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Genetic Landscape and Clinical Manifestations of Multiple Endocrine Neoplasia Type 1 in a Korean Cohort: A Multicenter Retrospective Analysis

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Background: Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterized by tumors in multiple endocrine organs, caused by variants in the *MEN1* gene. This study analyzed the clinical and genetic features of MEN1 in a Korean cohort, identifying prevalent manifestations and genetic variants, including novel variants.

Methods: This multicenter retrospective study reviewed the medical records of 117 MEN1 patients treated at three tertiary centers in Korea between January 2012 and September 2022. Patient demographics, tumor manifestations, outcomes, and *MEN1* genetic testing results were collected. Variants were classified using American College of Medical Genetics and Genomics (ACMG) and French Oncogenetics Network of Neuroendocrine Tumors propositions (TENGEN) guidelines.

Results: A total of 117 patients were enrolled, including 55 familial cases, with a mean age at diagnosis of 37.4±15.3 years. Primary hyperparathyroidism was identified as the most common presentation (84.6%). The prevalence of gastroenteropancreatic neuroendocrine tumor and pituitary neuroendocrine tumor (PitNET) was 77.8% (n=91) and 56.4% (n=66), respectively. Genetic testing revealed 61 distinct *MEN1* variants in 101 patients, with 18 being novel. Four variants were reclassified according to the TENGEN

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guidelines. Patients with truncating variants (n=72) exhibited a higher prevalence of PitNETs compared to those with non-truncating variants (n=25) (59.7% vs. 36.0%, P=0.040).

Conclusion: The association between truncating variants and an increased prevalence of PitNETs in MEN1 underscores the importance of genetic characterization in guiding the clinical management of this disease. Our study sheds light on the clinical and genetic characteristics of MEN1 among the Korean population.

Keywords: Multiple endocrine neoplasia; Multiple endocrine neoplasia type 1; Genotype; Phenotype; Variant; Multicenter; Korea

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder characterized by the development of tumors in multiple endocrine organs, including the parathyroids, pancreatic islets, anterior pituitary (3Ps), and others [1,2]. This disorder is caused by variants in the *MEN1* gene at locus 11q13.1 [3], which encodes menin, a 610-amino-acid protein expressed ubiquitously with nuclear localization. Menin acts as a tumor suppressor, and functions in transcriptional and epigenetic regulation [4]. Its loss-of-function leads to the enhanced proliferation of endocrine cells. MEN1 syndrome exhibits a high degree of penetrance, with nearly all variant carriers manifesting clinical symptoms by the age of 50 [5]. However, the phenotype of this disease can vary significantly among individuals, even among those within the same family, suggesting that additional genetic, epigenetic, or environmental factors may influence disease severity [6,7].

The prevalence of MEN1 is estimated at 1 to 3 in 100,000 individuals worldwide, but the incidence may be underreported due to its rarity and wide spectrum of clinical presentations [8]. The diagnosis of MEN1 is challenging and is based on clinical, familial, and genetic criteria. The primary clinical criterion is the occurrence of two or more MEN1-associated endocrine tumors, familial criterion is the occurrence of one of the MEN1-associated tumors with a first-degree relative with MEN1, and genetic criterion is the identification of a germline *MEN1* variant [9,10].

To date, over 1,500 variants have been identified spanning the entire *MEN1* gene [11]. Despite advances in genetic testing, the interpretation of these *MEN1* variants remains complex due to their large diversity and their variable impact on protein function. In 2019, the French Oncogenetics Network of Neuroendocrine Tumors (TENGEN) proposed specific adjustments to the American College of Medical Genetics and Genomics (ACMG) guidelines for *MEN1*, aimed at improving the accuracy of variant classification [12].

Korea, like other countries, faces challenges in diagnosing and managing MEN1 due to its rarity and the complexity of its genetic basis. Previous studies on the clinical and genetic characteristics of MEN1 in Korea have been small-scale and limited to single-center case series [13-16]. This present study bridges this gap by analyzing the clinical and genetic features of MEN1 patients in Korea through a multicenter approach. It specifically examined the distribution of *MEN1* variants and their correlation with clinical presentations, in alignment with the recent TENGEN proposition for interpreting *MEN1* variants.

METHODS

Study subjects

We included 117 patients diagnosed with MEN1 at tertiary centers including Seoul National University Hospital, Seoul National University Bundang Hospital, and Asan Medical Center in Korea between January 2012 and September 2022. Patients were included if they were diagnosed with MEN1 based on the clinical criteria set forth by the international guidelines for MEN1, had a familial occurrence of the disease, or identified with a pathogenic variant (PV) in the *MEN1* gene [10]. Clinical data were reviewed from electronic medical records, including sex, age, family history of MEN1, initial symptoms, timing of diagnosis, *MEN1* genetic testing results, clinical manifestation, and medical and surgical management. A patient who was identified at first in a family was named index case and a patient who was identified consequently was defined as relative case. A familial case was defined as a patient with at least one first-degree relative with MEN1, whereas a sporadic (non-familial) case was defined by the lack of any family history of the syndrome [10]. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB no.2209-146-1362), followed by the other participating centers. The requirement for informed consent was waived due to the retrospective nature of the study and patient data was anonymized and de-identified prior to analysis.

MEN1 variant analysis

Genetic testing of *MEN1* gene was conducted on genomic DNA extracted from peripheral blood samples of patients using PCR-based Sanger sequencing and/or multiplex ligation-dependent probe amplification in accordance with international standards [10]. All variants were described using the reference transcript, NM_130799.2, and classified according to the recommendations of the Human Genome Variation Society nomenclature. Each identified variant was reviewed and then reclassified following the ACMG guidelines and the TENGEN proposal [12,17]. The distribution and frequency of the identified *MEN1* variants were visually presented using ProteinPaint [18,19].

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical data, mean and standard deviation for continuous variables, and frequencies for categorical variables. Independent *t* tests or the Mann-Whitney *U* test were applied to the analysis of continuous variables, while either the chi-squared test or Fisher's exact test was used for categorical variables as appropriate. The significance of the differences in clinical presentations between familial and sporadic cases, as well as correlations between genetic variants and clinical features, were evaluated. We divided the variants into two groups whether they produce shorter protein, truncating (nonsense, frameshift, canonical splice site, and large deletion) or non-truncating, and analyzed the differences of these groups. All tests were two-tailed, with *P* values <0.05 con-

Table 1. Clinical Characteristics of Korean Patients with Multiple Endocrine Neoplasia Type 1

Characteristic	All (*n*=117)	Familial case (*n*=55)	Sporadic case (*n*=62)	*P* value
Female sex	70 (59.8)	36 (65.5)	34 (54.8)	0.242
Age, yr	45.7±15.5	43.8±17.3	47.4±13.5	0.277
Age at MEN1 diagnosis	37.4±15.3	34.8±16.9	39.6±13.4	0.089
MEN1 variant	97 (82.9)	49 (89.1)	48 (77.4)	0.058
PHPT	99 (84.6)	42 (76.4)	57 (91.9)	0.020
First manifestation	72 (61.5)	32 (58.2)	40 (64.5)	0.696
GEP-NET	91 (77.8)	39 (70.9)	52 (83.9)	0.092
First manifestation	26 (22.2)	14 (25.4)	12 (19.4)	0.533
Nonfunctioning	59	29	30	
Gastrinoma	9	2	7	
Insulinoma	19	7	12	
Somatostatinoma	1	1	0	
Unknown	3	0	3	
Pituitary NET	66 (56.4)	30 (54.5)	36 (58.1)	0.702
First manifestation	18 (15.4)	8 (14.6)	10 (16.1)	1.000
Nonfunctioning	23	13	10	
Prolactinoma	30	13	17	
Acromegaly	3	2	1	
Cushing	4	2	2	
Unknown	6	0	6	
Thymic NET	9 (7.7)	4 (7.3)	5 (8.1)	1.000
Adrenal tumor	16 (13.7)	6 (10.9)	10 (16.1)	0.374
Nonfunctioning	15	6	9	
Functioning	1	0	1	
Death	4 (3.4)	3 (5.5)	1 (1.6)	0.341

Values are expressed as number (%) or mean±standard deviation.
MEN1, multiple endocrine neoplasia type 1; PHPT, primary hyperparathyroidism; GEP-NET, gastroenteropancreatic neuroendocrine tumor; NET, neuroendocrine tumor.

sidered statistically significant. All statistical analyses were conducted using SPSS version 28.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Clinical characteristics of the MEN1 patients

A total of 117 patients were included in the study cohort, of which 84 were index cases and 33 were relative cases (Table 1). Familial cases accounted for 47.0% of the population (55/117), while sporadic cases constituted 53.0% (62/117). The cohort exhibited a female predominance of 59.8% (70/117). The mean age at MEN1 diagnosis was 37.4±15.3 years (range, 3 to 74). Primary hyperparathyroidism (PHPT) emerged as the most prevalent clinical manifestation, observed in 84.6% (99/117) of the patients, with a significant difference noted between familial and sporadic cases (76.4% vs. 91.9%, P=0.020). Gastroenteropancreatic neuroendocrine tumors (GEP-NET) and pituitary neuroendocrine tumors (PitNET) were the next most common, occurring in 77.8% (91/117) and 56.4% (66/117) of the patients, respectively. The mean age of diagnosis was 38.8 years in PHPT, 34.8 years in GEP-NET, and 40.4 years in PitNET, respectively. Among all and index cases, 40.2% (47/117) and 42.9% (36/84) presented the classic triad of PHPT, GEP-NET, and PitNET (Fig. 1). Thymic and adrenal tumors were less frequently observed, in only 7.7% and 13.7% of the patients, respectively. Additionally, four female patients developed breast cancer which has been recently suggested as an MEN1-related tumor. Notably, 3.4% (4/117) of the patients died in their 50s or 60s due to advanced thymic NET (two cases) or GEP-NET (two cases).

Genetic features of MEN1

MEN1 variants were identified in 92.7% of familial cases and in 80.6% of sporadic cases. Of the 117 patients in the total cohort, 97 (82.9%) harbored PV or likely pathogenic variants (LPV) of *MEN1* (Supplemental Table S1). Three variants (c.235_252del, c.484G>T, and c.694C>T) were classified as variants of uncertain significance (VUSs). Based on the TENGEN recommendations, we were able to reclassify four VUS to LPV (c.442A>C, c.818T>C, c.1253A>G, and c.1663A>T) and two LPV to PV (c.824G>A and c.830C>T). A total of 61 variants were detected in 101 patients across the *MEN1* gene (Fig. 2). Twenty-one frameshift (34.4%), 12 nonsense (19.7%), 18 missense (29.5%), five splice site (8.2%), three inframe deletion (4.9%), one large deletion (1.6%), and one intronic variant (1.6%) were detected (Fig. 3). Notably, 18 variants including one VUS (c.235_252del) had not been reported previously, thereby expanding the known

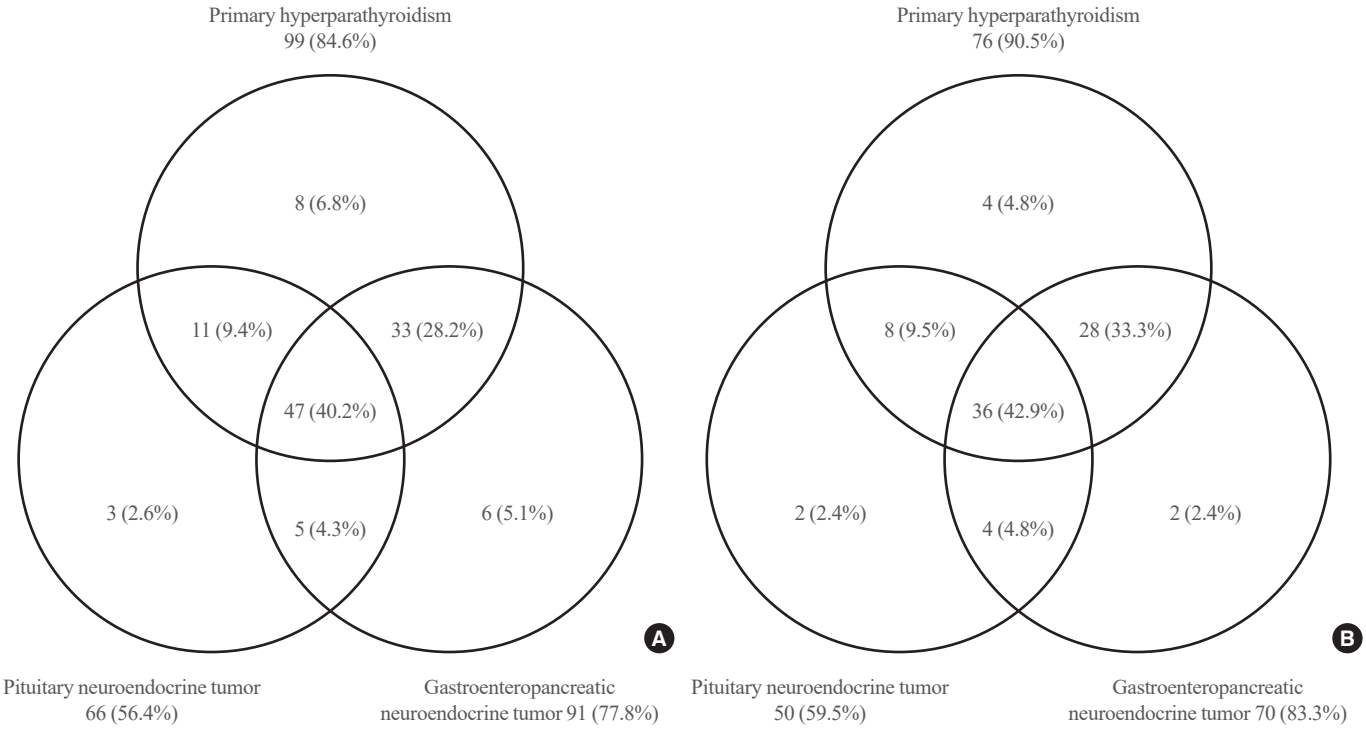

Fig. 1. Prevalence of the primary hyperparathyroidism, gastroenteropancreatic and pituitary neuroendocrine tumor triad among (A) the total multiple endocrine neoplasia type 1 (MEN1) cohort (n=117) and (B) the index cases (n=84).

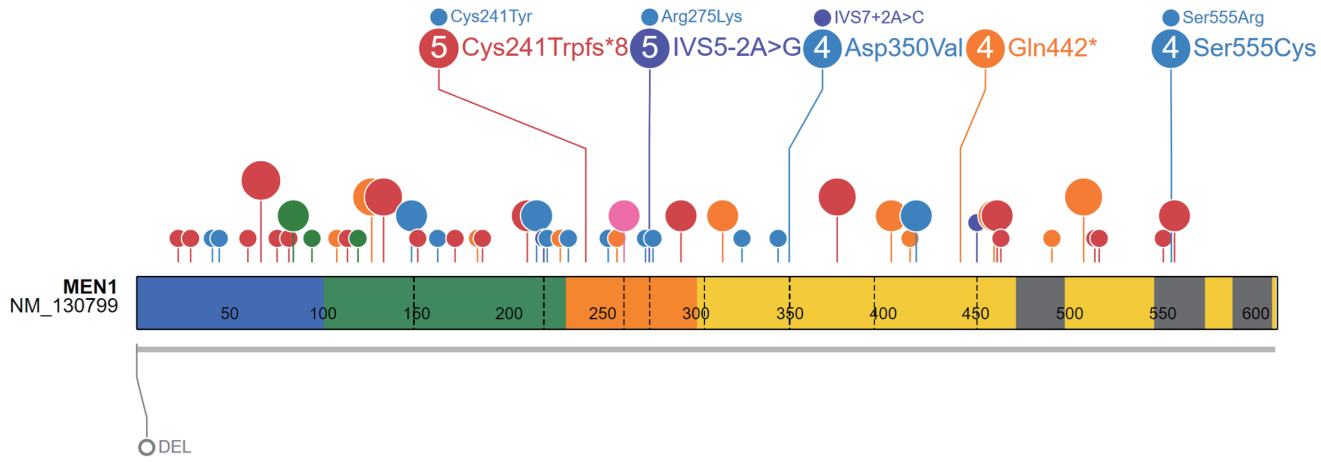

Fig. 2. Distribution of multiple endocrine neoplasia type 1 (*MEN1*) variants in the study cohort. The number of patients with each variant is indicated by the number within each circle, as well as circle size. Red, frameshift; orange, nonsense; green, in frame deletion; blue, missense; purple, canonical splice site; pink, intronic; gray, large deletion.

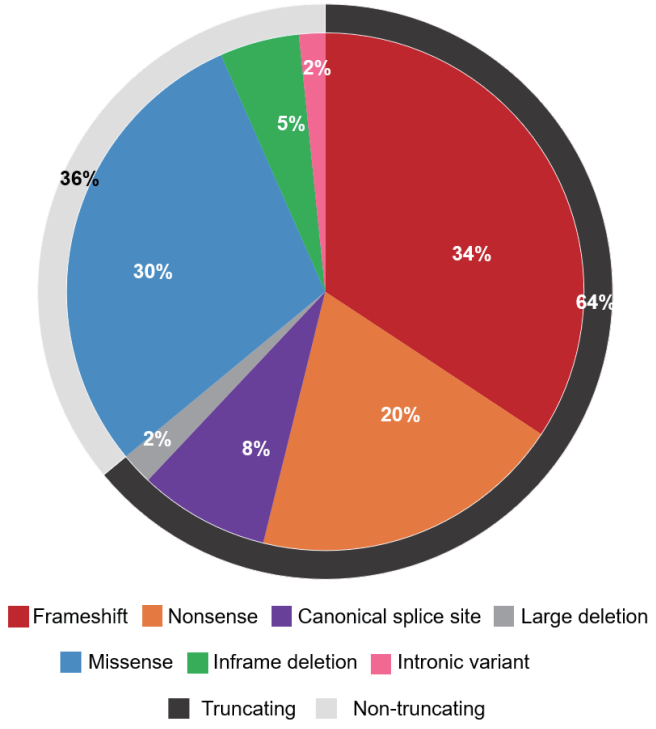

Fig. 3. Frequency of the types of multiple endocrine neoplasia type 1 (*MEN1*) variants in the study cohort (n=61).

genetic landscape of MEN1.

Phenotype and genotype correlations

We divided the study patients with PV/LPV of *MEN1* into two groups according to variant type, i.e., non-truncating and truncating. Patients who had truncating variants were presenting 3Ps more than those who had non-truncating variants but without statistical significance (P=0.065). There was no significant difference in age at diagnosis between these two groups (Table 2). In addition, no statistical correlations were evident between variant types and clinical presentations except for PitNET, the prevalence of which was higher in the patients with truncating variants (P=0.040). There was no statistical correlation found between the functionality of pitNET or GEP-NET and variant type (P=0.692 and P=0.776).

DISCUSSION

This study delineated the clinical and genetic characteristics of MEN1 within a Korean population. Our findings highlight PHPT as the most prevalent clinical presentation among MEN1 patients, consistent with global observations. The identification of 61 *MEN1* variants, including 18 novel variants, underscores the genetic diversity of this condition and expands the existing spectrum of known *MEN1* variants. Notably, our phenotype-genotype correlation analysis revealed a significant association between truncating variants and the presence of PitNETs, suggesting potential insights into disease pathogenesis and clinical management.

Although familial cases have been reported to represent about 90% of MEN1 patients [20], our cohort showed less familial cases than sporadic cases. This is likely due to a failure to recognize the disorder within families or a poor work-up of family members [21]. *MEN1* variant analysis should be recommended in index cases who meet the clinical criteria or are suspects of

Table 2. Clinical Characteristics of the 97 Study Patients with *MEN1* Pathogenic or Likely Pathogenic Variants

Characteristic	All (*n*=97)	Non-truncating variant (*n*=25)	Truncating variant (*n*=72)	*P* value
Female sex	59 (60.8)	17 (6.8)	42 (58.3)	0.394
Age, yr	45.4±15.7	49.0±13.3	44.1±16.4	0.175
Age at MEN1 diagnosis	36.9±15.4	41.8±15.1	35.1±15.3	0.061
Family history	49 (50.5)	10 (40.0)	39 (54.2)	0.222
PHPT	83 (85.6)	20 (80.0)	63 (87.5)	0.344
GEP-NET	76 (78.4)	19 (76.0)	57 (79.2)	0.740
Nonfunctioning	48	11	37	
Gastrinoma	8	2	6	
Insulinoma	16	5	11	
Somatostatinoma	1	0	1	
Unknown	3	1	2	
Pituitary NET	52 (53.6)	9 (36.0)	43 (59.7)	0.040
Nonfunctioning	18	4	14	
Prolactinoma	23	2	21	
Acromegaly	3	1	2	
Cushing disease	3	1	2	
Unknown	5	1	4	
Thymic NET	5 (5.15)	1 (4.0)	4 (5.6)	1.000
Adrenal tumor	13 (13.4)	5 (20.0)	8 (11.1)	0.317
Nonfunctioning	12	5	7	
Functioning	1	0	1	
Death	3 (3.1)	0	3 (4.2)	0.567

Values are expressed as number (%) or mean±standard deviation.
MEN1, multiple endocrine neoplasia type 1; PHPT, primary hyperparathyroidism; GEP-NET, gastroenteropancreatic neuroendocrine tumor; NET, neuroendocrine tumor.

this diagnosis, and first-degree relatives of MEN1 should be analyzed as soon as possible, including children [10].

Comparing our present result with international cohorts reveals both similarities and unique aspects of MEN1 among the Korean population. The mean age at diagnosis was 37.4 years similar to previous studies [21]. The age at diagnosis was older in sporadic cases than in familial cases (39.6 years vs. 34.8 years), but this difference was not significant. Like studies from Europe and North America, PHPT emerged as the dominant clinical feature, affirming its role as a central component of the MEN1 clinical spectrum. However, the incidence of PHPT in our present study population (84.4%) was relatively lower than in another prior study, which reported a frequency more than 93% of MEN1 patients [8]. This discrepancy might be attributable to the underdiagnosis of PHPT. In MEN1-related PHPT, the degree of hypercalcemia was lower than in sporadic PHPT, and surgical decisions were made more conservatively. Notably also, the prevalence of PHPT in sporadic cases was higher than that in familial cases, implying that patients diagnosed with PHPT at a young age had undergone more aggressive investigations for MEN1.

GEP-NET was identified in 77.8% of our subjects, slightly higher than the 55% to 70% range reported in other studies of MEN1 cases [8,22]. Consistent with previous research, nonfunctioning GEP-NETs were the most common type in our current cohort, accounting for 67% of cases. However, among functioning GEP-NETs, insulinoma was the most common type (21%) in contrast to other prior reports where gastrinomas predominated (21% to 70%). PitNETs were present in 56% of our current study patients, exceeding the 40% to 47.5% range reported in previous studies [8,22]. Similarly, 56.4% of our present cohort had PitNETs, with prolactinomas (*n*=30, 45.4%) being the most frequent, followed by nonfunctioning PitNETs (*n*=23, 34.8%). Thymic NETs occurred in 7.7% of our group, aligning with the

2.0% to 8.2% range noted in earlier research [8,23]. Ye et al. [23] reported in this regard that Asians exhibit a similar sex ratio (59.5%), whereas American/Europeans showed a male predominance (91.9%). Although variants in the JunD interacting domain are known to be associated with thymic NETs and poor outcomes [24], we here observed no specific correlation between genetic variants and thymic NETs.

The ACMG guidelines are universal for Mendelian diseases but have notable limitations in terms of their nonspecificity for these diseases. ClinGen has therefore been more recently trying to develop gene-specific and disease-specific guidelines [25]. We thus adopted TENGEN recommendations for our variant interpretations in relation to *MEN1* and thereby reclassified four missense variants in 11 patients. Of note, in particular, four VUS in nine patients were reclassified as LPVs and this could change the management of these patients in terms of cancer surveillance or family studies. The reclassification of variants via a gene-specific adjustment is therefore to be highly encouraged. We further identified 18 novel variants in our current analyses which underscores the importance of regional genetic studies in capturing the full genetic diversity of MEN1. The diversity of *MEN1* variant types, including frameshift, nonsense, and missense variants, aligns with global data, reinforcing the complex mutational landscape of the gene.

According to diagnostic criteria, nearly 90% of individuals who exhibit classic MEN1 symptoms have identifiable variants in the *MEN1* gene. Nonetheless, approximately 10% of families with MEN1 do not show any molecular alterations in this gene. In our present cohort, 13.7% of the patients (n=16) presented with a typical MEN1 phenotype but did not show any variants in the *MEN1* gene. These negative results from a genetic testing standpoint could be attributed to several factors, including the presence of undetectable variants with current testing methods, the existence of genetic mosaicism, or variants in other genes that are phenocopies of *MEN1*. Moreover, the current Sanger sequencing method does not detect deep intronic variants. In addition to this, Coppin et al. [26] have previously reported 12 cases with *MEN1* mosaicism with an allele frequency of between 2.3% and 15% using next-generation sequencing. Patients with mosaicism for MEN1 display a phenotype similar to that of a heterozygous PV in the *MEN1* gene. Phenocopies can also be a reason for negative genetic tests. Recently, cases of MEN4 caused by loss-of-function variants in cyclin dependent kinase inhibitor 1B (*CDKN1B*) gene (OMIM#610755) were identified that had similar phenotypes to MEN1 [27]. In addition, *CDKI* (*CDKN1A, 1B, 2A, 2C*), cell division cycle 73 (CDC73), calcium-sensing receptor (*CASR*), adaptor related protein complex 2 subunit sigma 1 (*AP2S1*), G protein subunit alpha 11 (*GNA11*), glial cells missing transcription factor 2 (*GCM2*), RE1 silencing transcription factor (*REST*), and aryl hydrocarbon receptor-interacting protein (*AIP*) variants can mimic MEN1-like diseases [28]. Hence, performing more comprehensive genetic analyses, including whole exome or whole genome sequencing, is necessary in MEN1 cases with negative genetic testing results.

MEN1 is known for having no genotype-phenotype correlation. However, some reports have demonstrated an association between variant types and clinical presentation. In our current cohort, PitNET was found to be associated with *MEN1* truncating variants. Similarly, PitNET has been reported to present a higher risk in Polish patients with *MEN1* frameshift variants [29]. Other studies have shown that the prevalence of GEP-NET was higher in patients with frameshift variants [30,31]. These findings support the possibility that *MEN1* variant types and clinical phenotypes may have associations, and further studies are needed. To the best of our knowledge, this is the first multicenter cohort study of MEN1 in a Korean population. In the case of rare diseases, including MEN1, it will be important in the future to establish a national cohort to better understand the clinical and epidemiological aspects of this syndrome [21,32]. Our present study could serve as a starting point for establishing the Korean MEN cohort.

Our study had several limitations of note. The retrospective design and the use of de-identified data restricted our ability to provide detailed descriptions for all patients including the detailed information for each tumor and other tumors accompanying MEN1, such as skin tumors and other non-endocrine tumors. In addition, patients who were lost to follow-up might have developed other clinical presentations not observed in our hospitals. Due to the small sample size, we had analyzed the clinical phenotype not according to the disease severity or clinical outcomes, but variant type. In cases with negative genetic testing results, whole exome sequencing or genome sequencing was not conducted. Hence, *MEN1* mosaicism, deep intronic variants, and other types of variations with phenocopies such as *CDKN1B* gene could exist.

In conclusion, our study sheds light on the clinical and genetic characteristics of MEN1 among the Korean population, revealing both commonalities and unique aspects in comparison to global cohorts. These insights underscore the importance of genetic analysis in the diagnosis and management of MEN1, and advocate for comprehensive and multidisciplinary approaches to treating this multifaceted disease.

CONFLICTS OF INTEREST

Jung Hee Kim is a deputy editor of the journal. But she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Conception or design: M.W.S., J.H.K. Acquisition, analysis, or interpretation of data: B.K., S.H.L., C.H.A., H.N.J., S.I.C., J.S.L., Y.M.L., S.J.K., T.Y.S., K.E.L., W.L., J.M.K., M.W.S., J.H.K. Drafting the work or revising: B.K., S.H.L., M.W.S., J.H.K. Final approval of the manuscript: B.K., S.H.L., M.W.S., J.H.K.

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