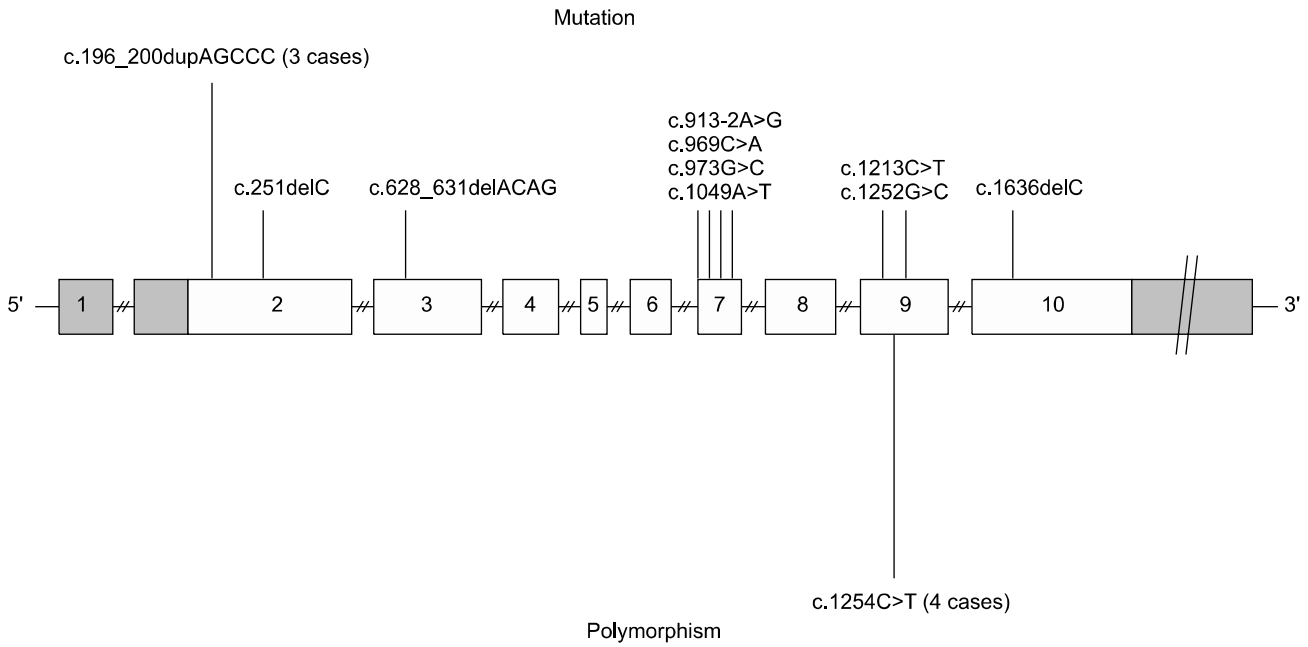

Fig. 1. Schematic representation of the *MEN1* gene. The upper part is the mutation and the lower part is the polymorphism. The length of the vertical line indicates the frequency of mutations. The shaded areas of exon 1 and part of exon 2 and 10 are non-translating regions.

Table 2. Germline mutations of MEN-1 cases in the literature review

Case	Exon	Codon	Original designation	New nomenclature	Mutation type	Effect	Previous report	Preclinical screening	Polymorphism	Ref
1	9	405	1213C>T	c.1213C>T	Nonsense	Q405X		Yes	c.1254C>T (homozygote)	(*10*)
2	2	66-67	200-201insAGCCC	c.196_200dupAGCCC	Frameshift	Stop at codon 120			c.1254C>T (homozygote)	(*10*)
3	7	325	973G>C	c.973G>C	Missense	A325P	No		c.1254C>T (heterozygote)	(*10*)
4	7	323	969C>A	c.969C>A	Nonsense	Y323X				(*10*)
5	Intron 6		1023A>G	c.913-2A>G	Splicing mutation		No	Yes		(*7*)
6	2	66-67	200-201insAGCCC	c.196>200dupAGCCC	Frameshift	Stop at codon 120				(*11*)
7	9	418	Codon 383 GAC>CAT	c.1252G>C	Missense	D418H		Yes	c.1254C>T (heterozygote)	(*8*)
8	2	66-67	200-201insAGCCC	c.196>200dupAGCCC	Frameshift	Stop at codon 120		Yes		(*12*)
9	3	210-211	628_631delACAG	c.628_631delACAG	Frameshift	Stop at codon 229		Yes		(*13*)
10	7	350	1159A>T	c.1049A>T	Missense	D350V	No			(*3*)
11	10	546	c.1652delC	c.1636delC	Frameshift	Stop at codon 558	No			(*9*)
12	2	84	c.251delC	c.251delC	Frameshift	Stop at codon 118	No			(*14*)

parathyroid and entero-pancreatic tumors. Four cases had no history of pituitary tumors. Case 11 was familial hyperparathyroidism without history of entero-pancreatic or pituitary tumors. The pedigrees were available in 6 cases.

In the position of mutation, four mutations were in exon 2, three in exon 7, two in exon 9 and one mutation in exon 3, 10 and intron 6 (Fig. 1). In the type of mutation, frameshift mutation was 6 cases, missense mutation was 3 cases, nonsense mutation was 2 cases and splice site mutation was one case. C.196_200dupAGCCC was reported in three families (case 2, 6 and 8). Five mutations (c.973G>C, c.913-2A>G, c.1049A>T, c.1636delC, c.251delC) had not been reported previously. The preclinical *MEN1* screening of offspring was not popular and only 5 families (case 1, 5, 7, 8 and 9) performed preclinical screening (Table 2).

In cases 1, 2, 3 and 7, a polymorphism (c.1254C>T, D418D) was found in exon 9. The polymorphism was homozygote in cases 1 and 2 and heterozygote in cases 3 and 7.

DISCUSSION

There were 1,133 germline mutations and 203 somatic mutations reported in the *MEN1* gene.(*5*) If the same mutations are excluded, there were 459 different mutations and 167 somatic mutations. Because 61 mutations included both germline and somatic mutations, 565 different mutations were reported. Germline mutations were distributed throughout 1,830 base pairs coding regions and consisted of 41% frameshift mutations, 23% nonsense mutations, 20% missense mutations, 9% splice site mutation, 6% in-frame deletion or insertion, and 1% whole or partial gene deletion.(*5*) This study also showed similar rates of mutational types.

There was no hot spot in *MEN1* mutations. However the frequency of c.249_252delGTCT in exon 2 codon 83-84 was 4.5%, c.628_631delACAG in exon 3 codon 210-211 was 2.5%, c.1378C>T in exon 10 codon 460 was 2.6% and c.1546_1547insC in exon 10 codon 516 was 2.7%. These four mutations comprised 12.3% of all *MEN1* mutations.

The mutation of c.196_200dupAGCCC was reported in

three Korean families (cases 2, 6 and 8), so there was a possibility of a founder mutation in Korea. Even though case 2 was sporadic, the pedigree of case 2 and 6 were not reported. So we could not confirm they were different families.

About 10% of the *MEN1* mutations occur without a family history.(*6*) In this study, 2 cases (case 2 and 4) had no family history. Family history was absent because both parents had already died in case 2 and the pedigree was not available in case 4. So we could not confirm they were *de novo* mutation.

It is known that there are 24 polymorphisms in the *MEN1* gene.(*5*) We found c.1254C>T polymorphisms in four Korean cases; two cases were heterozygote and two cases were homozygote. The frequency of c.1254C>T polymorphism has been reported as 42%.(*5*) Polymorphism should not be confused with mutations and this distinction might be helpful in segregation analysis in cases where the *MEN1* mutation is not found.(*5*)

In 2001, a new nomenclature system has been suggested for the description of mutations and polymorphisms.(*4*) Because 110 base pairs of exon 2 are not translated, the base pair number starts from the 111th nucleic acids. So the number of base pairs of the new system is smaller than that of the old system by 110.

We rechecked the sequencing data graphs of previous reports and found some mistakes. Because 1023A>G of exon 7 (*7*) was a splice site of exon 7, we thought it should be described as c.913-2A>C. Because GAC>CAT of codon 383 (*8*) was a codon 418 and c.1254C>T was a polymorphism, c.1252G>C was thought to be correct. The deletion of cytosine at the 1,652th nucleic acid of codon 551 (*9*) was deletion at the 1,636th nucleic acid of codon 546. Therefore, special efforts need to be taken to avoid making a mistake in the interpretation of the sequencing data graphs.

The *RET* gene test was included in the guidelines of the treatment of medullary thyroid cancer because of its usefulness in the prevention by prophylactic thyroidectomy.(*1*) However MEN-1 patients have malignancy less commonly, and only in the entero-pancreatic tumors. So the *MEN1* gene test is less clinically useful than the *RET* gene test.

If patients are suspected clinically to have MEN-1, a genetic study can confirm the diagnosis. If the *MEN1* mutation is found, a genetic study can diagnose MEN-1 in the offspring preclinically. Although prophylactic surgery is not possible in MEN-1, a negative genetic study indicates the person is free of disease and no more biochemical and radiological tests are needed. So the *MEN1* gene study is useful in the exclusion of the disease and will reduce the psychological stress of the patient.

In conclusion, we summarized the characteristics of germline *MEN1* mutations in Korea. Genetic tests of *MEN1* were rare in Korea but it will be useful in preclinical diagnosis and genetic counseling.

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