A large Turkish pedigree with multiple endocrine neoplasia type 1 syndrome carrying a rare mutation: c.1680_1683 del TGAG

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ABSTRACT

Background/Aims: Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant syndrome characterized by tumors arising from endocrine glands with no specific genotype-phenotype correlation. Here, we report the largest Turkish kindred with MEN1 syndrome which inherited a scarce MEN1 mutation gene.

Materials and Methods: A 64-year-old man, referred to our gastroenterology outpatient clinic for evaluation of a pancreatic mass lesion, was diagnosed with MEN1 syndrome after endoscopic ultrasound-guided sampling of the mass revealed pancreatic neuroendocrine tumor (pNET) and accompanying primary hyperparathyroidism (PHPT) and pituitary tumor. Genetic analysis by whole gene Sanger sequencing of the MEN1 gene identified a frame-shift mutation in exon 10 (c.1680_1683delTGAG). All the relatives of the index case were proposed for clinical and genetic evaluation for MEN1 syndrome.

Results: Of the 25 relatives of the index case, 17 were diagnosed with the MEN1 syndrome. Eighteen members among all relatives consented to genetic analysis, and 11 had the same mutation as the index case. All the mutation positive members had MEN1, while none of mutation-negative subjects had any sign of MEN1 syndrome. The frequencies of PHPT, pNET, and pituitary tumors in this kindred were 94.1% (16/17), 29.4% (5/17), and 29.4% (5/17) respectively.

Conclusion: We report a rare MEN1 gene mutation which has been descibed in a single sporadic patient earlier. It was inherited by at least three generations of a large family, proving the strong dominant effect of the MEN1 phenotype. Further research may be conducted to clarify potential candidacy of this mutation as a hotspot for MEN1 patients, especially in the Turkish population.

Keywords: Multiple endocrine neoplasia type 1, frame-shift mutation, endocrine gland neoplasms, pancreatic neuroendocrine tumor

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant syndrome characterized by combined tumors of the parathyroid glands, pancreas, and pituitary gland (1). The approximate prevalence of MEN1 has been reported as 1 in 30,000 individuals with no apparent gender bias, and with the widely used radiological imaging methods, even more patients may apply to gastroenterology outpatient clinics with pancreatic mass lesions. The main characteristic clinical features of MEN1 include at least two of the following three endocrine tumors in an individual: multiple parathyroid adenomas, anterior pituitary adenomas and entero-pancreatic neuroendocrine tumors (gastrinoma/Zollinger-Ellison syndrome and pancreatic neuroendocrine tumors) (2). Parathyroid tumors are the most common clinical manifestation and the prevalence of hyperparathyroidism is >90% in patients with MEN1, whereas pancreatic and pituitary tumors have a prevalence of 40-70% and 15-55% respectively (3-5). In addition to these main endocrine tumors that may cause relevant hormone excess, MEN1 patients may present other hormone-secreting, hormone non-secreting and non-endocrine tumors including adrenal cortical tumor, foregut carcinoids of the lung, thymus or gastric enterochromaffin-like cells, skin lesions such as facial angiofibroma, truncal collagenoma and lipoma, central nervous system tumors such as meningioma and ependymoma and smooth muscle tumors such as leiomyomas (5, 6).

Most of the inherited form of MEN1 is caused by germline mutations in the *MEN1* tumor suppressor gene linked to chromosomal locus 11q13 (7, 8). The *MEN1* gene, which was first identified in 1997, consists of 10 exons that encode the protein menin (9). Menin interacts with proteins involved in transcriptional regulation,

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genome stability, cell division and proliferation; however, its function is not fully understood (10). Heterozygous germline mutations of the *MEN1* gene have been identified in approximately 95% of familial MEN1 cases. Frame-shift mutations represent the highest rate with 42%, while the remaining are missense mutations (25.5%), nonsense mutations (14%), splicesite mutations (10.5%), inframe del/ins (5.5%), and gross deletions (2.5%) (11). To the best of our knowledge, more than 1600 mutations in *MEN1* gene and 1000 families presenting with MEN1 syndrome have been reported (12, 13), but penetrance of the mutation in large families could be demonstrated only in a small portion of them (14, 15). Analysis of vertical appearance of the MEN1 related tumors and *MEN1* mutation among generations in large families help us understand the syndrome better.

As with all familial cancer syndromes, genetic analysis is fundamental for prompt identification of asymptomatic mutation carriers within mutated kindreds before the appearance of any clinical or biochemical valuable alteration. However, a direct genotype-phenotype correlation from large series has not been identified in MEN1 (16-19). Herein, we report a large pedigree with multiple family members carrying the same rare mutation of the *MEN1* gene and consistently confirming typical MEN1 related tumors.

MATERIALS AND METHODS

Subjects and index case

The index case (III-8) was a 64-year-old man, who had suffered from fatigue, dizziness, and weight loss in the preceding four months, referred to our gastroenterology outpatient clinic for a suspicious pancreatic mass lesion.

MAIN POINTS

- *Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant syndrome characterized by combined tumors of the parathyroid glands, pancreas, and pituitary gland.*
- *Herein, we detected 17 patients with newly diagnosed MEN1 syndrome with all having the same frame-shift mutation in exon 10 (c.1680_1683delTGAG).*
- *All patients were relatives of an index case who referred to gastroenterology outpatient clinic for evaluation of a pancreatic mass lesion.*
- *We report a rare MEN1 gene mutation which has been described in a single sporadic patient earlier, and it was inherited by at least three generations of a large family, proving the strong dominant effect of the MEN1 phenotype.*

He had a family history of numerous parathyroid tumors and his sister had pancreatic neuroendocrine tumor (NET). Laboratory results showed mild hypercalcemia (Ca 10.8 mg/dL, reference range 8.5-10.5 mg/dL), and his subsequent neck magnetic resonance imaging (MRI) revealed parathyroid hyperplasia. Abdominal MRI revealed a 17×12 mm sized mass lesion in the distal part of the pancreas. Endoscopic ultrasound (EUS) was performed to clarify the pancreatic lesion and demonstrated a 19×12 mm sized, irregular, hypoechoic solid lesion in the tail of the pancreas. Cytological evaluation of the EUS-guided fine needle aspiration material confirmed the diagnosis of pancreatic NET. Subsequent Ga-68 DOTA-TATE PET-CT detected 18×14 mm sized lesion (SUVmax 14) in the distal part of pancreas without any other involvement. Cranial MRI, which was performed for further investigation of MEN-1-related endocrinopathies, revealed a pituitary non-functional 6 mm sized adenoma. He was diagnosed with MEN1 as he carried all the three main characteristic clinical features of the disease. Subsequently, he underwent total pancreatectomy for his pancreatic NET and parathyroidectomy which revealed PHPT.

After a careful study of the family history, a number of MEN1 related tumors were identified in the family members. Therefore, clinical screening and genetic counseling for MEN1 was offered to each member of the family. We contacted 28 of the 38 family members. Eighteen of them consented to participate in the genetic arm of the study, and blood samples were collected for *MEN1* mutation analysis along with their clinical data. For the clinical investigation, six more family members who did not participate in the genetic arm of the study and one deceased family member with a medical history suggestive of MEN1 were also included. A pedigree was constructed to draw the mutation and disease status (Figure 1).

Clinical approach

MEN1 was diagnosed according to: i) the presence of two or more primary MEN1-related endocrine tumors (parathyroid adenoma, enteropancreatic tumor, and pituitary adenoma) ii) individuals with at least one of the MEN1-associated tumors and a first-degree relative with MEN1 iii) individuals with the *MEN1* mutation who were asymptomatic and had not yet developed serum biochemical or radiological abnormalities indicative of tumor development (5). All the diagnosed or at-risk relatives were offered evaluation with radiological, biochemical and genetic tests for the main MEN1-related endocrine tumors and other clinical manifestations. Eventually, 25 family members were investigated clinically.

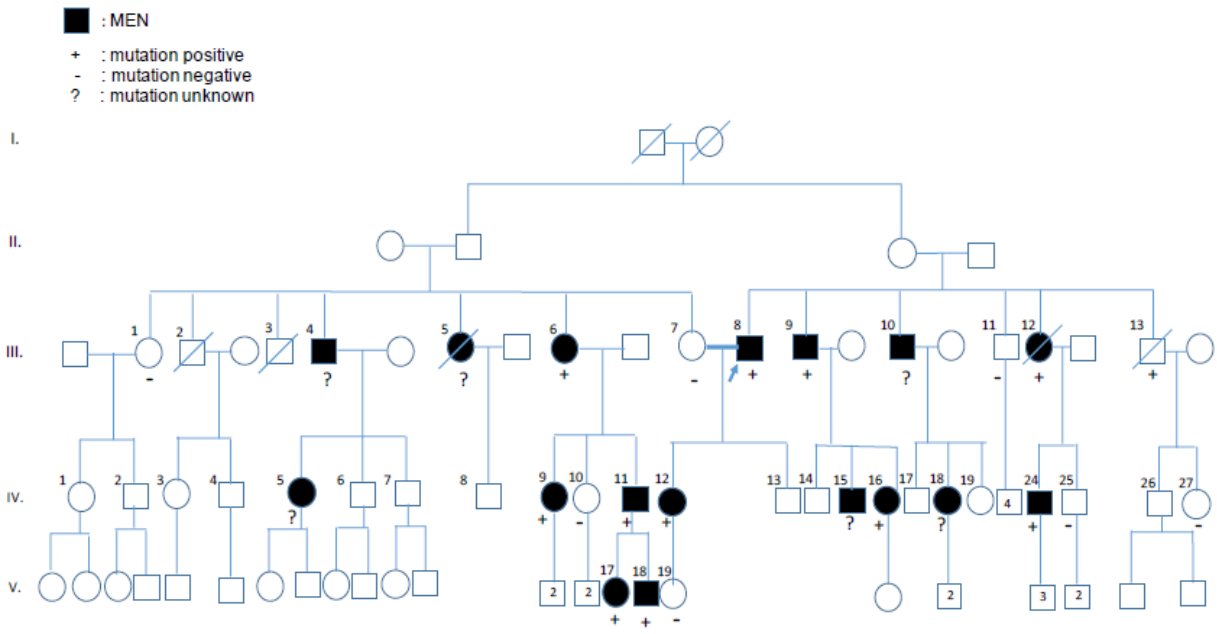

Figure 1. Pedigree of the family with MEN1 gene mutation.
* Individuals with MEN1 syndrome are indicated by solid symbols.
* The plus signs indicate mutation positive members and the arrow indicates the index patient.

Genetic approach and MEN1-gene analysis

Those family members who received genetic counseling and information and gave consent for *MEN1* gene mutation testing were included. The DNA was isolated from peripheral blood mononuclear cells using the Gentra genomic DNA isolation kit (Qiagene, Germany). After isolation, the quality and concentration of the DNA samples were analyzed with a Nanodrop spectrophotometer for purity. The index case (denoted with an arrow in the pedigree) was analyzed by whole gene Sanger sequencing of the *MEN1* gene (RefSeq number: NC_000011.10), and the relatives were investigated for the presence of that particular mutation p.ser560argfs*3(c.1680_1683 del TGAG) with Sanger sequencing analysis. The primers were established using primer 3, NCBI, IDT primer tools and their sequences were: forward 5-AAGCCTCCT-GGGACTGT-3 and reverse 5-GGTGGACACTTTCT-GCTTCT-3 (Figure 2). The PCR conditions for amplification of the *MEN1* gene were: 3 minutes of denaturation at 95°C with 35 cycles of 95°C for 20 seconds; annealing at 62°C for 20 seconds; elongation at 72°C for 30 seconds; and elongation at 72°C for 3 minutes. The resulting PCR amplicon was 234 nucleotides long. The amplicon was sequenced using a Big dye terminator kit and the GeneMapper program with ABI 310 Sanger Sequencer. With these techniques, 18 family members were genetically analyzed. In addition, *MEN1* sequencing analysis was performed on the pNET tissue of the deceased family member (III-12) using Illumina MiSeq (California, USA).

Ethics approval

Participants in this study were informed about the genetic study and its purpose. All adult participants gave written informed consent to participate in this study. For minors, consent was obtained from their legal guardians/parents. For the tissue analysis of the deceased family member, consent was obtained from her first-degree family member. This study was approved by the ethics committee of Marmara University, School of Medicine (Approval number: 09.2017.484, approval date: 14.07.2017).

Statistical Analysis

The analysis was primarily descriptive. Data were reported as number (%) of patients unless indicated otherwise. All statistical analyses were conducted using the Statistical Packages for the Social Sciences (SPSS) software version 20.0 (IBM Corp.; Armonk, NY, USA).

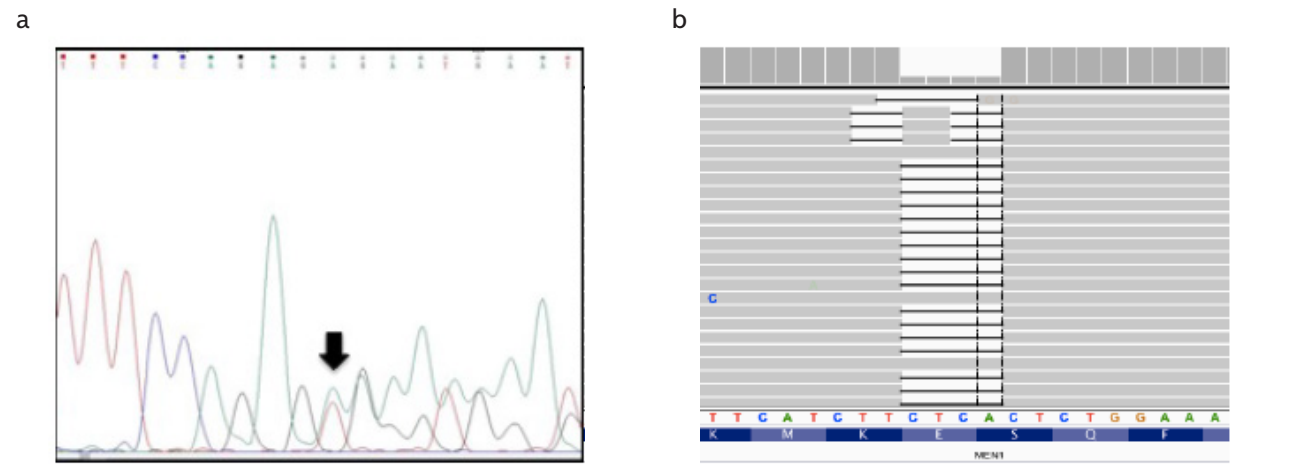

Figure 2. a, b. The Sanger Sequencing-forward strand (a) and Next Generation Sequencing-reverse strand (b) data of the MEN1 (RefSeq number: NC_000011.10) gene; heterozygous c.1665_1668delTGAG (p.Ser560Argfs) mutation.

RESULTS

Clinical features

The demographic data, clinical features, and mutational analysis results of all participants are summarized in Table 1. Twenty-five family members were evaluated for the presence of the MEN1 syndrome. Seventeen subjects were diagnosed with the MEN1 syndrome after clinical and genetic evaluation. Of these, 16 were diagnosed with PHPT and 6 of them were verified histologically after parathyroidectomy. The frequency of PHPT in the MEN1-affected family members was 94.1% (16/17). Pituitary tumor, including three prolactinomas and two non-functioning tumors, was found in five family members. Two of the prolactinoma cases required pituitary surgery due to unresponsiveness to dopamine agonists, and the other one was stable under medical treatment. Two non-functioning tumors were followed up with cranial MRI due to their small size. Pituitary tumors had a frequency of 29.4% (5/17) in the MEN1-affected family members. Pancreatic NET was detected in five family members using EUS-guided aspiration biopsy. Two of them underwent total pancreatectomy (III-8 and III-12), while the remaining three were followed up due to the small and stable size of their tumors on the subsequent abdominal MRIs. The occurrences of pituitary adenoma and pancreatic NET in family members with MEN1 were similar (29.4%). Only the index case (III-8) had all three main characteristic clinical features. Besides these, one prostate adenocarcinoma, one vaginal bartholin cyst, and one cervix nabothian cyst were found in the family members with MEN1. Eventually, of 25 investigated family members, 17 was diagnosed with MEN1.

Genetic analysis

Germline mutations of the *MEN1* gene were screened in 18 family members including the index case. A frame-shift mutation in codon 560 of exon 10 (c.1680_1683delTGAG) was identified in 10 members from the venous blood sample and one member (member III-12) from the post-mortem pancreatic tissue. This deletion mutation caused a frame shift and produced a premature termination codon (p.Ser560Argfs*3) in 11 family members. Of the 11 *MEN1* mutated patients, 9 PHPTs (81.8%), 5 pituitary adenomas (45.5%), and 4 pancreatic NETs (36.3%) were identified. Seven family members with an absent mutation did not exhibit any MEN1 related tumors.

DISCUSSION

In the present study, we identified a frame-shift mutation in exon 10 (c.1680_1683delTGAG) by performing whole gene Sanger sequencing of the *MEN1* gene in our index case who exhibited the main features of the syndrome. Thereafter, by demonstrating the presence of that particular mutation in 10 more family members with the MEN1 syndrome, we clearly showed the vigorous association of this rare mutation with the MEN1 syndrome. The 1680_1683delTGAG (p.Ser560Argfs*3) mutation has been reported only in one sporadic 46-year-old male patient from the Dutch MEN1 population who had hypercalcemia and thymus originated NET (16). Our index case and his wife were first-degree cousins; and the mu-

Table 1. Summary of the clinical features and mutational analysis of the family members.

	Age	Sex	PHPT	Pituitary adenoma	pNET	Other disorders	Mutation	MEN
III-1	65	F	-	-	-	-	-	-
III-4	69	M	+	-	-	Prostate cancer	unknown	+
III-5	77	F	+	-	+	Nephrolithiasis	unknown	+
III-6	79	F	+	-	-	Osteoporosis	+	+
III-7	59	F	-	-	-	-	-	-
III-8 *	69	M	+	+	+	-	+	+
III-9	68	M	+	-	-	-	+	+
III-10	65	M	+	-	-	Nephrolithiasis	unknown	+
III-11	75	M	-	-	-	-	-	-
III-12**	79	F	-	-	+	-	+	+
IV-5	47	F	+	-	-	Renal agenesis	unknown	+
IV-9	49	F	+	+	-	-	+	+
IV-10	48	F	-	-	-	-	-	-
IV-11	54	M	+	+	-	-	+	+
IV-12	42	F	+	-	+	Gastric polyp, vaginal bartholin cyst, cervix nabothian cyst	+	+
IV-13	34	M	-	-	-	-	-	-
IV-15	23	M	+	-	-	-	unknown	+
IV-16	32	F	+	-	-	-	+	+
IV-18	35	F	+	-	-	-	unknown	+
IV-24	54	M	+	-	+	-	+	+
IV-25	48	M	-	-	-	-	-	-
IV-27	53	F	-	-	-	-	unknown	-
V-17	33	F	+	+	-	-	+	+
V-18	34	M	+	+	-	-	+	+
V-19	8	F	-	-	-	-	-	-

*Index case
**Mutation detected from the pancreatic tissue.
PHPT: Primary hyperparathyroidism; pNET: pancreatic neuroendocrine tumor; MEN: Multiple endocrine neoplasia.

tation was spotted equally in the paternal and maternal relatives of our pedigree. Hence, the mutation was most likely inherited from the common grandparents of the index case and his wife. That common grandfather died from renal failure at a young age, which raised the suspicion of a possible unilluminated PHPT history. This study contributes to the literature by reporting the penetrance of an extremely rare germline mutation leading to MEN1 syndrome in a large kindred and affecting more than half of the family members.

Most of the mutations in the *MEN1* gene were found in exons 2, 9 and 10 (20). Our index case had a heterozygous frame-shift mutation at exon 10 that resulted in substitution of serine by arginine. Although exon 10 is a frequent site for *MEN1* mutations, codon 560 has not been reported earlier other than in the previous Dutch case. Herein, the present mutation causing a four-nucleotide deletion possibly resulted in truncated *MEN1* protein production, and product of this mutated gene had LoF (loss of function). The mutated *MEN1* protein cannot prevent tumorigenesis at the tissues where specifically it is expressed (21). Intensive penetration of the mutation described in three generations of this family gives strong evidence of the association of the mutation and its syndrome. Besides, the rarity of the mutation in healthy population also supports that causal relationship.

A number of recently published national MEN1 databases involving large patient populations described the differences in clinical expressions between families (16-19); yet a specific genotype-phenotype correlation is lacking. A specific genotype-phenotype correlation cannot be established for the present mutation either as the main endocrine gland tumor rates in this family were quite similar to the literature. The presence of the same mutation in all MEN1-affected members in this family, the heterogeneity between presentations, and tumors among relatives suggests polyclonal tumorigenesis triggered by a single mutation (22).

Current guidelines recommend analyzing the *MEN1* gene mutation in cases with two or more MEN1-associated endocrine tumors and in the first-degree relatives of a known *MEN1* mutation carrier. In patients presenting with a single MEN1 associated tumor, *MEN1* mutation analysis should be offered to those who present at an early age and have multiple lesions in the same gland. On the other hand, some suggest that genetic testing should be offered to the relatives of a patient with the *MEN1* mutation at an age as early as 5 years, prior to biochemical and radiological screening of the MEN1 associated tumors because genetic testing would help avoid the unnecessary screening procedures in mutation-negative cases. Individuals with the *MEN1* mutation are recommended for annual screening for MEN1-associated tumors (2, 23). In the light of this knowledge, we suggested that all the children in the present family with a mutation positive first-degree relative undergo *MEN1* genetic mutation analysis before the age of 5. Ten new cases were diagnosed with the MEN1 syndrome after clinical and genetic analysis based on the broad family history of parathyroid tumors in the family members of the index case. Nine PHPT, four pituitary tumors, and three pancreatic NETs were newly diagnosed in family members of different ages, including the index case himself.

The main limitation of our study is the lack of the genetic analysis of all the MEN1-affected participants of the family. We were not able to obtain genetic specimens from 7 of the 25 subjects due to their unwillingness to participate for genetic analysis and also because they lived in a distant area. Nevertheless, absence of the MEN1 syndrome in those who tested negative for the described mutation gives a clue about the causality of the mutation and the syndrome. The previous identification of this mutation in a single Dutch case prevented our findings from being interpreted as novel. However, the originality of the present study comes from the inheritance of this uncommon mutation in three generations of a large family with strong penetrance.

In conclusion, we report a large family carrying a frame-shift mutation in exon 10 (c.1680_1683delTGAG), which appears to be responsible for the familial MEN1 syndrome. This is the first report showing the highly penetrant feature of this mutation among family members who developed the MEN1 syndrome linked tumors. Our investigations expand the spectrum of the disease-causing *MEN1* gene mutation and highlight the importance of monitoring at-risk relatives in MEN1 pedigrees to identify asymptomatic carriers before the appearance of any tumor. In this regard, further research may be conducted to clarify the potential candidacy of this mutation as a hotspot for MEN1 patients, especially in the Turkish population. In addition, functional studies are necessary to evaluate and understand the impact of this frame-shift mutation.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Marmara University, School of Medicine (Approval number: 09.2017.484, approval date: 14.07.2017).

Informed Consent: Written informed consent was obtained from the patients and patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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